Janssen Research & Development *

Clinical Protocol

A Phase 2a Multicenter, Randomized, Double Blind, Parallel, Proof of concept Study Evaluating the Efficacy and Safety of Nipocalimab and Certolizumab Combination Therapy in Participants with Active Rheumatoid Arthritis despite Prior Treatment with Advanced Therapies (bDMARD or tsDMARD)

DAISY

Protocol 80202135ARA2002**;** Phase 2

Version: Amendment-3

JNJ-80202135 (nipocalimab)

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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)

Registry	ID
IND	154,384
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EDMS Number: EDMS-RIM-929994, 4.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, Regulation [EU] No 536/2014, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Country/Territory Affected**	**Date**
Amendment 3	All	05 October 2023
Amendment 2	All	27 September 2023
Amendment 1	All	7 September 2023
Original Protocol	All	28 March 2023

Amendment 3 (05 October 2023)

Overall Rationale for the Amendment: To address FDA comments regarding rescue criteria.

The changes made to the clinical protocol 80202135ARA2002 as part of Protocol Amendment 3 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in the previous protocol amendments are listed in Section 10.11 Appendix 11: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
1.3. SoA	Weight assessment has been removed from Week 24. Footnote a) has been modified as: "Participants who permanently discontinue study intervention, but do not withdraw from study participation, will be followed at all subsequent study visits through Week 30. At a minimum, participants who permanently discontinue study intervention, but do not withdraw from study participation, should return for a safety follow-up visit 8 weeks after the last dose of study intervention.~~Participants who complete dosing at Week 22 or discontinue study intervention administration early should return to the site after approximately 8 weeks after the last dose for a final safety follow-up visit.~~"	Since no study intervention will be administered during this visit, weight assessment is not necessary. To clarify follow-up of discontinued participants
2.3.1. Risks for Study participation	Table 2: Important Risks of Certolizumab for the treatment of Rheumatoid Arthritis has been modified: Deletion of exceptions for participants with malignancy or history of malignancy	To align with EU-CTR recommendation
3. Objectives and Endpoints	Evaluation timepoints for tertiary or exploratory Endpoints have been updated.	To align that efficacy and PRO endpoint evaluations are all set to Week 24 while Safety/PK/PD endpoint evaluations are all set to Week 30.
4.1. Overall Design	Sentence below has been added: "At Week 14, participants who have not achieved low disease activity (CDAI ≤10) will receive rescue medication".	To follow current SOC in RA.
4.4. End of Study Definition	Completion of the safety follow-up visit was added to the definition of participants who complete the study.	Further clarification on the definition of completing the study.
5.1 Inclusion Criteria; 5.2.	Inclusion and exclusion criteria concerning COVID-19 have been modified:	To align with sponsor protocol template update.

Section Number and Name	Description of Change	Brief Rationale
Exclusion Criteria; 5.3. Lifestyle Considerations	IC#27 has been removed and guidance is now included in Section 6.8.7. EC#25 has been modified to reduce the time interval participants have to be free of COVID-19 prior to baseline from 6 to 4 weeks. IC#22 has been modified.	
5.4. Screen Failures	Updated the text regarding screening logs.	To conform to the current sponsor protocol template.
6.3. Measures to Minimize Bias: Randomization and Blinding	Blinding sub-section has been modified to add: "At the Week 12 DBL, 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 subject-level data will be documented prior to unblinding. Investigative study sites and participants will remain blinded to initial treatment assignment until after the final database is locked."	To clarify that the Sponsor only has defined and limited persons to access to unblinded data after Week 12 DBL.
6.4. Study Intervention Compliance	Weighing of IV infusion bag has been removed.	Weighing of IV infusion bag is not part of the study procedures.
6.8. Concomitant Therapy	Table 3 outlining permitted concomitant medication use and dose stabilization requirements prior to randomization was added.	To clarify permitted concomitant medication use and dose stabilization requirements prior to randomization.
6.8.6. Rescue Medication	Rescue medication guidance at Week 14 was updated.	The guidance is updated to follow current SOC in RA.
8.2.3. Electrocardiograms	Section has been modified to add: "A 12-lead ECG will be performed locally at screening. Additional ECGs can be performed locally based on the investigator's judgment." Information about triplicate ECGs has been removed.	To follow the study design and SOA notes that ECG will be performed and evaluated per local practices.
8.2.13. Tuberculosis Evaluation	Added a Section to detail the assessments to be done for initial and continuous TB assessment.	To provide more detailed guidance to investigators.
8.3.5. Pregnancy	Updated text from template: "Any participant who becomes pregnant during the study must discontinue further study intervention."	To conform to the current sponsor protocol template.
9.4.2.1. Primary Estimand of Change from Baseline in DAS28-CRP at Week 12	ICE category 5 has been deleted.	To align with sponsor protocol template update.
9.4.4. Safety Analyses	Added information on the on-study Safety Analysis-Set, as well as details on exposure-adjusted supplementary on-treatment analysis for treatment emergent AEs.	The primary safety analysis will use the on-study Safety Analysis-Set, ie, participants who received at least one dose (complete or partial) of any study intervention.
Appendix 2: Clinical laboratory tests	Details have been added on the urine pregnancy testing:	To follow suggested contraception period on Cimzia label.

Section Number and Name	Description of Change	Brief Rationale
	"Participants of childbearing potential will be given urine pregnancy tests to be self-administered at home until 5 months after their last dose of the study intervention. The site is responsible for contacting these participants on a monthly basis to confirm that the pregnancy test has been performed. If a participant tests positive for pregnancy, the site is required to report this to the sponsor within 24 hours of becoming aware of the event".	
10.3.6. Long-term Retention of Samples for Additional Future Research	Updated text from template: "No additional research on study participants, study samples, or data derived from the study will be conducted by the institution(s) or by a third party, without the prior written consent of the Sponsor."	To conform to the current sponsor protocol template.
10.3.11. Source Documents	Updated text from template: "Given that patient-reported outcomes (PROs) are reports of a patient's health condition that come directly from the patient, 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."	To conform to the current sponsor protocol template.
10.5. Appendix 5: Contraceptive and Barrier Guidance	Updated text from template: Replaced "woman" by "female participant". Deletion of footnote b).	To conform to the current sponsor protocol template.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase 2a Multicenter, Randomized, Double Blind, Parallel, Proof of concept Study Evaluating the Efficacy and Safety of Nipocalimab and Certolizumab Combination Therapy in Participants with Active Rheumatoid Arthritis despite Prior Treatment with Advanced Therapies (bDMARD or tsDMARD)

DAISY

DESCRIPTION OF COMPOUND

Nipocalimab (also referred to as JNJ-80202135 and M281) is a fully human aglycosylated IgG1 monoclonal antibody designed to selectively bind, saturate, and block the IgG binding site on the endogenous neonatal Fc receptor.

Certolizumab (Cimzia®) is an approved anti-TNFα agent indicated for active Crohn's disease, RA, PsA, AS, nr-axSpA, and PsO.

BENEFIT-RISK ASSESSMENT

The study population with moderately to severely active RA has already had inadequate initial response, loss of response, or intolerance to ≥1 advanced therapy (bDMARDs or tsDMARDs), therefore combination therapy may provide a higher chance of lower disease activity and remission. Multiple risk mitigation measures are in place to manage a potential increase in infections risk with certolizumab and nipocalimab combination therapy. Based on the well characterized safety profile of certolizumab and the available safety data of nipocalimab to date, the overall anticipated benefits outweigh the risks of participation in this clinical study.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of combination therapy with nipocalimab and certolizumab compared to certolizumab monotherapy in participants with moderately to severely active RA despite ≥1 advanced therapy (bDMARDs or tsDMARDs).	• Change from baseline in DAS28-CRP at Week 12
Secondary	
• To evaluate the efficacy of combination therapy with nipocalimab and certolizumab compared to certolizumab monotherapy in participants with moderately to severely active RA	• ACR20, ACR50, ACR70, and ACR90 responses at Week 12 • DAS28-CRP remission at Week 12 • DAS28-CRP LDA at Week 12 • Change from baseline in HAQ-DI score at Week 12 • Change from baseline in CDAI at Week 12

Objectives	Endpoints
• To evaluate the safety and tolerability of combination therapy with nipocalimab and certolizumab	• Treatment-emergent AE • Treatment-emergent SAEs • Treatment-emergent AEs leading to discontinuation of study intervention • Treatment-emergent AESIs

HYPOTHESIS

The primary hypothesis is that treatment with nipocalimab in combination with certolizumab is superior to certolizumab monotherapy in participants with moderately to severely active RA despite treatment with ≥1 advanced therapy (bDMARDs or tsDMARDs) as assessed by the mean change from baseline in DAS28-CRP at Week 12.

OVERALL DESIGN

This is a randomized, double-blind, parallel, multicenter, interventional study in participants with moderately to severely active RA despite ≥1 advanced therapy (bDMARDs or tsDMARDs).

The total duration of the study is up to 36 weeks, consisting of 3 study periods, a 6-week screening period, a 24-week double-blind study period (22 weeks of treatment), and 6 weeks of safety follow-up (8 weeks after last dose).

Participants who have had an IR to at least one advanced therapy (bDMARDs or tsDMARDs) but are certolizumab naïve, will be enrolled. Participants will be randomized into 1 of 2 arms. The experimental arm will receive nipocalimab and certolizumab combination therapy. A placebo and certolizumab control arm will be used to allow for blinded evaluation of the efficacy and safety of certolizumab and nipocalimab combination therapy in participants with moderately to severely active RA.

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

The primary endpoint (change from baseline in DAS28-CRP at Week 12) and secondary endpoints will be evaluated after all participants have completed the Week 12 visit or have discontinued. Tertiary or exploratory efficacy endpoints will be evaluated by visit through Week 24 (efficacy and PRO endpoints) or Week 30 (safety/PK/PD endpoints) after all participants have completed the Week 24 visit or have discontinued.

An external independent DMC will be commissioned for this study.

NUMBER OF PARTICIPANTS

A total of approximately 85 participants are planned to be enrolled.

INTERVENTION GROUPS AND DURATION

Participants will be randomly assigned to 1 of 2 treatment groups using a 2:3 randomization ratio.

- Control arm: placebo matching nipocalimab and certolizumab (certolizumab monotherapy)
- Experimental arm: Nipocalimab and certolizumab (combination therapy)

Nipocalimab will be administered at 30 mg/kg Q2W. Certolizumab will be administered at 400 mg as a loading dose at Week 0, 2, 4 and then reduced to 200 mg Q2W as a maintenance dose. Both groups will receive their assigned treatment for 22 weeks (Week 0 through Week 22).

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
  - Joint Pain Severity Numeric Rating Scale
  - Health Assessment Questionnaire – Disability Index
- Clinician-reported outcomes
  - Joint assessment
  - Physician's Global Assessment of Disease Activity

PHARMACOKINETIC EVALUATIONS

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

IMMUNOGENICITY EVALUATIONS

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

PHARMACODYNAMIC, BIOMARKER EVALUATIONS

Samples for the analysis of PD biomarkers will be collected from all participants as specified in the SoA, where local regulations permit. Serum or plasma concentrations of immunoglobulins, albumin, and disease biomarkers (eg, autoantibodies, circulating immune complexes) will be measured to assess the PD effect of nipocalimab and certolizumab combination therapy.

Blood samples for serum and plasma biomarker analyses will be collected from all participants where local regulations permit. Serum and plasma will be analyzed for levels of circulating proteins, autoantibodies (eg, ACPA, RF), and other inflammation-related molecules and disease-associated serologies relevant to RA, treatment, and response to nipocalimab and certolizumab combination therapy.

PHARMACOGENOMIC (DNA) EVALUATIONS

A pharmacogenomic blood sample may be collected to allow for pharmacogenomic research, as necessary and where local regulations permit. Participation in the pharmacogenomic research is optional.

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 85 participants are planned to be randomized in a 2:3 ratio to the control and experimental arm. The sample size selection was determined based on the primary endpoint of the change from baseline in DAS28-CRP at Week 12. For this study, assuming a difference of 0.67 in the change from baseline in DAS28-CRP and a pooled standard deviation of 1.2 between control arm and experimental arm, a sample size of

- Control arm: 34 participants receiving certolizumab + placebo
- Experimental arm: 51 participants receiving combination therapy of nipocalimab + certolizumab

will provide a power of approximately 80% to detect a significant treatment difference at a 1-sided significance level of α=0.05 using a T-test. The difference of 0.67 is a meaningful improvement in this population over an effective monotherapy treatment in RA.

Statistical Analysis

General Considerations

In general, descriptive statistics (eg, mean, median, SD, interquartile range, minimum, and maximum) will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables. Graphical data displays (eg, line plots) may also be used to summarize data.

Analyses suitable for categorical data (eg, chi-square tests, CMH tests or logistic regression, as appropriate) will be used to compare the proportions of participants achieving selected endpoints (eg, ACR response). In cases of rare events, the Fisher's exact test will be used for treatment comparisons. Continuous response parameters will be compared using ANCOVA, a MMRM, or a cLDA, as appropriate.

Primary Endpoint

Unless otherwise specified, efficacy analyses will be based on the Full Analysis Set, defined as all randomized participants who had at least one study intervention administration. Participants will be analyzed according to the study treatment arm to which they were randomized regardless of the study intervention they received.

The primary endpoint is the mean change from baseline in DAS28-CRP at Week 12. Analysis will be based on the primary estimand, ie, a precise definition of the primary targeted treatment effect, that is defined by 5 attributes (treatment, population, variable, ICE, and population-level summary) for the primary endpoint as stated below.

The comparison for the primary endpoint will be tested at a 1-sided α level of 0.05. Nominal p-values (1-sided) will be displayed for all other endpoint comparisons. Full details of the analysis of the primary, secondary, and exploratory endpoints will be included in SAP.

Secondary Endpoints

Secondary efficacy endpoints are:

- ACR20, ACR50, ACR70, and ACR90 at Week 12
- DAS28-CRP remission at Week 12
- DAS28-CRP LDA at Week 12
- Change from baseline in HAQ-DI score at Week 12
- Change from baseline in CDAI at Week 12

Analyses will compare between combination therapy (certolizumab + nipocalimab) and monotherapy (certolizumab + placebo). The methods of analysis, as well as the data handling rules, will be provided in the SAP.

Safety Analyses

Safety data including but not limited to, AEs, SAEs, AESIs, vital signs, and changes in laboratory assessments, will be summarized by study treatment arm for the safety analysis set, defined as all participants who received at least 1 dose of study intervention.

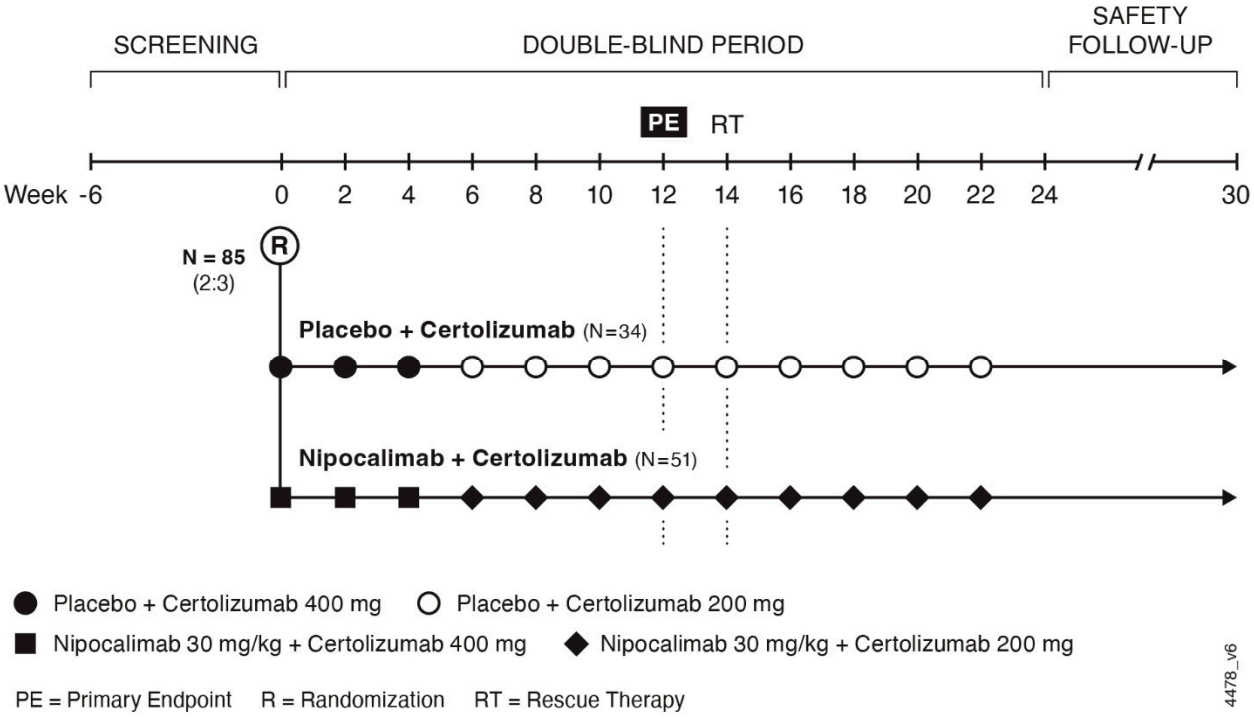
Listings of all participants with MACE (nonfatal MI, nonfatal stroke, and cardiovascular death) will be provided.

Other Analyses

- **Pharmacokinetic Analyses**: Serum nipocalimab concentrations over time will be summarized for each treatment arm 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 and certolizumab. 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.
- **Biomarker Analyses:** Changes in biomarkers over time may be summarized by treatment arm. Associations between baseline levels and changes from baseline in select biomarkers and clinical response will be explored. Results of biomarker analyses will be presented in a separate report.
- **Pharmacokinetic/Pharmacodynamic Analyses:** If data permit, the relationship between serum concentrations of nipocalimab and certolizumab and the efficacy measures and relevant PD biomarkers 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 (DNA) analyses may be conducted only in participants who sign the consent form to participate in the pharmacogenomic sampling. These analyses are considered exploratory. Results of analyses will be presented in a separate technical report.
- **Immunogenicity Analyses:** The incidence and titers of antibodies to nipocalimab will be summarized for all exposed 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.

1.2. Schema

Figure 1: Schematic Overview of the Study



1.3. Schedule of Activities (SoA)

Period	Screening	Double-blind Study Intervention													Follow-up	
Week	≤6 weeks	0	2	4	6	8	10	12	14	16	18	20	22	24	30 or Final Safety Follow-up Visit (8 weeks after last dose)[a]	
Visit Window		±3 days													±7 days	
Study Procedure																Notes
Screening/Administrative																
ICF	X															Must be signed before first study-related activity.
ICF for optional genetic research samples	X															
Demographics	X															
Review medical history requirements	X	X														
Review prestudy medications	X	X														
Preplanned surgery/procedure(s)	X	X														
12-lead ECG	X															Local procedure evaluated by investigator. Previous ECG-results may be used if not older than 30 days at the time of screening.
HIV, HBV, HCV testing	X															
QF®-TB	X															
Chest X-ray	X															Only if no chest radiograph done within the last 90 days before first administration of study intervention,

Period	Screening	Double-blind Study Intervention													Follow-up	
Week	**≤6 weeks**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**30 or Final Safety Follow-up Visit (8 weeks after last dose)[a]**	
Visit Window		±3 days													±7 days	
Study Procedure																**Notes**
																and required for tuberculosis screening as per local standard procedures.
FSH (for menopausal women)	X															
Inclusion/exclusion criteria	X	X														
Study Intervention Administration																
Randomization		X														
Dispense/administer study intervention		X	X	X	X	X	X	X	X	X	X	X	X			
Efficacy Assessments																
PRO																To be conducted prior to study intervention administration. Before ClinROs and any other study procedures to prevent influencing participants' perceptions. PRO assessments should be conducted in the order shown in the SoA.
PtGA of disease activity		X	X	X	X	X	X	X	X	X	X	X	X	X		
Pain VAS		X	X	X	X	X	X	X	X	X	X	X	X	X		
Joint Pain Severity NRS		X			X			X			X			X		
HAQ-DI		X	X	X	X	X	X	X	X	X	X	X	X	X		
ClinROs																To be completed prior to administration of
Joint assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
PGA of disease activity		X	X	X	X	X	X	X	X	X	X	X	X	X		

Period	Screening	Double-blind Study Intervention													Follow-up	
Week	**≤6 weeks**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**30 or Final Safety Follow-up Visit (8 weeks after last dose)[a]**	
Visit Window		±3 days													±7 days	
Study Procedure																**Notes**
																study intervention and should be conducted in the order shown here in the SoA.
Safety Assessments[a]																
Height	X															
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X		X	Needed for IV preparation (dose calculation)
Physical examination	X															
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine Pregnancy test (highly sensitive)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Injection site reaction and infusion reaction evaluation[b]		X	X	X	X	X	X	X	X	X	X	X	X	X		
Questions for early detection of active TB	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical Laboratory Tests																
Chemistry	X	X	X	X		X		X		X		X		X	X	Nonfasting blood samples are collected at screening and Week 2 only. All other visits from baseline to the end of study requires fasting condition
Hematology	X	X	X	X		X		X		X		X		X	X	
Coagulation	X	X	X	X		X		X		X		X		X	X	
Lipid panel	X	X		X		X		X		X		X		X	X	

Period	Screening	Double-blind Study Intervention												Follow-up	
Week	**≤6 weeks**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**30 or Final Safety Follow-up Visit (8 weeks after last dose)[a]**	
Visit Window		±3 days													±7 days	
Study Procedure																**Notes**
																due to lipid sample collections.
Urinalysis	X	X		X		X		X		X		X		X	X	
PD and Disease Biomarkers (Central Laboratory)																
ACPA (central laboratory)	X	X														
CRP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ESR		X	X	X	X	X	X	X	X	X	X	X	X	X	X	Local laboratory
Immunoglobulin (IgG/M/E/A)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
IgG subtypes		X		X				X						X	X	
RF (total)	X	X		X				X						X	X	
IgG/IgM RF		X		X				X						X	X	
Circulating Immune Complexes		X		X				X						X	X	
Complement Activation Markers		X		X				X						X	X	
Clinical Pharmacology Assessments																
Serum nipocalimab concentrations		2x	2x	X		2x		2x		X				X	X	See footnote "c" for details
Serum certolizumab concentrations		X	X	X		X		X		X				X	X	
Random nipocalimab population PK concentration		X														
Random certolizumab population PK concentration			X													
Antibodies to nipocalimab		X	X	X		X		X		X				X	X	
Pharmacodynamics and Biomarkers (eg, plasma, serum, urine, biopsy sample collection)																

Period	Screening	Double-blind Study Intervention													Follow-up	
Week	**≤6 weeks**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**30 or Final Safety Follow-up Visit (8 weeks after last dose)[a]**	
Visit Window		±3 days													±7 days	
Study Procedure																**Notes**
Serum biomarkers [d]		X	X	X		X		X		X				X	X	
Plasma biomarkers		X		X				X						X	X	
Whole blood (bulk RNAseq)		X		X				X						X		
PBMCs (cellular analysis)[e]		X						X						X		
Pharmacogenomic (DNA) (optional)		X[f]												X[f]		

Footnotes:

a. Participants who permanently discontinue study intervention, but do not withdraw from study participation, will be followed at all subsequent study visits through Week 30. At a minimum, participants who permanently discontinue study intervention, but do not withdraw from study participation, should return for a safety follow-up visit 8 weeks after the last dose of study intervention.

b. Participants will be observed for safety during and for 1 hour after the first 3 study intervention administrations at the study site (Week 0, 2, and 4); if no clinically relevant AEs related to the study intervention administrations are observed, the post-intervention administrations observation period may be reduced to 30 minutes for the remaining study intervention administrations.

c.

i) 2x means 2 samples (for nipocalimab or placebo concentrations) will be collected (1 sample will be collected prior to IV infusion and the other collected 45 minutes [±15 minutes] after the end of the IV infusion) for all participants. The sample should be drawn from the opposite arm of the IV line. For all other visits, only a predose serum sample will be collected

ii) For visits with study intervention administration, all blood samples for assessing predose nipocalimab and certolizumab concentrations and antibodies to nipocalimab MUST be collected BEFORE the administration of the study intervention

iii) One random population PK nipocalimab concentration sample will be collected from all participants any time between 3 to 7 days after the Week 0 or Week 2 visit other than the scheduled samples

iv) One random population PK certolizumab concentration sample will be collected from all participants any time between Week 2 and Week 8 other than at the time of the Week 2, Week 4, Week 6, and Week 8 visits; this sample must be collected at least 24 hours prior to or after a study intervention administration and must not be collected at a regularly scheduled visit.

v) When samples for both PK ("nipocalimab and certolizumab concentration") and ADA ("antibodies to nipocalimab") are collected, 1 sample (instead of 2) will be collected for both assays

d. Serum biomarkers may include but are not limited to ACPA, RF, and cytokines

e. Samples for PBMC collection will only be done at sites where it is logistically feasible

f. The sample should be collected at the specified time point, but may be collected at a later point without constituting a protocol deviation

2. INTRODUCTION

For the most comprehensive nonclinical and clinical information regarding nipocalimab, refer to the latest version of the IB and Addenda for nipocalimab. For nonclinical and clinical information regarding certolizumab refer to available SmPC and USPI.

The term "study intervention" throughout the protocol, refers to study drugs as defined in Section 6.1.

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.

2.1. Study Rationale

The goal of RA treatment is to achieve low arthritis disease activity and remission if possible, minimizing joint damage, and enhancing physical function and quality of life. The available treatment options, including csDMARDs, and more notably the bDMARDs and tsDMARDs, have revolutionized the clinical management of RA. A therapeutic approach has included combining multiple interventions to address the significant unmet medical need in patients with RA with inadequate responses to advanced therapies (Smolen 2020). However, despite multiple approved drugs in RA, about 20 to 30% of patients continue to have refractory disease (Smolen 2020). This reflects the complex and heterogenous nature as well as the unmet need of the disease (Lin 2020; Smolen 2020).

A meta-analysis of studies combining an anti-TNFα agent and anakinra, an anti-TNFα agent and abatacept, an anti-TNFα agent and rituximab, abatacept and anakinra, and rituximab combined with tocilizumab showed no clear evidence of an efficacy advantage in participants with RA while the risk of SAEs and total AEs appeared to increase (Boleto 2019), most likely due to significant exacerbation of immunosuppression.

A combination therapy of the anti-FcRn agent nipocalimab with the anti-TNFα agent certolizumab has been chosen as mechanistic observations suggest that these treatment agents modulate the RA disease driving pathways and cellular functions in an orthogonal and complementary manner. Specifically, nipocalimab uniquely and significantly suppresses pathogenic processes downstream of autoantibodies, while anti-TNFα agents prominently suppress the myeloid immune system and reduce joint inflammation resulting in decreased joint damage. In addition, downstream effects of nipocalimab could suppress pro-inflammatory cytokines and osteoclastogenesis which are potential disease modifying mechanisms shared with anti-TNFα agents. Moreover, certolizumab has a well-established safety and efficacy profile in the treatment of patients with active RA (Cimzia EMA SmPC, USPI). Therefore, certolizumab was chosen for further evaluation in this study.

CCI [redacted].

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, IV nipocalimab induced serum IgG decreases in rodents or nonhuman primates and ameliorated disease pathology in animal models of pathogenic IgG-driven autoimmune disease. Pharmacokinetic and 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 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. 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.

Clinical Studies

Human Pharmacokinetics

Nipocalimab exhibited dose-dependent nonlinear PK due to TMDD with much more rapid clearance at concentrations <10 µg/mL. Following single IV administration of 0.3 to 60 mg/kg, C_{max} of nipocalimab increased in a dose-proportional manner, whereas AUC increased in a greater than dose-proportional manner. CCI [redacted]

PK of nipocalimab in participants with gMG was generally consistent with PK in healthy participants. Pharmacokinetic accumulation appeared to be negligible based on C_{trough} and C_{eoi} at the dose regimens tested (ie, 5 mg/kg and 30 mg/kg q4w, and 60 mg/kg q2w).

PK of nipocalimab was generally comparable between Japanese and non-Japanese healthy participants after single IV administration of 10, 30, and 60 mg/kg doses based on cross-study comparisons.

Following a single 30 mg/kg IV dose in healthy participants, nipocalimab exposure (C_{max} and AUC) was largely similar regardless of infusion rate (0.5 mg/kg/min to 4 mg/kg/min when given during 7.5 to 60 minutes), as were the terminal $t_{1/2}$ values.

Human Pharmacodynamics

The efficacy of nipocalimab is related to saturation of the FcRn target, thereby lowering the total serum IgG concentrations, including the levels of IgG-based pathogenic autoantibodies.

Pharmacodynamic responses of full target saturation measured as FcRn receptor occupancy (defined as <10% unoccupied receptors) and asymptomatic, self-limited, recoverable decreases from baseline in total serum IgG concentrations of up to 85% were observed in the completed Phase 1 and Phase 2 studies, confirming the MoA of nipocalimab. Asymptomatic, self-limited, dose-dependent, recoverable decreases from baseline in serum albumin of up to 25% were also observed.

CCI [redacted]

Efficacy/Safety Studies

The Phase 2a study (80202135ARA2001), a double-blind, parallel-group, placebo-controlled, PoC, multicenter study of nipocalimab in participants with moderately to severely active RA despite standard therapy has been completed.

CCI [redacted]

CCI

[redacted]

[redacted]

[redacted]

[redacted]

2.2.1. Combination Therapy

More detailed information about the known and expected benefits and risks of nipocalimab can be found in the IB and addenda. For risks associated with certolizumab, please refer to the Cimzia country-approved label.

2.3. Benefit-risk Assessment

No new risks were identified in Study 80202135ARA2001 in participants with moderate to severe RA.

The important potential risks of exposure to nipocalimab based on its MoA as well as the relevant risks of exposure to certolizumab based on the Special Warnings and Precautions for Use described in the USPI for Cimzia are summarized in Section 2.3.1.

More detailed information about the known and expected benefits and risks of nipocalimab may be found in the IB and addenda. For risks associated with certolizumab, please refer to the Cimzia country-approved label.

The inclusion and exclusion criteria have been chosen based on the risks of both compounds. In cases of differing risks, the most conservative approach has been chosen.

2.3.1. Risks for Study Participation

Inclusion and exclusion criteria based on the below risks of nipocalimab and certolizumab for the treatment of RA can be found in Section 5. Study intervention stopping criteria can be found in Section 7.1, and study stopping criteria in Section 7.1.2. The study safety review process by an independent DMC can be found in Section 9.5.

Table 1: Important Potential Risks of Nipocalimab for the Treatment of Rheumatoid Arthritis		
Potential Risks of Clinical Significance	**Summary of Data/ Rationale for Risk**	**Mitigation Strategy**
Lack of clinical benefit/Clinical worsening of RA	The benefit-risk of certolizumab and nipocalimab combination therapy in treatment of RA has not been established.	• During the study, participants will be permitted to continue treatment of RA with certain standard-of-care medications (Section 6.8). • Participants may discontinue study intervention if it is not in their best interest or if they need to initiate certain protocol-prohibited medications including certain biologics (Section 6.8.5). • Participants will be allowed to use rescue medication from Week 14 (Section 6.8.6).
Risks Due to Study Intervention(s)		
Potential increased risk for infection due to decreased serum IgG concentrations	As predicted based on its MoA, nipocalimab was associated with dose-dependent reductions in IgG of up to 80% to 85% of baseline in cynomolgus monkey and human studies. However, nipocalimab did not increase the incidence, severity, or duration of infection in any of the nonclinical and clinical studies conducted to date.	• Participants with severe acute or chronic infections requiring anti-infective therapies are excluded from participation in the study. • Participants with serum total IgG <6 g/L (<600 mg/dL) at screening will be excluded from the study. • Study intervention stopping criteria for profound hypogammaglobulinemia (serum total IgG <1 g/L [<100 mg/dL]) and infections are included in in the protocol. • Study stopping rules based on serious infections are included in the protocol. • All infections will be monitored closely. Treatment-emergent infections meeting the AESI criteria must be reported to the sponsor within 24 hours (Section 8.3.6). • Participants who have had a live vaccine within 4 weeks prior to the first administration of study intervention or longer as either indicated on the package insert of the relevant vaccine or according to local regulations (or within 12 months prior to first administration of study intervention for BCG), or has a known need to receive a live vaccine during the study, or within at least 8 weeks after the last dose of study intervention in this study are excluded from participation in the study.

Table 1: Important Potential Risks of Nipocalimab for the Treatment of Rheumatoid Arthritis		
Potential Risks of Clinical Significance	**Summary of Data/ Rationale for Risk**	**Mitigation Strategy**
Reduced effectiveness of routine vaccines due to decreased IgG	Due to the expected reduction in IgG as a result of the overall effect of nipocalimab on total IgG concentrations, a reduction in vaccine-specific IgG titers can be expected. While decreases in vaccine titers were observed in the FIH study, there has been no increase in the incidence, severity, or duration of infection in any of the nonclinical and clinical studies conducted to date.	• It is recommended that participants are up-to-date on all age-appropriate vaccinations prior to screening as per routine local medical guidelines. • Non-live vaccinations should be administered as per the assessment of the investigator.
Activation of latent virus due to decreased IgG	Due to the expected reduction in IgG as a result of the overall effect of nipocalimab on IgG concentrations, activation of latent virus is a potential risk. To date, there has been no observed increase in the frequency of latent virus activation in clinical studies with nipocalimab.	• Serology testing is done at screening to exclude participants with HIV, HBV, or HCV infections. • Permanent study intervention stopping criteria for infections are included in the protocol. • Infections will be monitored closely; treatment-emergent infections meeting the AESI criteria must be reported to the sponsor within 24 hours (Section 8.3.6).
Clinical manifestations of hypoalbuminemia	While nipocalimab selectively targets the FcRn-IgG binding site, its binding to FcRn may result in some steric hinderance at the albumin binding site of FcRn and thereby partially impair albumin recycling. Nipocalimab was associated with modest reductions in albumin, reversible off-treatment in both the nonclinical and clinical studies conducted to date.	• Participants will be monitored for albumin abnormalities by regular safety laboratory assessments. • Hypoalbuminemia <20 g/L must be reported as an AESI within 24 hours (Section 8.3.6). • Study intervention discontinuation rules for 3+ pedal edema, ascites, or pleural or pericardial effusions are included in the protocol.
Infusion reaction	Infusion reactions have been observed with the administration of biologics, particularly monoclonal antibodies. In study MOM-M281-010 with Japanese participants, one participant who received nipocalimab 30 mg/kg IV had an infusion reaction that required treatment with diphenhydramine. [redacted]	• Participants will be monitored for infusion reactions. • For injection/infusion/hypersensitivity reaction management refer to Section 8.2.
Drug-drug interaction	Nipocalimab is expected to reduce exposure of therapeutic agents that contain the Fc region of IgG (eg, IVIg, Fc-based biologics like eculizumab, rituximab, infliximab, adalimumab, and Fc fusion proteins). One	• Participants who are on IgG Fc-containing protein therapeutics are excluded from the study.

Table 1: Important Potential Risks of Nipocalimab for the Treatment of Rheumatoid Arthritis		
Potential Risks of Clinical Significance	**Summary of Data/ Rationale for Risk**	**Mitigation Strategy**
	DDI study (MOM-M281-008) is completed as of IB data cutoff date (28 April 2022). The DDI observed in this study was consistent with the MoA of nipocalimab and confirmed the hypothesis that nipocalimab could reduce the PK exposure of IgG-based mAbs via inhibition of FcRn-mediated recycling High doses of nipocalimab may reduce serum albumin up to 25%. The concomitant use of drugs with both high protein binding (>95%) and narrow therapeutic index may lead to higher free drug concentrations which could increase the risk for potential toxicities.	• Participants treated with nipocalimab and who are on concomitant medications which have high protein binding (>95%) and narrow therapeutic index (such as but not limited to warfarin, sulfasalazine, mycophenolate mofetil, leflunomide), should be monitored for potential impacts of nipocalimab on efficacy and safety of those medications.
Increased lipids	Elevations in total cholesterol and LDL were reported recently with another experimental drug in the same pharmacologic class of FcRn antagonists. In the MOM-M281-001 and MOM-M281-004 studies, asymptomatic, dose-dependent, reversible elevations in nonfasting mean total cholesterol were observed up to 25% of baseline. In both studies, elevations in total cholesterol appear to mirror the kinetics of the decreases in albumin observed with nipocalimab. In pregnant women, a preliminary review suggested a possible treatment-emergent increase in non-fasting total 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.	• Participants with recent MI, stroke, or unstable angina within 12 weeks of study entry will be excluded from participation in the study. • Routine laboratory investigations for lipid panel (total cholesterol, HDL, LDL, triglycerides) will be performed in the study. • 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 as per local health guidelines. In participants with persistently elevated lipids (above the 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.
Placental infarction	Abnormal placental infarctions were observed in 4/26 available placentas from 55 pregnant cynomolgus monkeys exposed to nipocalimab in a reproductive and developmental toxicology study. While 3 of the 4 cases resulted in fetal mortality, there was no evidence of growth restriction or hypoxia; and one of the 3 fetuses was observed with umbilical entrapment. Overall fetal loss in the study was not different between nipocalimab-treated and placebo	• Pregnant women are excluded from this study and participants must agree to use highly effective methods of contraception (Section 10.5). • Pregnancy tests are conducted throughout. Participants who become pregnant will be withdrawn and followed up until delivery or termination of pregnancy.

Table 1: Important Potential Risks of Nipocalimab for the Treatment of Rheumatoid Arthritis		
Potential Risks of Clinical Significance	**Summary of Data/ Rationale for Risk**	**Mitigation Strategy**
	treated groups and no nipocalimab-related developmental toxicity was identified. One patient with IUGR and another with placental abruption have been reported from a study involving antenatal treatment of pregnant women at risk of EOS-HDFN.	
Low IgG in infants born to mothers with EOS-HDFN receiving nipocalimab during pregnancy	Low IgG concentrations in infants born to mothers with EOS-HDFN receiving nipocalimab during pregnancy (between Week 14 and Week 35) were observed. The IgG concentrations at or below the lower limit of normal occurred in 5/5 infants with available IgG data at 24 weeks (n=3), 34 weeks (n=1), and 1-year (n=1) post birth. As the study is ongoing, the duration of low IgG in these infants is currently unknown. As of 31-December-2020, there have been no infections reported in these infants, with the exception of one infant who had a self-limited episode of thrush reported at 2.5 months of age and lasting 2 weeks.	• Pregnant women are excluded from this study and participants must agree to use highly effective methods of contraception (Section 10.5). • Pregnancy tests are conducted throughout. Participants who become pregnant will be withdrawn and followed up until delivery or termination of pregnancy.

Table 2: Important Risks of Certolizumab for the treatment of Rheumatoid Arthritis		
Risks for Study Participation	**Summary of Data/ Rationale for Risk**	**Mitigation Strategy**
Serious infections and reactivation of latent infections	Serious infections, including sepsis and tuberculosis (including miliary, disseminated and extrapulmonary disease), and opportunistic infections (eg, histoplasmosis, nocardia, candidiasis) have been reported in patients receiving certolizumab. Some of these events have been fatal.	• Participants with a history of, or ongoing chronic or recurrent infectious disease, including HIV, HBV, and HCV will be excluded. • Monitoring for signs and symptoms of infection, including TB, is part of the protocol. Participants with evidence of active or untreated latent TB will be excluded from the study. • Participants who received BCG vaccine within 1 year or any other live vaccine within 4 weeks before the first dose of study intervention will be excluded from the study. In addition, participants must agree not to receive a live viral or live bacterial vaccine during the study and for 12 weeks after receiving the last dose of study intervention. • A participant's study intervention must be discontinued if the participant develops a (1) an infection that is unresponsive or worsening while on anti-infective therapy, (2) any serious infection (i.e., meets AE seriousness criteria), (3) a clinically significant opportunistic infection, or (4) any of the TB-related conditions • Study stopping rules for serious infection are included.
Malignancies and lymphoproliferative disorders	The potential role of TNF-antagonist therapy in the development of malignancies is not known. With the current knowledge, a possible risk for the development of Lymphomas, leukemia or other malignancies in patients treated with an anti-TNFα agent cannot be excluded.	• Those participants who currently have a malignancy or have a history of malignancy within 5 years prior to screening will be excluded from the study. • Additionally, participants who have a history of lymphoproliferative disease, including lymphoma, a history of monoclonal gammopathy of undetermined significance or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy or splenomegaly will be excluded from the study. • During the conduct of the study, participants will undergo regular clinical monitoring including routine

Table 2: Important Risks of Certolizumab for the treatment of Rheumatoid Arthritis		
Risks for Study Participation	**Summary of Data/ Rationale for Risk**	**Mitigation Strategy**
		safety laboratory assessments to evaluate any changes in health status that may indicate a possible malignancy. • Participants who develop a malignancy during the study will be discontinued from study intervention.
CHF	Cases of worsening CHF and new onset CHF have been reported with certolizumab.	• Participants with a history of, or concurrent CHF including medically controlled, asymptomatic CHF, will be excluded from the study. • Any participant who develops CHF during the study must discontinue study intervention.
Hematological reactions	Reports of pancytopenia, including aplastic anemia, have been rare with anti-TNFα agents. Adverse reactions of the hematologic system, including medically significant cytopenia (e.g., leukopenia, pancytopenia, thrombocytopenia) have been reported with certolizumab.	• Participants medically unstable based on clinical laboratory tests performed at screening will be excluded from the study. All participants should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) in study. • Participants with confirmed significant hematological abnormalities during the study must discontinue study intervention.
Neurological events	Use of anti-TNFα agents has been associated with rare cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of demyelinating disease, including multiple sclerosis. Rare cases of neurological disorders, including seizure disorder, neuritis, and peripheral neuropathy, have been reported in patients treated with certolizumab.	• Participants with a history of demyelinating disorders, such as MS or optic neuritis, will be excluded from the study. • Any participant who develops a demyelinating disorder during the study must discontinue study intervention.
Hypersensitivity reactions, including serious hypersensitivity reactions and anaphylaxis	Severe hypersensitivity reactions have been reported rarely following certolizumab administration. Some of these reactions occurred after the first administration of certolizumab.	• Participants with known allergy, hypersensitivity, or intolerance to certolizumab or its recipients will be excluded from the study. • All participants must be observed carefully for signs and symptoms of

Table 2: Important Risks of Certolizumab for the treatment of Rheumatoid Arthritis		
Risks for Study Participation	**Summary of Data/ Rationale for Risk**	**Mitigation Strategy**
	Hypersensitivity reactions to natural rubber latex of CIMZIA prefilled syringe cannot be completely excluded in latex-sensitive individuals.	a hypersensitivity reaction (eg, urticaria, pruritis, angioedema, wheezing, dyspnea, or hypotension; Section 8.2.10). • Any participant who develops a serious hypersensitivity reaction such as anaphylaxis must discontinue study intervention.
Autoimmunity/ Lupus-like syndrome	Treatment with certolizumab may result in the formation of antinuclear antibodies (ANA) and, uncommonly, in the development of a lupus-like syndrome	• Participants with a history of severe, progressive, or uncontrolled rheumatologic disturbances, or signs and symptoms thereof that, in the opinion of the investigator, would pose a risk to participant safety will be excluded from the study. • Any participant who develops symptoms suggestive of lupus-like syndrome and is positive for antibodies to double-stranded DNA must discontinue from study intervention.
aPTT assay	Interference with certain coagulation assays has been detected in patients treated with certolizumab. Certolizumab may cause erroneously elevated aPTT assay results in patients without coagulation abnormalities. This effect has been observed with the PTT-LA test and STA-PTT Automate tests from Diagnostica Stago, and the HemosIL APTT-SP liquid and HemosIL lyophilised silica tests from Instrumentation Laboratories. Other aPTT assays may be affected as well. There is no evidence that certolizumab therapy influences coagulation in vivo.	• After patients receive certolizumab, careful attention should be given to interpretation of abnormal coagulation results. Interference with TT and PT assays have not been observed.

*For full list of certolizumab risks and mitigation measures, please refer to certolizumab SmPC or USPI

2.3.2. Benefits for Study Participation

This study will enroll participants who are naïve to certolizumab and all participants in the study will receive certolizumab. Certolizumab is an approved anti-TNFα agent mAb for the treatment of RA and has been shown to effectively reduce pain, swelling, and improve physical function in patients with RA.

Participation in the study may provide access to new treatment options, including certolizumab and nipocalimab combination therapy. CCI [redacted] Combination

of the orthogonal MoAs of certolizumab and nipocalimab may provide broader suppression of pathogenic pathways and potential greater clinical efficacy in participants with RA refractory to previous treatments.

Participants in the study will also help in evaluating this study intervention in the treatment of RA. Thus, the knowledge gained from this study has the potential to benefit patients suffering from RA and thus offers potential public health benefits.

Participants may also experience some benefit from participation in a clinical study irrespective of receiving study intervention, due to regular visits and assessments monitoring their overall health.

2.3.3. Benefit-risk Assessment for Study Participation

The study population with moderately to severely active RA has already had inadequate initial response, loss of response, or intolerance to ≥1 advanced therapy (bDMARDs or tsDMARDs), therefore combination therapy may provide a higher chance of lower disease activity and remission. Multiple risk mitigation measures are in place to manage a potential increase in infections risk with certolizumab and nipocalimab combination therapy. Based on the well characterized safety profile of certolizumab and the available safety data of nipocalimab to date, the overall anticipated benefits outweigh the risks of participation in this clinical study.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of combination therapy with nipocalimab and certolizumab compared to certolizumab monotherapy in participants with moderately to severely active RA despite ≥1 advanced therapy (bDMARDs or tsDMARDs).	• Change from baseline in DAS28-CRP at Week 12
Secondary	
• To evaluate the efficacy of combination therapy with nipocalimab and certolizumab compared to certolizumab monotherapy in participants with moderately to severely active RA	• ACR20, ACR50, ACR70, and ACR90 responses at Week 12 • DAS28-CRP remission at Week 12 • DAS28-CRP LDA at Week 12 • Change from baseline in HAQ-DI score at Week 12 • Change from baseline in CDAI at Week 12
• To evaluate the safety and tolerability of combination therapy with nipocalimab and certolizumab	• Treatment-emergent AE • Treatment-emergent SAEs • Treatment-emergent AEs leading to discontinuation of study intervention • Treatment-emergent AESIs
Tertiary OR Exploratory	
• To evaluate the safety and tolerability of combination therapy with nipocalimab and certolizumab	• Laboratory parameters and change from baseline in laboratory parameters through Week 30 • Vital sign parameters and change from baseline in vital sign parameters through Week 30
• To evaluate the PK and immunogenicity of combination therapy with nipocalimab and certolizumab	• Serum nipocalimab and certolizumab concentrations through Week 30 in participants receiving active study intervention • Incidence and titers of antibodies to nipocalimab (ADA and NAbs) through Week 30
• To evaluate the efficacy of combination therapy with nipocalimab and certolizumab in participants with baseline ACPA high (#1) and baseline csDMARD use (#2)	• Change from baseline in DAS28-CRP through Week 24 • ACR20, ACR50, ACR70, and ACR90 responses through Week 24

Objectives	Endpoints
	• DAS 28-CRP remission through Week 24 • DAS28-CRP LDA through Week 24 • Change from baseline in HAQ-DI score through Week 24 • Change from baseline in CDAI through Week 24 • CDAI LDA through Week 24 • CDAI remission through Week 24
• To evaluate the efficacy of combination therapy with nipocalimab and certolizumab	• ACR20, ACR50, ACR70, and ACR90 responses through Week 24 • Percent improvement from baseline in ACR components through Week 24 • Change from baseline in ACR components through Week 24 • DAS28-CRP (and DAS28-ESR) LDA through Week 24 • DAS28-CRP (and DAS28-ESR) remission through Week 24 • Change from baseline in DAS28-CRP (and DAS28-ESR) through Week 24 • CDAI LDA through Week 24 • Change from baseline CDAI through Week 24 • CDAI remission through Week 24 • Change from baseline in SDAI through Week 24 • SDAI LDA through Week 24 • SDAI-based ACR/EULAR remission through Week 24 • Boolean-based ACR/EULAR remission through Week 24
• To evaluate the efficacy on PROs of combination therapy with nipocalimab and certolizumab	• Proportion of participants achieving a decrease of ≥0.22 points from baseline in HAQ-DI score through Week 24

Objectives	Endpoints
	• Change from baseline in Joint Pain severity score through Week 24
• To evaluate the impact of combination therapy with nipocalimab and certolizumab on PD and disease biomarkers	• Change from baseline in serum Immunoglobulin profile (IgG/M/E/A) and IgG subtype levels through Week 30 • Change from baseline in biomarker levels through Week 30 by treatment group

ESTIMANDS

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

HYPOTHESIS

The primary hypothesis is that treatment with nipocalimab in combination with certolizumab is superior to certolizumab monotherapy in participants with moderately to severely active RA despite treatment with ≥1 advanced therapy (bDMARDs or tsDMARDs) as assessed by the mean change from baseline in DAS28-CRP at Week 12.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double blind, parallel, multicenter, PoC interventional study to evaluate the efficacy and safety of a combination therapy with nipocalimab and certolizumab in participants between 18 and 75 years old, with moderately to severely active RA despite ≥1 advanced therapy (bDMARDs or tsDMARDs) but are certolizumab naïve.

The total study duration is up to 36 weeks, consisting of a 6-week screening period, a 24-week double-blind period (22 weeks of treatment), and a 6-week safety follow-up period (8 weeks after last dose).

A target of approximately 85 participants will be randomly assigned in this study with 34 participants in the certolizumab monotherapy and 51 participants in the nipocalimab in combination with certolizumab group.

An IV administered placebo will be used in the certolizumab monotherapy group to allow for double blinded evaluation of efficacy and safety.

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

The primary endpoint (change from baseline in DAS28-CRP at Week 12 in participants receiving nipocalimab with certolizumab combination therapy compared to participants receiving certolizumab monotherapy) will be evaluated after all participants have completed the Week 12 visit (or have discontinued study participation). At Week 14, participants who have not achieved low disease activity (CDAI ≤10) will receive rescue medication (see Section 6.8.6).

Every reasonable effort will be made to keep concomitant therapy stable (Section 6.8). All concomitant therapies, as well as changes to concomitant therapy will be recorded throughout the study including screening.

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

The PK of nipocalimab and certolizumab, as well as antibodies to nipocalimab will be evaluated in serum samples. Blood-based biomarkers will be evaluated for inflammation associated proteins and other analytes to improve understanding of the biology of RA and the biologic response to treatment in participant with moderately to severely active RA; more specifically, to elucidate the difference between responders and non-responders, to assess loss of response, and the potential of biomarkers to predict treatment outcomes in individual participants.

Two DBLs are planned at Week 12 and at the end of the study, defined as the last follow-up assessment for the last participant.

An independent DMC is commissioned for this study (Section 9.5).

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

4.2. Scientific Rationale for Study Design

Blinding, Control, Study Phase/Periods, Treatment Arm

Randomization will be used to minimize bias in the assignment of participants to treatment arms, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment arms, and to enhance the validity of statistical comparisons across treatment arms. Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

In this study, all participants will receive certolizumab. Participants in the experimental arm will receive both nipocalimab and certolizumab, while participants in the control arm will receive certolizumab and placebo. The placebo in the control arm will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of nipocalimab intervention.

Specific laboratory tests that may be unblinding (eg, nipocalimab concentrations, IgG, albumin, total protein, CICs, autoantibody levels) will not be reported (eg, will remain masked) to the investigator, study team members, or participants during study conduct after randomization. However, test results required for decisions on screening or randomization will be available to the investigator and study team. Given that albumin laboratory results are masked, the Investigator will be notified if their participant has hypoalbuminemia <20 g/L (<2.0 g/dL). These AESI cases will be handled similarly to an SAE for reporting purposes and reviewed by an independent DMC as they occur.

Stratification is implemented to minimize the risk for baseline imbalance(s) across treatment arms on potentially confounding variables such as concomitant therapy, ACPA levels, disease markers, and study site. Baseline imbalances of these factors could impact efficacy and safety assessments of combination therapy versus certolizumab monotherapy. For details on stratification, please refer to Section 6.3.

CCI [redacted]

DNA and Biomarker Collection

Biomarker samples will be collected, where local regulations permit, to evaluate the cellular and molecular MoA of nipocalimab and certolizumab or help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to an intervention. Biomarkers will be analyzed in blood samples to evaluate disease activity and to assess PD markers associated with nipocalimab and certolizumab. The goal of the biomarker analyses is to evaluate the PD of nipocalimab and certolizumab and aid in evaluating the intervention-clinical response relationship.

Optional pharmacogenomic samples may be obtained from participants only when specific consent is provided by signing the optional genetic research ICF. It is recognized that genetic variation can be an important contributory factor to interindividual differences in intervention distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes

and may help to identify population subgroups that respond differently to an intervention. The goal of the pharmacogenomic component is to collect DNA to allow the identification of genetic factors that may influence the PK, PD, efficacy, safety, and tolerability of nipocalimab and certolizumab and to identify genetic factors associated with RA or the response to nipocalimab and certolizumab treatment. Additionally, pharmacogenomic samples may be collected after exposure to nipocalimab and certolizumab. Epigenetic data from these samples may be compared with baseline samples to identify epigenetic changes that may associate with the disease or the treatment.

DNA and Biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies. Collection of biomarker samples, including samples from the optional pharmacogenomic collection, will only occur where local regulations permit and may not occur at all clinical sites.

4.2.1. Participant Input into Design

In setting the strategy for the development of a novel treatment of RA, patients were engaged early, systematically, and directly across important aspects of the drug development process. Specifically for this study, the Sponsor sought feedback from RA patients on the trial protocol to identify key drivers and barriers to enrollment with the aim to improve patient experience and optimizing protocol design.

Patient input was used to design the following elements of this study:

- The Schedule of Activities was modeled to ensure the number of visits, frequency of visits, and tests within each visit were manageable for a patient with moderately to severely active RA.
- Number of PRO and ClinRO assessments were reduced to shorten visits
- A visit window of ±3 days was added to increase flexibility to accommodate participant's schedule
- Sample taking was designed to be done in as few blood draws as possible to avoid unnecessary needle sticking

The results of the study may be made available to all participants through a plain language summary; a technical summary of results on clinicaltrials.gov and/or clinicaltrialsregister.eu and/or other national registries at the conclusion of the study according to local standards/restrictions.

4.2.2. 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/assent 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 nipocalimab is currently not approved in any indication. CCI [redacted] The hypothesis of superior efficacy of combination therapy of certolizumab and nipocalimab compared to monotherapy with either compound is based on the theoretical assessment of their orthogonal MoA. Both groups will receive certolizumab at the approved dose for treatment of RA including the control group. Additionally, the study population will consist exclusively of participants refractory to available treatments (including anti-TNFα agents).

The total blood volume to be collected will be below 710 mL over a 24-week period and 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 (475 mL q8w).

4.3. Justification for Dose

The objective of this Phase 2a study is to establish PoC for a combination therapy approach with an anti-FcRn and an anti-TNFα agent in participants with moderately to severely active RA despite ≥1 advanced therapy (bDMARDs or tsDMARDs) by demonstrating clinically relevant benefit of nipocalimab and certolizumab combination therapy compared to certolizumab monotherapy. Nipocalimab will be administered at the 30 mg/kg IV Q2W dose and certolizumab will be administered at the approved dosing regimen for RA, 400 mg SC injections at Week 0, 2, and 4, followed by 200 mg SC injections Q2W.

4.3.1. Nipocalimab

Nipocalimab as an anti-FcRn agent, was specifically engineered to bind to FcRn and block FcRn-mediated IgG recycling and redirect internalized IgG from early endosomes to lysosomes for catabolism. CCI [redacted]

CCI [redacted]

Population PK/PD modeling and simulation analysis using the SAD and MAD data from the FIH study in healthy participants (MOM-M281-001) was performed to guide the dose selection for participants with RA. Nipocalimab PK and the interaction with FcRn (ie, RO) was described by a one-compartment, target-mediated drug disposition model. Effects from nipocalimab on IgG reduction and albumin lowering, through the bound nipocalimab-FcRn complex, were described by 2 independent indirect response models, where nipocalimab effects were assumed to facilitate degradation of IgG and albumin lowering, respectively. The nipocalimab PK-RO-IgG/albumin models adequately described the relationships between nipocalimab dosing, PK, FcRn RO, and total serum IgG reduction/serum albumin lowering which also agreed with observed data from the Phase 2a nipocalimab monotherapy study. Pharmacokinetic/PD simulations for the RA population were performed using the aforementioned PK/RO/PD model and incorporating the typical RA

population body weight. CCI [redacted] Study results from CCI [redacted]

In terms of safety, the predicted exposure of nipocalimab CCI [redacted]

Using the PK-RO-IgG model, simulations were performed on 1000 virtual participants to evaluate the risk of a steady-state IgG nadir from crossing 1 g/L, a threshold set as the exit criterion due to the chance of increased infections below this threshold. CCI [redacted]

Based on the above, the safety profile of the CCI [redacted] dose regimen in RA is expected to be acceptable.

4.3.2. Certolizumab

Certolizumab pegol is an anti-TNFα agent which is a Fab fragment targeted against TNF which is conjugated to PEG. The planned certolizumab dose regimen is CCI [redacted]

For detailed information regarding the safety and efficacy profile, please refer to the Cimzia package insert/ SmPC.

4.3.3. Nipocalimab and Certolizumab Combination

In nonclinical toxicology studies, neither nipocalimab nor certolizumab presented any apparent overlapping toxicities that could be expected to be potentiated when administered in combination. In consideration of specific anti-TNFα agents which may be optimal to combine with nipocalimab, specific attention was paid to the potential DDI between the combination partners. Nipocalimab could reduce the PK exposure of IgG-based mAbs via inhibition of FcRn-mediated recycling. As certolizumab lacks an Fc region, no drug-drug interactions are foreseen with nipocalimab. Moreover, certolizumab has a well-established safety and efficacy profile in the treatment of

patients with active RA consistent with the class of anti-TNFα agents and was chosen as the combination agent with nipocalimab.

Given the acceptable nonclinical and clinical safety profiles for nipocalimab and certolizumab and the duration of the combination administration (approximately 22 weeks), any potential safety risk in the combination setting is considered to be manageable with careful monitoring and early intervention, including risk mitigation strategy, discontinuation of study intervention rules, and pre-defined stopping rules (Section 2.3 and Section 7).

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.

For participants who complete treatment and who are eligible for continued access program (post study access or other open-label extension study under a different/separate protocol), the end of study is defined as the end of treatment visit.

For participants who complete this study and who are eligible for a continued access program (see Section 6.6 or other long-term extension under a different/separate protocol) the safety follow-up period will be waived. In such case enrollment into the continued access program should occur on the same day as the last visit in this study, ie, end of study visit.

Participant Study Completion Definition

A participant will be considered to have completed the study if the participant has completed assessments at Week 24 of the double-blind phase and the final safety follow-up visit.

Participants who prematurely discontinue study intervention for any reason before completion of the double-blind phase, or miss the final safety follow-up visit, will not be considered to have completed the study.

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 repetition of any screening procedures is 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

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

Age

1. Criterion modified per Amendment 1
   1.1 18 to 75 years of age, inclusive

Type of Participant and Disease Characteristics

2. Medically stable on the basis of physical examination, medical history, vital signs, and 12-lead ECG performed at screening. Any abnormalities must be consistent with the underlying illness in the study population and this determination must be recorded in the participant's source documents and initialed by the investigator.
3. Medically stable on the basis of clinical laboratory tests performed at screening. If the results of the serum chemistry panel, hematology, or urinalysis are outside the normal reference ranges, the participant may be included only if the investigator judges the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under study. This determination must be recorded in the participant's source documents and initialed by the investigator. See exclusion criterion 13 for permitted laboratory reference ranges.
4. Diagnosis of RA and meeting the 2010 ACR/ EULAR Criteria for RA for at least 12 weeks before screening.
5. Has moderate to severe active RA as defined by persistent disease activity with at least 6 of 66 swollen joints and 6 of 68 tender joints at the time of screening and at baseline.
6. Is positive for ACPA or RF by the central laboratory at the time of screening.
7. Has CRP ≥0.3 mg/dL by the central laboratory at the time of screening.
8. Criterion modified per Amendment 1
   8.1 If has received prior anti-TNF agent (including biosimilars), has demonstrated IR to ≥1 anti-TNF agent (including biosimilars), as assessed by the treating physician (see Appendix 10 [Section 10.10]):
   a. After at least 12 weeks dosage of etanercept, adalimumab, golimumab (including biosimilars), and/or
   b. After at least 14 weeks dosage (ie, at least 4 doses) of infliximab (including biosimilars)

Documented IR may include inadequate improvement or loss in response after initial improvement in joint counts or other parameters of disease activity.

9. Criterion modified per Amendment 1
   9.1 If has received prior bDMARDs (or biosimilars) other than anti-TNF agent in RA, has demonstrated IR or intolerance to the therapy based on one of the following:
   a. IR to at least 1bDMARD (or the biosimilars) other than anti-TNF agents, as assessed by the treating physician (see Appendix 10 [Section 10.10]), after at least 12 weeks of therapy including but not limited to abatacept, anakinra, tocilizumab, and sarilumab or at least 16 weeks of therapy with rituximab.
   Documented IR may include inadequate improvement or loss in response after initial improvement in joint counts or other parameters of disease activity.
   b. Intolerance to bDMARD (or biosimilars) other than anti-TNF agent, as assessed by the treating physician. Documented intolerance includes side effects and injection/infusion reactions.
10. Criterion modified per Amendment 1
    10.1 If has received prior JAKi therapy for RA, has demonstrated IR or intolerance to the therapy based on 1 of the following:
    a. IR to at least 1 JAKi agent, as assessed by the treating physician (see Appendix 10 [Section 10.10]), after at least 12 weeks of therapy with a JAKi which includes but is not limited to tofacitinib, baricitinib, upadacitinib.
    Documented IR may include inadequate improvement or loss in response after initial improvement in joint counts or other parameters of disease activity.
    b. Intolerance to JAKi agent as assessed by the treating physician. Documented intolerance includes side effects.

Concomitant or Previous Medical Therapies Received

11. 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 csDMARDs:
    a. If using MTX: on stable dosage of no more than 25 mg/week IM, SC or PO
    b. If using SSZ: on 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 stable dosage of 10-20 mg/day.
12. 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.
13. 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.
14. 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.
15. 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

16. A female participant of childbearing potential must have a negative urine pregnancy test at screening and Week 0 prior to administration of study intervention.
17. Criterion modified per Amendment 2
    17.1 Is not currently breastfeeding, pregnant, intends to become pregnant during the study, or within 5 months after the last administration of study intervention.
18. Criterion modified per Amendment 2
    18.1 A female participant must be (as defined in Appendix 5, Contraceptive and Barrier Guidance)
    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 5 months 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 Appendix 5: Contraceptive and Barrier Guidance.

19. Criterion modified per Amendment 2
    19.1 A female participant must agree not to donate eggs (ova, oocytes) or freeze for future use for the purposes of assisted reproduction during the study and for a period of 5 months after the last administration of study intervention.
20. A male participant who has not had a vasectomy, must agree not to plan to father a child while enrolled in this study or within 90 days after the last dose of study intervention.
21. Criterion modified per Amendment 1
    21.1 A male participant must wear a condom when engaging in any activity that allows for passage of ejaculate to another person during the study and for a period of 90 days after the last administration of study intervention; male participants must also be advised of the benefit for a female partner of childbearing potential to use a highly effective method of contraception as condom may break or leak.
22. Criterion modified per Amendment 3
    22.1 A male participant must agree not to donate or freeze sperm for the purpose of reproduction during the study and for a minimum of 90 days after receiving the last dose of study intervention.

Informed Consent

23. Criterion modified per Amendment 1
    23.1 Must sign an ICF indicating that participant understands the purpose of, and procedures required for, the study and is willing to participate in the study.
24. Criterion modified per Amendment 1

24.1 Must sign a separate informed consent form if the participant agrees to provide optional DNA samples for research (where local regulations permit). Refusal to give consent for the optional DNA research samples does not exclude a participant from participation in the study. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

25. Must be willing and able to adhere to the lifestyle restrictions specified in this protocol.
26. Must be able to read and write. Visually impaired subjects may participate with the support of a legally acceptable representative.

Vaccination history

27. Criterion has been removed per Amendment 3

5.2. Exclusion Criteria

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

Medical Conditions

1. Has a diagnosed or reported history or current signs or symptoms indicating severe, progressive, or uncontrolled hepatic, renal, cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic (except RA), psychiatric, or metabolic disturbances, which are detected at screening assessments (ie, laboratory testing, physical examination, vital signs) or reported by the participant.
2. Has a confirmed or suspected clinical immunodeficiency syndrome not related to treatment of RA or has a family history of congenital or hereditary immunodeficiency unless confirmed absent.
3. Has other inflammatory diseases that might confound the evaluation of benefit in this study, including but not limited to Crohn's disease, ulcerative colitis, interstitial lung disease, ankylosing spondylitis, psoriatic arthritis, primary Sjogren's syndrome, SLE, and Lyme disease.
4. Has a history of any clinically significant adverse reaction to therapeutic proteins (eg, mABs), including, but not limited to, allergic reactions or severe immediate hypersensitivity reactions, such as anaphylaxis.
5. Allergies, hypersensitivity, or intolerance to nipocalimab or certolizumab or their excipients (refer to the nipocalimab IB or the Cimzia SmPC).
6. Is (anatomically or functionally) asplenic
7. Has experienced MI, unstable ischemic heart disease, or stroke ≤12 weeks of screening.
8. Has a diagnosis of congestive heart failure including medically controlled, asymptomatic congestive heart failure.
9. Has a history of known demyelinating disease such as multiple sclerosis or optic neuritis.
10. Had an organ transplant (with exception of corneal transplant >12 weeks prior to screening)
11. Had major surgery, (eg, requiring general anesthesia) within 8 weeks before screening, or has undergone surgical treatment for RA, including synovectomy and

arthroplasty ≤12 weeks prior to first dose of study intervention, or will not have fully recovered from surgery, or has surgery planned during the time the participant is expected to participate in the study or ≤14 weeks after the last dose of study intervention administration .
Note: Participants with planned surgical procedures to be conducted under local anesthesia may participate.

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

Laboratory Tests

13. Has any of the following screening laboratory test result:
    a. Hemoglobin <8.0 g/dL (International system of Units [SI]: <80 g/L)
    b. 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 using the CKD-EPI formula (Levey 2009)
    f. Liver function test (aspartate aminotransferase [AST] OR alanine aminotransferase [ALT]) results that are ≥2 × the upper limit of normal (ULN)
    g. Serum total IgG <6 g/L (<600 mg/dL)

Malignancy or Increased Potential for Malignancy

14. Criterion modified per Amendment 1
    14.1 Currently has or history of malignancy within 5 years before screening
15. Has a history of lymphoproliferative disease, including lymphoma, or signs suggestive of possible lymphoproliferative disease such as lymphadenopathy of unusual size or location, or splenomegaly

Infections or Predisposition to Infections

16. History of HIV positive tests, or tests positive for HIV at screening.
17. Tests positive for HBV infection (refer to Protocol Appendix 9).
18. Is seropositive for antibodies to HCV, unless they satisfy 1 of the following conditions:
    a. Has a history of successful treatment, defined as being negative for HCV 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.
19. Has a chronic or recurring infection (eg, bronchiectasis, chronic osteomyelitis, chronic pyelonephritis) or requires chronic treatment with anti-infectives (e.g., antibiotics, antivirals).
20. Has a severe infection including opportunistic infections (e.g., 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 weeks exclusionary period has passed.

21. 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.
22. Has a history of latent or active granulomatous infection, including but not limited to tuberculosis (see exclusion #24 on the detailed TB screening criteria below), cryptococcosis, histoplasmosis or coccidioidomycosis, prior to screening.
23. Has a herpes zoster infection within 8 weeks before the first dose of study intervention.
24. Criterion modified per Amendment 1
24.1 Criterion modified per Amendment 2
24.2 Meet ANY of the following TB screening criteria (See Section 8.2.13):

Note: IGRA testing includes QuantiFERON-TB®.

a. Have a history of active TB or show signs or symptoms suggestive of active TB upon medical history and/or physical examination at screening.

b. Have a history of untreated latent TB prior to screening.

Note: For participants with a history of treated latent TB there must be documentation of appropriate completed treatment prior to the first administration of study intervention. It is the responsibility of the investigator to verify the adequacy of previous TB treatment and provide appropriate documentation.

c. Have had recent close contact with a person with active TB.

d. Have a positive IGRA test result within 60 days prior to the first administration of study intervention. An exception is made for participants who:

i. have a history of adequately treated latent TB described above.

ii. have a false-positive IGRA test as determined by the following:

Participants with indeterminate/borderline results should have the test repeated. Participants with persistent indeterminate/borderline results or positive results on repeat test will be excluded. If repeat testing is NOT positive, the participant must be referred to a physician specializing in TB to determine if the initial test can be considered a false-positive. This evaluation must be adequately documented prior to the first administration of study intervention. If repeat testing is positive, however, it will be considered a true-positive.

e. Have a chest radiograph (posterior-anterior and lateral views, or per country regulations where applicable), taken within 90 days before the first administration of study drug and read by a qualified radiologist, with evidence of current, active TB or old, inactive TB

25. Criterion modified per Amendment 3

25.1 Have tested positive for or been exposed to COVID-19 within 4 weeks prior to the first dose of study intervention.

Exceptions: Participants who have tested positive for or been exposed to COVID-19 may participate if they have both an absence of symptoms and a negative validated COVID-19 test obtained at least 2 weeks after symptom onset (or the first positive test for asymptomatic infection) or exposure.
Follow local regulations/guidelines for validated COVID-19 testing procedures and standard definition of COVID-19 exposure.

Prior/Concomitant Therapy

26. Is naïve to bDMARDs and tsDMARDs.
27. Has taken any disallowed therapies (within the period of time detailed in Section 6.8.5) prior to the planned first administration of study intervention.
28. Currently taking IgG Fc- related therapies.
29. Has received certolizumab or nipocalimab previously.
30. Has received plasmapheresis, immunoadsorption therapy, or IVIg within 6 weeks prior to screening.
31. Has received BCG vaccine within 1 year or any other live vaccine within 4 weeks before first dose of study intervention. Non-live vaccines approved or authorized for emergency use (eg, COVID-19) by local health authorities are allowed. Has a known need to receive a live vaccine during the study or within 8 weeks of the last study intervention administration.
32. Has received anti-TNF agent (or its biosimilars) within 30 days or 5 half-lives (whichever is longer), prior to the first administration of study intervention.
33. Has received biologic therapy or targeted synthetic DMARDs including but not limited to the below within 30 days or 5 half-lives, whichever is longer, prior to the first administration of study intervention:
    a. anti-interleukin (IL)-6 receptor mAb (e.g., tocilizumab or sarilumab)
    b. anti-IL-1 blockers (e.g., anakinra)
    c. Co-stimulatory inhibitors (e.g., abatacept)
    d. Janus kinase inhibitors (JAKi, e.g., tofacitinib, baricitinib, upadacitinib).
34. Has received rituximab within 26 weeks prior to first administration of study intervention.
35. Currently using MTX and leflunomide combination therapy.
36. Has used oral cyclophosphamide within 12 weeks or IV cyclophosphamide within 24 weeks prior to first administration of study intervention.
37. Has received cyclosporine A, azathioprine, tacrolimus, mycophenolate mofetil, oral or parenteral gold, or D-pencillamine within 4 weeks prior to first administration of study intervention.
38. Has received intraarticular, intramuscular, intra-bursal, intra-lesional, intra-vertebral, epidural, or IV glucocorticoids, including intramuscular adrenocorticotropic hormone within 4 weeks prior to first study intervention.
39. 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

40. Received an investigational intervention or used an invasive investigational medical device ≤12 weeks or 5 half-lives (whichever is longer) before the planned first dose of study intervention or received an investigational biological product within 12 weeks or 5 half-lives, whichever is longer, before the planned study intervention, or is currently enrolled in an investigational study.

Other Exclusions

41. 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.
42. 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.
43. History of drug or alcohol abuse according to Diagnostic and Statistical Manual of Mental Disorders (5th edition; DSM-V) criteria within 1 year before screening or positive test result(s) for alcohol or drugs of abuse (including barbiturates, opiates, cocaine, cannabinoids, amphetamines, and benzodiazepines) at screening.
44. Currently participating or intends to participate in any other study using an investigational agent or procedure during the conduct of this study.
45. Lives in an institution on court or authority order.

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. Section 5.4, describes options for retesting. The required source documentation to support meeting the enrollment criteria is noted in Appendix 3: Regulatory, Ethical, and Study Oversight Considerations.

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 Concomitant Therapy (Section 6.8) 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 requirements

3. Must agree to not receive a BCG vaccination, live attenuated viral or bacterial vaccination during the study and for 12 weeks after receiving the last dose of study intervention
4. Must be willing and able to complete study-related questionnaires and document clinical symptoms, AEs, and concomitant medications
5. 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. This study will use IWRS. The investigator will not generate screening and enrollment logs directly from IWRS.

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.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants must be assigned new participant numbers.

Retesting Criteria

Exceptional and limited retesting of abnormal screening values that lead to exclusion are allowed only once using an unscheduled visit during the screening period (to reassess eligibility).

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 values 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 analyzed by the central laboratory may be repeated more than once in the event of a 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 a new participant number, 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 10.7.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Intervention(s) Administered

6.1.1. Authorization Status in the EU (EU-CTR)

Designation	Product
IMP	Unauthorized: nipocalimab, placebo Authorized: certolizumab
AxMP	Authorized: csDMARDs (MTX, SSZ, HCQ, CQ, leflunomide); folinic/folic acid; NSAIDs, paracetamol/acetaminophen and other analgesics; oral corticosteroids

6.1.2. Administration

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

Study intervention administration must be captured in the source documents and the eCRF.

For details on rescue medications, refer to Section 6.8.6. For a definition of study intervention overdose, refer to Section 6.7.

Description of Interventions

Arm Name	Control arm	Experimental arm
Intervention Name	Certolizumab+placebo	Certolizumab+nipocalimab
Type	Biologic	Biologic
Dose Formulation	Certolizumab: prefilled syringe	Certolizumab: prefilled syringe; nipocalimab: vial for IV preparation
Unit Dose Strength(s)	Certolizumab 200 mg/mL	Certolizumab 200 mg/mL Nipocalimab 30 mg/mL
Dosage Level(s)	Certolizumab: 2 injections of 200 mg at Week 0, 2, 4 then 200 mg Q2W Placebo IV Q2W	Certolizumab: 2 injections of 200 mg at Week 0, 2, 4 then 200 mg Q2W Nipocalimab 30 mg/kg IV Q2W
Route of Administration	Certolizumab SC; placebo IV	Certolizumab SC; nipocalimab IV
Use	Control	Experimental
Investigational Medicinal Product (IMP)	yes	yes
Current/Former Name(s) or Alias(es)[a]	Certolizumab/Cimzia	Certolizumab, Cimzia; nipocalimab, JnJ-80202135, MOM281

[a] Labels will contain information to meet the applicable regulatory requirements.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

Nipocalimab IV solution will be prepared by the unblinded pharmacist or designee according to the instructions provided to the clinical sites in the IPPI. Saline will be used as placebo.

Refer to the IPPI and study site investigational product and procedures manual for 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. 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.

Study intervention must be handled in strict accordance with the protocol and 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, and study intervention returned by the participant, must be available for verification by the sponsor’s study site monitor during on-site monitoring visits. The return to the sponsor of unused study intervention, or used returned study intervention for destruction, will be documented on the intervention return form. 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.

Potentially hazardous materials such as used ampules, needles, syringes, and vials, should be disposed of immediately in a safe manner and therefore will not be retained for intervention accountability purposes.

Study intervention should 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 supplied 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 interventions 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 conducting this study. Participants will be assigned to 1 of 2 treatment arms based on an algorithm implemented in the IWRS before the study.

Dynamic central randomization minimizes the imbalance in the distribution of the number of participants across treatment arms within the levels of each individual stratification factor:

1) csDMARDs usage at baseline (yes or no)
2) Screening ACPA level (high ≥400 U/mL; low <400 U/mL)
3) Baseline DAS28-CRP (high ≥5.8; low <5.8, CRP at screening)
4) Study country/territory
5) Investigator site

Based on the algorithm, the IWRS will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant.

Blinding

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.

Data that may potentially unblind the intervention assignment (ie, study intervention serum concentrations, anti-study intervention antibodies, study intervention preparation/accountability data, intervention allocation, biomarker or other specific laboratory data) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

At the Week 12 DBL, 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 subject-level data will be documented prior to unblinding. Investigative study sites and participants will remain blinded to initial treatment assignment until after the final database is locked.

Under normal circumstances, the blind should 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 IVRS/IWRS. 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, time, and reason for the unblinding must be documented by the IVRS/IWRS, in the appropriate section of the eCRF, and in the source document. The documentation received from the IVRS/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.

In rare circumstances when a potential safety issue that may impact the overall benefit-risk assessment of the investigational product has been identified in this study, selected Sponsor personnel may be unblinded to safety-related data in order to investigate the safety issue and determine if additional actions are required. The safety data should be kept blinded to any personnel not essential to the safety review.

If other rare, unforeseen circumstances arise that may necessitate unblinding of selected sponsor personnel, these will be assessed and documented on a case-by-case basis. The data should be kept blinded to any personnel not essential to the review or investigation.

In general, randomization codes will be disclosed fully only if the study is completed and the clinical database is closed.

6.4. Study Intervention Compliance

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

Study intervention will be administered as a SC injection for certolizumab and as an IV infusion for nipocalimab by qualified study site personnel. The details of each administration will be recorded in the eCRF (including date, start and stop times of the IV infusion, and volume infused).

6.5. Dose Modification

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

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

Investigators may recontact the participant to obtain long-term follow-up information regarding the participant's safety or survival status including endpoint status as noted in the ICF (refer to Appendix 3: Regulatory, Ethical, and Study Oversight Considerations).

No continued access will be proposed for this study. At the end of their participation in the study, the participants will be instructed that they should return to their primary physician to determine standard of care, if applicable.

6.7. Treatment of Overdose

For this study, any dose of nipocalimab greater than 10% above the highest dose of a single dosing visit specified in this protocol will be considered an overdose. The sponsor does not recommend specific treatment for an overdose. For overdose considerations regarding Cimzia, please refer to the SmPC/ US package insert.

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

- Contact the Medical Monitor immediately.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study intervention must be interrupted or whether study intervention must be discontinued.

- Closely monitor the participant for adverse event/serious adverse event and laboratory abnormalities
- Obtain a plasma sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis including at what timepoints).
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF.

6.8. Concomitant Therapy

Prestudy therapies administered up to 60 days before first dose of study intervention must be recorded at screening.

Concomitant therapies must be recorded throughout the study beginning with start of the first dose of study intervention to 8 weeks after the last dose of study intervention.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; Covid-19 vaccination and anti-Covid-19 mAb for emergency use; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, or other specific categories of interest) different from the study intervention must be recorded in the CRF. Recorded information will include a description of the type of therapy, treatment duration, dose regimen, route of administration, and indication. Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a participant into the study.

Every effort should be made to keep participants' concomitant medications stable through Week 24. The concomitant medication dose may be reduced, or the medication temporarily discontinued because of abnormal laboratory values, side effects, concurrent illness, or the performance of surgical procedure(s), but the change and reason for the medication change should be clearly documented in the subject's medical record.

Table 3: Permitted Concomitant Medications for 80202135ARA2002, the Minimum Stabilization Period before Randomization, and the Maximum Allowed Doses at Study Randomization

outlines permitted concomitant medication use and dose stabilization requirements.

Table 3: Permitted Concomitant Medications for 80202135ARA2002, 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 • SSZ: 1000-2000 mg/day • HCQ or CQ: 200-400 mg/day • 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. Acetaminophen/Paracetamol

The use of stable dose acetaminophen during the study is permitted if it does not exceed recommended dose of 3 g/day. Acetaminophen is not permitted as a part of combination products such as over-the-counter "cold remedies" or in combination with opioids if the total acetaminophen/ paracetamol dose exceeds 3 g/day. Acetaminophen/Paracetamol should not be initiated within 24 hours before a study visit involving joint counts and pain assessments.

6.8.2. Nonsteroidal Anti-inflammatory Drugs and Other Analgesics

Participants treated with NSAIDs, including acetylsalicylic acid (aspirin) and selective cyclooxygenase-2 inhibitors, and other analgesics should receive the usual marketed doses approved in the country in which the study is being conducted. In this study, aspirin is considered an NSAID, except for low-dose aspirin prescribed for CV 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 agent and through Week 24. The dose and the type of NSAIDs or other analgesics may be changed at the discretion of the investigator if the subject develops unacceptable side effects or a contraindication to their use. NSAIDs and other analgesics should not be initiated within 24 hours before a study visit involving joint counts and pain assessments.

6.8.3. Disease Modifying Antirheumatic Drugs/Systemic Immunosuppressives

If using a non-biologic csDMARD such as MTX, SSZ, HCQ, CQ, or leflunomide, the participant must be on a stable dose for at least 8 weeks prior to the first administration of study intervention and should have no serious toxic side effects attributable to the DMARD. If using MTX, the recommended doses are within the range of 7.5 up to 25 mg IM, PO, or SC weekly, and treatment should have started at least 12 weeks prior to the first administration of study intervention. If using

SSZ, hydroxychloroquine, or CQ should have started treatment at least 12 weeks prior to the first administration of study agent. If currently not using MTX, SSZ, HCQ, CQ, or leflunomide, the participant must not have received these DMARDs for at least 4 weeks prior to the first administration of the study agent.

All participants receiving MTX will also receive at least 5 mg of oral folic acid or 5 mg folinic acid weekly. Participants must have been on a stable dose of folic acid (>5 mg) for at least 4 weeks prior to the first administration of the study intervention. Folic acid or folinic acid should not be given on the day of MTX dosing. In the event of clinically significant decreases in neutrophils or platelet counts, MTX should be temporarily or permanently discontinued.

6.8.4. Corticosteroid Therapy

Oral Corticosteroids

Participants treated with oral corticosteroids should receive a stable dose equivalent to ≤ 10 mg prednisone per day for at least 2 weeks prior to their first administration of the study agent and continue to receive this dose through Week 24. Initiation of oral corticosteroids is prohibited during the study for any indication (except as rescue therapy after Week 14, see Section 6.8.6). However, the dose and the type of oral corticosteroid may be changed at the discretion of the investigator to manage comorbidities or unacceptable side effects. Any changes should be discussed with the Medical Monitor.

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.

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

6.8.5. Prohibited Medications

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 (other than MTX, SSZ, HCQ, CQ, and leflunomide) such as azathioprine, oral cyclosporine A, tacrolimus, mycophenolate mofetil, oral or parenteral gold
- Cytotoxic drugs such as cyclophosphamide, chlorambucil, nitrogen mustard, or other alkylating agents

- Anti-TNFα therapy such as: infliximab, golimumab, etanercept, adalimumab, and biosimilars to those anti-TNFs
- Anti-IL-6 receptor mAb (eg, tocilizumab or sarilumab)
- Anti-IL-1 receptor mAb (eg, anakinara)
- B-cell depleting biologic therapy (eg, rituximab)
- Co-stimulatory inhibitors (eg, abatacept)
- JAKi (eg, tofacitinib, baricitinib, upadacitinib)
- Any other targeted biologic therapy
- Any investigational intervention or use of an invasive investigational medical device
- Use of complementary therapies or traditional medicine (eg, Chinese, acupuncture, ayurvedic) through Week 24
- Live virus or live bacterial vaccination during the study

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

6.8.6. Rescue Medication

The following rescue medications may be used:

- csDMARDs such as MTX, SSZ, HCQ, CQ, and LEF
- oral corticosteroids

At Week 14, participants who have not achieved low disease activity (defined as CDAI ≤10) will receive the current SoC treatment starting from Week 14 (investigator's choice of SoC treatment appropriate for the participant).

If participants initiate or increase their dose of csDMARDs, oral corticosteroids and/or NSAIDs, there will be no need to discontinue study intervention, and data collection will continue through Week 30.

The study intervention must be discontinued if rescue medications are the prohibited medications listed in Section 6.8.5 Prohibited Medications.

It is recommended that participants who permanently discontinue study intervention, but do not withdraw from study participation, be followed at all subsequent study visits through Week 30. At a minimum, participants who permanently discontinue study intervention, but do not withdraw from study participation, should return for a safety follow-up visit 8 weeks after the last dose of study intervention.

The date of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

6.8.7. Vaccinations (Including COVID-19)

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 labelling, guidelines, and standards-of-care for patients receiving immune-targeted therapy when determining an appropriate interval between vaccination and study enrolment.

In order to help differentiate between vaccine- and study intervention-related reactions, it is recommended that vaccine and study intervention be administered on different days, separated by as large an interval as is practical within the protocol.

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. Refer to Section 10.5
- 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 clinically significant opportunistic infection (eg, active TB, invasive fungal infection)
- The participant develops a malignancy during the study
- The participant develops congestive heart failure
- The participant is diagnosed with demyelinating disorder
- The participant develops symptoms suggestive of a lupus-like syndrome and is positive for antibodies against double-stranded DNA
- 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 participant has serum total IgG<1 g/L (<100 mg/dL)
- The participant initiates a prohibited therapy as described in Section 6.8.5.

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

- Two sequential absolute neutrophil counts $<0.75\times10^3/\mu L$ (SI: $<0.75\times109/L$)
- Two sequential absolute lymphocyte counts $<0.5\times10^3/\mu L$ (SI: $<0.5\times109/L$)
- Two sequential hemoglobin values <7.5 g/dL (SI: <75.0 g/L) or a decrease of >30% from baseline
- Two sequential platelet counts $<75\times10^3/\mu L$ (SI: $<75\times10^9/L$)

Note: These laboratory abnormalities should be discussed with the Medical Monitor or designee, and study intervention should be withheld until the clinical assessment is complete.

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, then the end-of-intervention assessments must be obtained and scheduled assessments off study intervention should be continued. Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant. Additional participants will not be entered to ensure the protocol-specified number of participants complete the study.

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 Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments , 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 DMC and sponsor believe that participants would incur undue risk by continuing the study
- Serious Infection: There is a serious infection event that the DMC and sponsor believe would incur undue risk to participants in the study. A potential serious infection safety concern will be identified via statistical sequential monitoring framework and evaluated for each event. Additional details are provided in the DMC charter and DMC SAP.

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 CRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent then 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 (eg, consult with family members, contacting the participant's other physicians, medical records, database searches, use of locator agencies at study completion,) as local regulations permit.

Prior to a participant withdrawing consent for follow-up, the investigator should offer the participant an opportunity for one of the alternative reduced follow-up mechanisms described below. 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 samples 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 Long-Term Retention of Samples for Additional Future Research in Appendix 3: Regulatory, Ethical, and

Study Oversight Considerations). 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 summarizes the frequency and timing of efficacy, PK, immunogenicity, PD, biomarker, pharmacogenomic, and safety measurements applicable to this study.

All PRO assessments must be conducted/completed before any tests, procedures, or other consultations to prevent influencing participant responses. Refer to the PRO completion guidelines for instructions on the administration of PROs.

If multiple assessments are scheduled for the same timepoint, it is recommended that procedures be performed in the following sequence: PtGA of disease activity, Pain VAS, Joint Pain Severity NRS, and HAQ-DI. Urine and blood collections for PK and PD assessments should be kept as close to the specified time as possible. Other measurements may be done earlier than specified timepoints if needed. Actual dates and times of assessments will be recorded in the source documentation and/or the CRF.

Screening Phase

The screening phase is up to 6 weeks before administration of study intervention. After written ICF 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 and can therefore be enrolled in the study. Every effort should be made to adhere to the SoA for each participant. The collection of AEs will start at the time the ICF is obtained.

Blood Sample Collection

The total blood volume to be collected from each participant will be approximately 710 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 CRF or laboratory requisition form.

Refer to the SoA for the timing and frequency of all sample collections (Section 1.3).

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)

- SmPC/Package Insert for certolizumab
- Sample ICFs
- Laboratory manual and laboratory kits
- IVRS/IWRS Manual
- eCRF completion instructions
- Electronic ClinRO and PRO equipment (tablet device questionnaires, completion instructions)
- Patient recruitment materials

8.1. Efficacy Assessments

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 each other.

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. 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).

8.1.1.4. 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).

8.1.1.5. 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 "nonevaluable" 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).

8.1.2. 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 DAS28-ESR is a statistically derived index combining tender joints (28 joints), swollen joints (28 joints), 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 4 (van Riel 2000).

Table 4: 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 ≤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 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 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 Data Monitoring Committee are provided in Appendix 3

Adverse events will be reported and followed by the investigator as specified in Section 8.3, and Appendix 4.

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

Adverse events must include the reporting of any observed effects on organ maturation and growth and development, including fertility.

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.

8.2.1. Physical Examinations

Physical examinations will be performed as indicated in the SoA. Clinically significant findings should be reported as AEs.

Full physical examinations will include a review of the following body systems:

- General appearance
- Thorough skin and oral mucosa evaluation
- Eyes, ears, nose, and throat
- Cardiovascular
- Respiratory
- Abdomen
- Peripheral pulsation
- Lymph nodes
- Neurologic
- Musculoskeletal
- Head, neck, and thyroid

8.2.2. Vital Signs

Temperature, pulse/heart rate, respiratory rate, blood pressure will be assessed.

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.

Blood pressure 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).

8.2.3. Electrocardiograms

A 12-lead ECG will be performed locally at screening. Additional ECGs can be performed locally based on the 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 and hematology and a random urine sample for urinalysis will be collected as noted in Appendix 2: Clinical Laboratory Tests. 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 CRF. The laboratory reports must be filed with the source documents.

8.2.5. Pregnancy Testing

Additional serum or urine pregnancy tests (highly sensitive) 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.

8.2.6. Concomitant Medication Review

Concomitant medication 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 during and for 1-hour post-infusion after the first 3 infusions, if no clinically relevant AEs related to the infusion are observed, participants will be observed for 30 minutes after subsequent infusions.

8.2.8. Infusion Reactions

An infusion reaction is defined as any AE that occurs during the infusion or post-infusion and that is reported by the investigator to represent an infusion reaction.

Minor infusion-related AEs may be managed by slowing the rate of the IV infusion and treating with antihistamines and acetaminophen 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. Injection Site Reactions

An injection site reaction is any adverse reaction at a SC study intervention injection site. Injection sites will be evaluated for reactions and any injection site reaction will be recorded as an AE.

8.2.10. Hypersensitivity Reactions

Before any administration of study intervention, 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 reactions (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 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.

8.2.11. 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, chronic, or recurring infection. Study intervention must be discontinued if a participant develops any serious infection (ie, that meets criteria for a SAE or AESI), or develop a moderate or severe opportunistic infection or an infection that is unresponsive or worsening while on anti-infective therapy (Section 7.1).

8.2.12. 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 investigator initiate appropriate therapy or modify current therapy for dyslipidemia per local health guidelines.

8.2.13. Tuberculosis Evaluation

Initial Tuberculosis Evaluation

Participant medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. The participant should be asked about past testing for TB, including chest imaging results and responses to tuberculin skin or other TB testing. Investigators have the option to use the tuberculin skin test in addition to IGRA testing to screen for latent TB if preferred by local health authorities, or if they believe based on their judgment that both tests are clinically indicated to evaluate a participant at high risk for latent TB.

Participants with a negative IGRA test result are eligible to continue with prerandomization procedures. Participants with a newly identified positive IGRA test result must undergo an evaluation for active or latent TB, or suspected false-positive initial testing.

Participants with indeterminate/borderline IGRA test results should have the test repeated. Participants with persistently indeterminate/borderline IGRA test results should be screening failure or discontinued from the study treatment during the study.

Appropriate treatment for active or latent TB is defined according to local country guidelines for immunocompromised patients. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

Ongoing Tuberculosis Evaluation

To aid in the early detection of TB infection or exposure during study participation, participants must be evaluated for TB signs, symptoms, and close contacts at scheduled visits (refer to Section 1.3). The following series of questions is suggested for use during the evaluation:

- “Have you had a new cough of > 14 days’ duration or a change in a chronic cough?”

- "Have you had any of the following symptoms:
  - Persistent fever?
  - Unintentional weight loss?
  - Night sweats?"
- "Have you had close contact with an individual with active TB?" (If there is uncertainty as to whether a contact should be considered "close," a physician specializing in TB should be consulted.)

If the evaluation raises suspicion for TB infection or the participant has had a close contact exposure to TB, study intervention must be withheld and an immediate and thorough investigation must be undertaken, including consultation with a physician specializing in TB to determine if treatment is warranted.

Note: Investigators should be aware that TB reactivation in immunocompromised participants may also present as extrapulmonary or disseminated disease.

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

Timely, accurate, and complete reporting and analysis of safety information, including AEs, serious AEs, and 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 Appendix 4, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

See Appendix 4, Adverse Events, Adverse Device Effects, Serious Adverse Events, Serious Adverse Device Effects, Unanticipated Serious Adverse Device Effects, and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies, for details regarding AEs, product malfunctions, and deficiencies of a medical device under evaluation in the study.

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 non-serious, 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 8 weeks 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 24 hours of their knowledge of the event.

Serious adverse events, including those spontaneously reported to the investigator within 8 weeks 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 8 weeks after study treatment discontinuation must be recorded 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 x ULN, ALP <2 x ULN together with Tbili ≥2 x ULN or INR >1.5 (if measured). Any possible Hy's Law case is considered an important medical event and must be reported to the sponsor in an expedited manner, 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 CRF, which must be completed and reviewed by a physician from the study site and transmitted to the sponsor immediately but no later than within 24 hours of their knowledge of the event. 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 EAC. For such events investigators will be asked to provide a 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 adverse events or serious adverse events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

Solicited Adverse Events

Solicited AEs are predefined local and systemic events for which the participant is specifically questioned and which are noted by participants in their diary (see Section 8, Study Assessments and Procedures).

Unsolicited Adverse Events

Unsolicited AEs are all AEs for which the participant is not specifically questioned in the participant diary.

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

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

The sponsor assumes responsibility for appropriate reporting of safety information to Regulatory Authorities/ IECs / IRBs in each respective country/territory, as applicable.

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 anticipated events: worsening of RA.

These anticipated events will be periodically analyzed in aggregate by the sponsor during study conduct. The sponsor will prepare a safety report in narrative format if the aggregate analysis indicates that the anticipated event occurs more frequently in the treatment arm than in the control arm 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 events 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 events according to the requirements of the countries/territories 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 the Serious Adverse Event 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 male participant and his partner, and any postnatal sequelae in the infant will be required.

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. Clinically significant opportunistic infection (eg, active TB, invasive fungal infections)
3. Hypoalbuminemia with albumin <20g/L (<2.0 g/dL)
4. Any newly identified malignancies
5. These AEs occurring after the first administration of study intervention in participants in the clinical study must be reported by the investigator to the sponsor or designee within 24 hours after being made aware of the vent, according to the procedures in Appendix 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 post infusion 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 nipocalimab and certolizumab samples will be used to evaluate the PK of nipocalimab and certolizumab, 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 concentrations of nipocalimab and certolizumab 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 divided into 3 aliquots (1 aliquot for serum nipocalimab and certolizumab concentration, antibodies to nipocalimab, and a backup).

Samples must be collected before study intervention administration at visits when a study intervention administration is scheduled.

For nipocalimab administrations, at Week 0, Week 2, Week 8 and Week 12, a blood sample before study intervention and another blood sample 45 minutes (±15 minutes) after the end of infusion will be collected. The sample should be drawn from the opposite arm than the IV line.

One random nipocalimab concentration sample will be collected from all participants any time between days 3 to 7 after the Week 0 or Week 2 visit other than the scheduled samples.

One random certolizumab concentration sample will be collected from all participants any time between Week 2 and Week 8 other than at the time of the Week 2, Week 4, Week 6 and Week 8 visits; this sample must be collected at least 24 hours prior to or after a study intervention administration and must not be collected at a regularly scheduled visit.

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 from participants who received at least one dose of certolizumab will be analyzed to determine concentrations of certolizumab. Serum samples from participants who received at least one dose of nipocalimab and certolizumab will be analyzed to determine concentration of certolizumab and nipocalimab. Analysis will be performed using a validated, specific, and sensitive Immunoassay method by 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 and certolizumab will be derived using population PK modeling. Baseline covariates (eg, body weight, age, sex, CrCL, race) may be included in the model, if relevant.

8.5. Genetics and Pharmacogenomics

Pharmacogenomic blood samples may be collected from participants who consent separately to this component of the study to allow for pharmacogenomic research, as necessary (where local regulations permit). Participant participation in pharmacogenomic research is optional.

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.

Pharmacogenomic blood samples will be collected to allow for identification of genetic and epigenetic factors that may be associated with the disease or the response to 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. Whole blood samples of approximately 6 mL will be collected for the genetic and pharmacogenomic analyses.

8.6. Biomarkers

Biomarker assessments will be made to examine the biologic response to treatment and to identify biomarkers that are relevant to certolizumab or certolizumab/nipocalimab combination therapy and RA, where local regulations permit. Assessments (detailed below) will include the evaluation of relevant biomarkers in serum, plasma, whole, 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 certolizumab monotherapy and nipocalimab/certolizumab combination therapy
2. To understand RA pathogenesis
3. To understand why individual participants may respond differently to certolizumab monotherapy and nipocalimab/certolizumab combination therapy
4. To understand the impact of certolizumab monotherapy and nipocalimab/certolizumab combination therapy on RA or systemic inflammation
5. To develop diagnostic tests to identify RA populations that may be responsive or nonresponsive to treatment with certolizumab monotherapy and nipocalimab/certolizumab combination therapy

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

Venous blood samples will be collected at time points shown in the SoA.

Serum concentrations of total IgG, IgM, IgE, and IgA will be measured to assess the PD effect. IgG subclasses (IgG1, IgG2, IgG3, IgG4), albumin, CICs, and inflammatory markers (eg, CRP) may also be evaluated using separate assays to assess the PD effect of nipocalimab and certolizumab. The relationship between PD effects and clinical responses may be assessed.

8.6.2. Serum and Plasma Biomarkers

Blood samples for serum and plasma biomarker analyses will be collected from all participants, where local regulations permit. Serum and plasma may be analyzed for levels of circulating proteins, autoantibodies (eg, ACPA, RF), other inflammation-related molecules, and disease-associated serologies relevant to RA and treatment and response to nipocalimab and certolizumab.

8.6.3. Whole Blood Gene Expression Profile

Whole blood will be collected by venipuncture from participants for RNA expression analysis, where local regulations permit. Total RNA will be isolated and used for differential gene expression analyses to identify gene expression patterns that are relevant to nipocalimab and certolizumab treatment or RA and to evaluate markers that can predict clinical response. Transcriptomic studies may be conducted using microarray or alternative equivalent technologies, which facilitate the simultaneous measurement of the relative abundance of multiple RNA species for each blood sample. The samples may also be used for targeted assessment of genes relevant to RA and nipocalimab/certolizumab treatment. These analyses may be used to evaluate the changes in gene expression profiles that may correlate with biologic response relating to RA and the action of nipocalimab and certolizumab and may be used to identify population subtypes that respond differently to an intervention.

8.6.4. Peripheral Blood Mononuclear Cells

If operationally feasible, whole blood may also be collected and processed for PBMC isolation and cryopreserved for later analysis. Analysis may include but is not limited to flow cytometric assessment of cell populations, single cell transcriptomics, or functional assessment of cells. The samples may also be used to evaluate cellular and molecular changes in response to nipocalimab/ certolizumab treatment or related to RA pathogenesis. These analyses may not be performed if cryopreserved PBMC samples do not meet the quality or quantity standards.

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.

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 nipocalimab serum concentration 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).

8.8. Health Economics

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.

9.1. Statistical Hypotheses

The primary hypothesis is that treatment with nipocalimab in combination with certolizumab is superior to certolizumab monotherapy in participants with moderately to severely active RA despite treatment with ≥1 advanced therapy (bDMARDs or tsDMARDs) as assessed by the mean change from baseline in DAS28-CRP at Week 12.

9.2. Sample Size Determination

Approximately 85 participants are planned to be randomized in a 2:3 ratio to the control arm and experimental arm into the study. The sample size selection was determined based on the primary endpoint of the change from baseline in DAS28-CRP at Week 12. For this study, assuming a difference of 0.67 in the change from baseline in DAS28-CRP and a pooled standard deviation of 1.2 between control arm and experimental arm, a sample size of

- control arm: 34 participants receiving monotherapy certolizumab + placebo
- experimental arm: 51 participants receiving combination therapy of nipocalimab + certolizumab

will provide a power of approximately 80% to detect a significant treatment difference at a 1-sided significance level of α=0.05 using a T-test. The difference of 0.67 is a meaningful improvement over an effective treatment in RA.

Table 5 below shows the power to detect difference in the change from baseline in DAS28-CRP between the control arm and experimental arm.

Table 5: Statistical Power for Treatment Difference in Change from Baseline in DAS28-CRP at Week 12

Sample Size	Delta	SD	Power (%)
34:51	0.6	1.1	79
	0.6	1.2	72
	0.6	1.3	66
	0.67	1.1	86
	0.67	1.2	80
	0.67	1.3	75
	0.7	1.1	89
	0.7	1.2	83
	0.7	1.3	79
	0.8	1.1	95

	0.8	1.2	91
	0.8	1.3	87

9.3. Participant Analysis Sets

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

Analysis Sets	Description
Enrolled	All participants who sign the ICF.
Full Analysis Set (FAS)	All participants who were randomized in the study and received at least one (complete or partial) administration of study intervention.
Safety Analysis Set (SAS)	All participants who were randomized in the study and received at least one (complete or partial) administration of study intervention.
Immunogenicity Analysis Set	The immunogenicity analysis set is defined as all participants who received at least one (partial or complete) administration of nipocalimab and have appropriate serum samples for ADA detection.
Pharmacokinetics (PK) Analysis Set	The PK analysis set is defined as all participants who received at least one (partial or complete) administration of nipocalimab or certolizumab and have at least one valid post-dose blood sample collection.
Pharmacodynamic (PD) Analysis Set	The PD analysis set is defined as participants who received at least 1 dose (partial or complete) of study intervention and have at least 1 valid post-dose blood sample drawn for PD analysis.

9.4. Statistical Analyses

A DBL for primary efficacy analysis is planned at Week 12, when 100% of participants complete their Week 12 assessments or terminate study prior to Week 12 (Week 12 DBL). A final DBL is planned at Week 30, when all participants complete the study or have terminated the study prior to Week 30 (final DBL). The end of the study is defined as the last follow-up assessment (6 weeks after the last visit) for the last participant.

The primary endpoint is change from baseline in DAS28-CRP at Week 12, primary analysis will be performed at Week 12 DBL.

The statistical analysis plan 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 (eg, mean, median, SD, interquartile range, minimum, and maximum) will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables. Graphical data displays (eg, line plots) may also be used to summarize data.

Analyses suitable for categorical data (eg, chi-square tests, CMH tests or logistic regression, as appropriate) will be used to compare the proportions of participants achieving selected endpoints (eg, ACR response). In cases of rare events, the Fisher's exact test will be used for treatment comparisons. Continuous response parameters will be compared using ANCOVA, a MMRM or a cLDA, as appropriate.

The comparison for the primary endpoint will be tested at a 1-sided α level of 0.05. Nominal p-values (1-sided) will be displayed for all other endpoint comparisons. Full details of the analysis of the primary, secondary, and exploratory endpoints will be included in SAP.

9.4.2. Primary Endpoint(s)

Unless otherwise specified, efficacy analyses will be based on the FAS, defined as all randomized participants who had at least one study intervention administration. Participants will be analyzed according to the study treatment arm to which they were randomized regardless of the study intervention they received.

The primary endpoint is the mean change from baseline in DAS28-CRP at Week 12. Analysis will be based on the primary estimand, ie, a precise definition of the primary targeted treatment effect, is defined by 5 attributes (treatment, population, variable, ICE, and population-level summary) for the primary endpoint as stated below.

9.4.2.1. Primary Estimand of Change from Baseline in DAS28-CRP at Week 12

The composite estimand is defined by the following 5 components:

- **Treatment by Week 12**:
  - Control arm: Certolizumab 400 mg at Week 0, 2, 4; then 200mg Q2W; Placebo IV q2w
  - Experimental arm: Certolizumab 400 mg at Week 0, 2, 4; then 200 mg Q2W; Nipocalimab 30 mg/kg IV q2w
- **Population:** Participants between the ages 18 and 75, inclusive, with moderately to severely active RA despite ≥1 advanced therapy (bDMARD or tsDMARD).
- **Variable (Endpoint):** Change from baseline in DAS28-CRP at Week 12. A participant who initiates or adjusts medication or discontinues or experiences an ICE in categories 1, 2, 3, or 4 (categories 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. The observed change from baseline in the DAS28-CRP score will not be used and will be assumed to follow a MAR assumption.
- **ICE and Corresponding Strategies:**

Event category	Definition	Analysis Strategy
1	Initiated protocol prohibited medications/therapies for RA	**Composite Strategy:** A participant with any of these intercurrent events is considered as to have no change from baseline after this event; the occurrence of this ICE has been captured in the variable definition.
2	Initiation or dose increase of csDMARDs (such as MTX, SSZ, HCQ, CQ, or leflunomide) or oral corticosteroid therapy above the baseline dose for RA	
3	Discontinuation of study intervention due to lack of efficacy or an AE of RA worsening	
4	Discontinuation of study intervention due to COVID-19 infection or for reasons other than those in ICE 3	

Note: If a participant experiences more than one ICE in ICEs 1-4 then the overall strategy will be based on the first ICE to occur in ICEs 1-4 categories

- **Population- level summary:** Differences in the mean change in DAS28-CRP score at Week 12 as defined in the Variable attribute above between the combination therapy (certolizumab + nipocalimab) group and the monotherapy (certolizumab + placebo) group.

9.4.2.2. Estimator for the Primary Endpoint

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.

Participants who have protocol prohibited medications changes, or changed their baseline medication, or had an intercurrent events before Week 12 visit will be considered as to have no change from baseline in DAS28-CRP at Week 12, regardless of the observed changes.

After intercurrent event rules are applied, any remaining missing data will be imputed by using MI assuming MAR assumption. Full details of imputation models will be provided in the SAP.

The treatment effect of the combination therapy (certolizumab + nipocalimab) versus monotherapy (certolizumab + placebo) will be compared using an ANCOVA model, including treatment group, baseline DAS28-CRP and randomization stratification factors:

- csDMARDs usage at baseline (yes or no)
- Screening ACPA level (high ≥400 U/mL; low <400 U/mL)
- DAS-28-CRP at baseline
- Study country
- Territory/Investigator site

The least Square Mean difference and 90% CIs (equivalent to the 1-sided 0.05 level test) between the combination therapy group and monotherapy group will be presented. In addition, 95% confidence interval will be reported. The comparison for the primary endpoint will be tested at a 1-sided α level of 0.05.

To evaluate the robustness of the primary analysis results, additional supplemental analyses (eg, alternative estimands) and a sensitivity analysis using re-randomization test to evaluate the impact of the dynamic randomization will be performed, details will be described in the SAP.

9.4.2.3. Subgroup Analysis

To evaluate the consistency of the primary analysis results, subgroup analyses based on demographic characteristics, baseline disease characteristics, and baseline medications will be performed if sufficient participant data is available in the subgroup. Further details will be provided in the SAP.

9.4.3. Secondary Endpoint(s)

Secondary efficacy endpoints are:

- ACR20, ACR50, ACR70, and ACR90 at Week 12
- DAS28-CRP remission at Week 12
- DAS28-CRP LDA at Week 12
- Change from baseline in HAQ-DI score at Week 12
- Change from baseline in CDAI at Week 12

Analyses will compare between combination therapy (certolizumab + nipocalimab) and monotherapy (certolizumab + placebo). The methods of analysis, as well as the data handling rules, will be provided in the SAP.

9.4.4. Safety Analyses

The primary safety analysis will use the on-study Safety Analysis-Set, ie, participants who received at least one dose (complete or partial) of any study intervention.

Adverse Events

The verbatim terms used in the CRF by investigators to identify AEs will be coded using the MedDRA. Any AE occurring at or after the initial administration of study intervention through the day of last dose plus 8 weeks is considered to be treatment-emergent. All reported treatment-emergent AEs 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 treatment arm.

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 a SAE.

Listings of all participants with MACE (nonfatal MI, nonfatal stroke, and cardiovascular death) will be provided.

In addition, an exposure-adjusted supplementary on-treatment analysis for treatment emergent AEs: infection, SAE, and AE leading to treatment discontinuation based on primary safety analysis will be performed. An exposure adjusted on-study safety analysis based on primary safety analysis will only be performed when the rate of dropout from study is high. Full details will be provided in the SAP.

Clinical Laboratory Tests

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

Vital Signs

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

9.4.5. Tertiary or Exploratory Efficacy Endpoints

Exploratory endpoints are provided in Section 3. They will be descriptively summarized either at a single time point or over time (through Week 24) by treatment groups. The methods of analysis and the data handling rules will be provided in the SAP.

9.4.6. Other Analyses

9.4.6.1. 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 the 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 and/or certolizumab. 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.

9.4.6.2. Biomarkers Analyses

The biomarker analyses will be used to understand RA, characterize the effects of nipocalimab and certolizumab to identify PD markers and biomarkers relevant to treatment, and to determine if these markers can predict response to nipocalimab and certolizumab. The biomarkers may include but are not limited to serum immunoglobulins, autoantibodies, inflammatory markers, whole blood RNA profile, and other categories of biomarkers potentially involved in the development and the progression of RA.

Changes in biomarkers over time will be summarized by treatment arm. Associations between baseline levels and changes from baseline in select markers and clinical response may be explored. Results of biomarker analyses may be summarized in a separate technical report.

Planned biomarker analyses may be deferred if emerging study data show no likelihood of providing useful scientific information or if an insufficient number of samples are available for analysis. Any biomarker samples received by the contract vendor or sponsor after the cutoff date will not be analyzed, and therefore, excluded from the biomarker analysis.

9.4.6.3. Pharmacokinetic/Pharmacodynamic Analyses

If data permit, the relationship between serum concentrations of nipocalimab and certolizumab and the efficacy measures and relevant PD biomarkers 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.

9.4.6.4. Pharmacogenomic Analyses

Genetic (DNA) analyses may be conducted only in participants who sign the consent form to participate in the pharmacogenomic sampling. These analyses are considered exploratory.

DNA samples will be used for research related to nipocalimab and certolizumab or RA. They may also be used to develop tests/assays related to nipocalimab certolizumab and RA. Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic and epigenetic markers throughout the genome or analysis of the entire genome (as appropriate) in relation to the disease and treatments.

Results of analyses may be presented in a separate technical report.

9.4.6.5. Immunogenicity Analysis

The incidence and titers of antibodies to nipocalimab will be summarized for all exposed 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 generated immune response.

9.5. DMC

An external independent DMC will be established and will meet periodically to review interim unblinded safety data to ensure the continuing safety of the participants enrolled in the study. The DMC will consist of 2 physicians and a statistician. The DMC responsibilities, authorities, and procedures will be documented in a separate DMC Charter and DMC SAP.

The DMC's initial responsibility will be careful review of the safety data from the first 15 participants randomized to any treatment arm and treated. Similar to conduct of a Phase 1 study, the safety of these first 15 participants will be monitored weekly for any potential safety concerns. Detailed guidance for the DMC regarding these reviews will be provided in the DMC charter. Once the 15th participant is randomized, the DMC will perform a review of unblinded safety tables. If no new safety concerns are identified during this initial review period, then the subsequent DMC reviews will include monthly reports of all SAEs in enrolled participants as well as review of unblinded safety tables at least every 3 months. After each safety review, the DMC will make recommendations regarding the continuation of the study.

Details of the Committees Structure can be found in Appendix 3, Regulatory, Ethical, and Study Oversight Considerations.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations and Definitions

ACPA	Anti-citrullinated protein/peptide antibody
ACR	American College of Rheumatology
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
AxMP	Auxiliary Medicinal Product (also known as NIMP)
BCG	Bacilli Calmette Guerin
β-hCG	β-human chorionic gonadotropin
BP	blood pressure
CDAI	Clinical Disease Activity Index
CHF	Congestive heart failure
cLDA	constrained longitudinal data analysis
CIC	circulating immune complex
ClinRO	clinician-reported outcome
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease of 2019
CrCL	creatine clearance
CRO	Contract research organization
CTM	clinical trial manager
CPK	Creatine phosphokinase
CQ	chloroquine
CRP	C-reactive protein
CRF	case report form(s) (paper or electronic as appropriate for this study)
csDMARD	conventional synthetic disease modifying antirheumatic 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
DDI	drug-drug interaction
DILI	drug induced liver injury
DMARD	disease modifying antirheumatic drug
DMC	Data Monitoring Committee
DNA	desoxyribonucleic acid
EAC	Event adjudication committee
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
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
HBsAg	hepatitis B surface antigen

HBV	hepatitis B virus
HCQ	hydroxychloroquine
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HRQOL	Health-Related Quality of life
HRT	Hormone replacement therapy
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
IGRA	Interferon-gamma release assay
IL	interleukin
IM	intramuscular
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
IPPI	Investigational Product Preparation and Administration Instructions
IR	inadequate response
IRB	Institutional Review Board
IUGR	Intra-uterine growth restriction
IV	intravenous(ly)
IWRS	interactive web response system
JAKi	janus kinase inhibitors
LA	Lupus anticoagulant
LDA	low disease activity
LDH	lactase dehydrogenase
LDL	low-density lipoprotein
LEF	leflunomide
LLOQ	lower limit of quantification
LTM	local trial manager
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
MoA	mode-of-action
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
nr-axSpA	Non-radiographic axial spondyloarthritis
NSAID	nonsteroidal anti-inflammatory drug
PBMC	peripheral blood mononuclear cell
PBO	placebo
PCC	protocol clarification communication
PCS	physical component score
PD	pharmacodynamic(s)
PEF	peak expiratory flow

PEG	polyethylene glycol
PGA	Physician's Global Assessment (of Disease Activity)
PIP	proximal interphalangeal
PK	pharmacokinetic(s)
PO	oral (by mouth)
PoC	proof-of-concept
PQC	Product Quality Complaint
PRO	patient-reported outcome
PsO	psoriasis
PT	prothrombin time
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
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
SSG	Statistical support group
SSZ	sulfasalazine
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TMDD	Target-mediated drug disposition
TNF	tumor necrosis factor
TT	thrombin time
UC	ulcerative colitis
ULN	upper limit of normal
USPI	United States prescribing information
VAS	visual analog scale
wAIHA	warm autoimmune hemolytic anemia
WBC	white blood cell

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the SoA by the central or local laboratory:

The actual date of assessment and, if required, the actual time of the assessment of laboratory samples will be recorded in the source documentation and in the eCRF or laboratory requisition form.

Protocol Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet count Red blood cell count Hemoglobin Hematocrit	<u>RBC Indices:</u> MCV MCH % Reticulocytes	<u>WBC count with Differential:</u> Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. A RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory. In addition, any other abnormal cells in a blood smear will also be reported.		
Clinical Chemistry	Sodium Potassium Chloride Bicarbonate Blood urea nitrogen (BUN) Creatinine Glucose Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic transaminase (SGOT) Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase (SGPT) Gamma-glutamyltransferase (GGT)	Total bilirubin Alkaline phosphatase CPK Lactic acid dehydrogenase (LDH) Uric acid Calcium Phosphate Albumin Total protein Cholesterol Triglycerides Magnesium Lipid panel (total cholesterol, HDL, LDL [calculated], triglycerides)	
	Note: Details of liver chemistry stopping criteria and required actions and follow-up are given in Appendix 6: Liver Safety. Potential Hy's Law case reporting requirements are defined in Section 8.3.1.		
Routine Urinalysis	<u>Dipstick</u> Specific gravity pH Glucose Protein Blood Ketones Bilirubin Urobilinogen Nitrite Leukocyte esterase	Sediment (if dipstick result is abnormal) Red blood cells WBCs Epithelial cells Crystals Casts Bacteria	

	If dipstick result is abnormal, flow cytometry or microscopy will be used to measure sediment. In case of discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically. In the microscopic examination, observations other than the presence of WBC, RBC and casts may also be reported by the laboratory. Dipstick and flow cytometric analysis of the urine samples will be performed in parallel, ie, in the same sample at the same time. Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, and urobilinogen will be determined using a dipstick. Red blood cells, WBCs, epithelial cells, crystals, casts, and bacteria will be measured using flow cytometry or microscopy. If there is discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically. Dipstick and flow cytometric analysis of the urine samples will be performed in parallel, in the same sample at the same time. Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, and leukocyte esterase will be determined using dipstick. Red blood cells, WBCs, and epithelial cells will be measured using flow cytometry. In case of discordance between the dipstick results and the flow cytometric results, the sediment will be examined microscopically. Crystals, casts, and bacteria will only be reported if they are present.
Other Screening Tests	• Urine Pregnancy Testing (highly sensitive) for female participants of childbearing potential only (Participants of childbearing potential will be given urine pregnancy tests to be self-administered at home until 5 months after their last dose of the study intervention. The site is responsible for contacting these participants on a monthly basis to confirm that the pregnancy test has been performed. If a participant tests positive for pregnancy, the site is required to report this to the sponsor within 24 hours of becoming aware of the event). • Serology (HIV antibody; hepatitis B surface antigen [HBsAg] and Hepatitis B surface antibody [anti-HBs], Hepatitis B core antibody [anti-HBc] HBV DNA [if applicable]; hepatitis C virus antibody, and HCV RNA [if applicable]) • Coagulation (prothrombin time, activated partial thromboplastin time, INR) • CRP • ACPA • RF • CIC • Immunoglobulin isotype profile (total IgG, IgG1, IgG2, IgG3, IgG4, IgA, IgM, and IgE) • Antibodies to nipocalimab- done by sponsor laboratory

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 ICH guidelines on GCP, and applicable regulatory and country-or territory-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 PCC may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, LTMs, CTMs, and/or CROs who will ensure that the PCC explanations are followed by the investigators.

The PCC Document may be shared by the sites with Independent 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 non-acceptance, 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) involves 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 CRF 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/territory, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy 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 (if applicable, the notification will be submitted through the head of investigational institution).

Country/Territory Selection

This study will only be conducted in those countries/territories 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 4.2.1., Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

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 Prestudy Documentation (above) for details on financial disclosure.

10.3.3. Informed Consent Process

Each participant 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 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 for the treatment of their disease. Participants will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. 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 is authorizing such access, which includes permission to obtain information about their 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 physician may also recontact the participant for the purpose of obtaining consent to collect information about his or her survival status.

The participant 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 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 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 may be used for the required DNA component of the study.

10.3.4. Recruitment Strategy

Each site will be asked to identify participants from their patient database and their community of practice, the identified patient may be invited to participate in the study. Additionally, Janssen will provide sites with participant thank you communication, a doctor-to-doctor communication, a patient brochure, general study posters/flyer, a participant welcome message, a participant Study Visit Guide Booklet, a participant inclusion/exclusion criteria booklet, participant appointment card, and a branded study blanket. Sites are provided with reference materials to assist in study conduct such as mini protocol, and study reference cards. Each country may also opt to use a recruitment vendor, with sponsor approval.

10.3.5. 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 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/territories.

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 biomarker 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.

10.3.6. Long-term Retention of Samples for Additional Future Research

No additional research on study participants, study samples, or data derived from the study will be conducted by the institution(s) or by a third party, without the prior written consent of the Sponsor.

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 and certolizumab, to understand RA, to understand differential intervention responders, and to develop tests/assays related to nipocalimab and certolizumab and RA. The research may begin at any time during the study or during the post study 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 in Future Research).

10.3.7. Committees Structure

Data Monitoring Committee

A Data Monitoring Committee (DMC) will be established to monitor data on an ongoing basis to ensure the continuing safety of the participants enrolled in this study. This committee will consist of at least one medical expert in the relevant therapeutic area and at least one statistician; committee membership responsibilities, authorities, and procedures will be documented in its charter. The committee will meet periodically to review interim data. After the review, the DMC will make recommendations regarding the continuation of the study.

10.3.8. 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 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 the goals of 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 Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as 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 analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in the 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 sub-study 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 the interim results of clinical studies as required by law. The disclosure of the study results will be performed after the end of study in order to ensure the statistical analyses are relevant. Study results will be uploaded to the CTIS database within one year after end of trial in accordance with EU CTR Annex IV.

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

Guidelines for CRF completion will be provided and reviewed with study site personnel before the start of the study.

The sponsor may review the CRF 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.

10.3.10. 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 CRF. All CRF 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 CRF are accurate and correct.

The study data will be transcribed by study site personnel from the source documents onto an electronic CRF, 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 CRF. Any such worksheets will become part of the participant's source documents. Data must be entered into CRF in English. The CRF 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 eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, 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.

10.3.11. 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 patient-reported outcomes (PROs) are reports of a patient’s health condition that come directly from the patient, 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).

The following data will be recorded directly into the CRF and will be considered source data.

- Race
- History of smoking all nicotine use, eg, cigarettes (including e-cigarettes or the equivalent of e-cigarettes), cigars, chewing tobacco, patch, gum

- Blood pressure and pulse/heart rate
- Height and weight
- Details of physical examination
- Investigator-completed scales and assessments PRO Health Economics data

The minimum source documentation requirements for Section 5.1., Inclusion Criteria and Section 5.2, Exclusion Criteria 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. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the CRF in the protocol include the eSource system, but information collected through eSource may not be limited to that found in the CRF.

10.3.12. 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 CRF with the source documents (eg, hospital/clinic/physician's office medical records). At these visits, the monitor will compare data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records); a sample may be reviewed. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF 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.

10.3.13. 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.

10.3.14. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF 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.

10.3.15. Study and Site Start and Closure

First Act of Recruitment

The first subject 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

Use International Organization for Standardization (ISO) definitions and procedures detailed in Section 10.4.5: Adverse Events, Adverse Device Effects, Serious Adverse Events, Serious Adverse Device Effects, Unanticipated Serious Adverse Device Effects, and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

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 (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Council on Harmonisation [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).

For combination products with a device constituent, AEs include those resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the device. It includes any AE resulting from use error or from intentional misuse of the investigational device.

Serious Adverse Event

A SAE based on ICH and EU 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).

For combination products with a device constituent, SAEs include adverse device effects that resulted in any of the consequences characteristic of an SAE. An unanticipated serious adverse device effect is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see Section 2.3. Benefit-Risk Assessment).

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 study drugs with a marketing authorization, the expectedness of an AE will be determined by whether or not it is listed in the package insert.

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

Participant-specific special reporting situations must be recorded in the CRF. Any special reporting situation that meets the criteria of an SAE must be recorded on the SAE page of the CRF.

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 CRF. 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 CRF 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 CRF). 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 and safety report form of the CRF, which must be completed and reviewed by a physician from the study site, and transmitted in a secure manner to the sponsor immediately, but no later than within 24 hours of their knowledge of the event. The initial and follow-up reports of an SAE should be transmitted in a secure manner electronically or 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 product quality complaint (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.

All complaints related to ANY part of the Combination Product must be reported within 1 business day. In the event of public holiday, measures must be taken to ensure reporting no later than calendar day 3.

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

Definitions

Female Participants of Childbearing Potential

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

Female Participants 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 FSH level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in female participants not using hormonal contraception or hormonal 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 female participants on HRT, the female participant will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if they wish 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 female participant experiences menarche) or the risk of pregnancy changes (eg, a female participant who is not heterosexually active becomes active), a female participant 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 male participants or female participants 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 **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
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Tubal closure (eg, bilateral tubal occlusion, bilateral tubal ligation)
• Azoospermic partner (vasectomized or due to medical cause) *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the female participant 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 **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 – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation – oral – injectable
• Sexual abstinence *(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
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)

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.

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

Phase 2 liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology.

Liver Chemistry Stopping Criteria	
ALT /AST absolute	ALT **or AST** ≥5xULN
ALT /AST Increase	**If cannot monitor:** ALT **or AST** ≥3 x ULN and cannot be monitored weekly for 4 weeks **Or if able to monitor:** ALT **or AST** ≥3xULN persists for ≥4 weeks
Total bilirubin[1, 2]	ALT **or AST** ≥3xULN **and** total bilirubin ≥2xULN (or at least a doubling of direct bilirubin in known Gilbert's syndrome)
INR[2]	ALT or AST ≥3xULN **and** INR >1.5, if INR measured
Symptomatic[3]	ALT **or AST** ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Suggested Actions, Monitoring and Follow-up Assessments

Actions	**Follow-up Assessments**
• **Immediately** stop study intervention • Report the event to the sponsor **within 24 hours** • Complete the CRF according to CRF completion guidelines, and complete a SAE data collection tool if the event also met the criteria for an SAE[2] • Perform follow-up assessments as described in the Follow-Up Assessment column • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see **MONITORING**) **MONITORING:** **If ALP <2 x ULN, ALT or AST ≥3xULN AND total bilirubin ≥2xULN (or at least a doubling of direct bilirubin in known Gilbert's syndrome) or INR >1.5 (if measured):** • Repeat liver chemistry tests (include ALT, aspartate transaminase [AST], alkaline phosphatase, total and direct bilirubin and INR) and perform liver event follow-up assessments within **24 hours** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for PK analysis 45 minutes (±15 minutes) after the most recent dose[5] • Obtain serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma-glutamyltransferase [GGT], glutamate dehydrogenase [GLDH], and serum albumin • Fractionate bilirubin • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the CRF as per CRF completion guidelines • Record use of concomitant medications (including acetaminophen, herbal remedies, recreational drugs and other over-the-counter medications)

• A specialist or hepatology consultation is recommended **If ALT or AST ≥3xULN AND total bilirubin <2xULN and INR ≤1.5:** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total and direct bilirubin and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline **RESTART/RECHALLENGE** • **If liver event causality is determined to be "not related", restart may be permitted upon written approval of the sponsor**. See restart guidelines	• Record alcohol use on the [CRF as per CRF completion guidelines]. **<u>If ALT or AST ≥3xULN AND total bilirubin ≥2xULN or INR >1.5 (if measured)</u>** obtain the following in addition to the assessments listed above**:** • Antinuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins • Serum acetaminophen adduct assay, when available, to assess potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete CRF as per CRF completion guidelines • Liver biopsy may be considered and discussed with local specialist if available: o In participants when serology raises the possibility of autoimmune hepatitis (AIH) o In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention o In participants with acute or chronic atypical presentation • If liver biopsy conducted complete **CRF as per CRF completion guidelines**

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention if ALT ≥3xULN **and** total bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.
2. All events of ALP <2 x ULN, ALT **or AST** ≥3 x ULN **and** total bilirubin ≥2xULN (or at least a doubling of direct bilirubin in known Gilbert's sydnrome) or ALP <2 x ULN, ALT **or AST** ≥3 x ULN **and** INR >1.5 (if measured) may indicate severe liver injury **(possible 'Hy's Law') and must be reported to sponsor in an expedited manner and as an SAE if SAE criteria are met**

(excluding studies of hepatic impairment or cirrhosis). The INR stated threshold value will not apply to participants receiving anticoagulants.

3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
4. Includes: hepatitis A immunoglobulin M (IgM) antibody; HBsAgG and HBcAB; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.
5. PK sample may not be required for participants known to be receiving placebo or non-comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Study Reference Manual.

10.7. Appendix 7: Study Conduct During a Pandemic

GUIDANCE ON STUDY CONDUCT DURING COVID-19 PANDEMIC

It is recognized that the COVID-19 pandemic may have an impact on the conduct of this clinical study due to, for example, 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 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 travel to the study site is considered to be dangerous, study participation may be interrupted, and study follow-up conducted. If it becomes necessary to discontinue participation in the study, the procedures outlined in the protocol for discontinuing study intervention will be followed.

If, as a result of the COVID-19 pandemic scheduled 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. 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 pandemic-related" in the CRF.

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. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

If the participant has tested positive for SARS-CoV-2, the investigator should contact the sponsor's responsible medical officer 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 clinical study report.

10.8. Appendix 8: 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			STATUS
Hepatitis B surface antigen (HBsAg)	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc total)**	
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.

10.9. 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: Definition of Inadequate Initial Response, and Loss of Response to Advanced Therapies (bDMARD or tsDMARD) in RA

The criteria for (I) inadequate initial response, and (II) loss of response to Advanced Therapies (bDMARD or tsDMARD) are described below.

I. Inadequate initial response (primary nonresponse) to prior therapy with Advanced Therapies (bDMARD or tsDMARD).

Eligible participants must satisfy criteria A and B.

A. Have received adequate dosing (including induction doses) of Advanced Therapies (bDMARD or tsDMARD) see protocol section 5.1 for required adequate dosing period**.**

AND

Did not improve with at least 50% reduction in disease activity to these doses within 3 months and/or did not achieve target (ie, remission or low disease activity) within 6 months as assessed by a treating physician.

B. Have documentation available to the investigator that meets the following 2 requirements:

1) Provide the dates and doses of the failed Advanced Therapies (bDMARD or tsDMARD).

2) Documents that the participant had persistence of disease activity following Advanced Therapies (bDMARD or tsDMARD).

Examples of acceptable documents include medical records, letter provided by a referring physician, or other “reason for referral” documents (eg, insurance authorization form).

II. Initial response followed by loss of response (secondary nonresponse) to current or prior Advanced Therapies (bDMARD or tsDMARD).

Eligible participants must satisfy criteria A, B, and C.

A. Have received adequate dosing (including induction doses). see protocol section 5.1 for required adequate dosing period:

AND

Initially responded, that is improved with at least 50% reduction in disease activity within 3 months and achieved target (remission or low disease activity) within the first 6 months to therapy (including induction therapy).

B. Have or had at least 1 of the following signs or symptoms related to recurrence of rheumatoid arthritis, as assessed by a treating physician:

3) Worsening in tender joint count

4) Worsening in swollen joint count

5) Worsening in physical function

6) Worsening in disease activity

These signs and symptoms of rheumatoid arthritis offered only as a benchmark of the minimally acceptable criteria required to designate a participant as having a loss of response to Advanced Therapies (bDMARD or tsDMARD). It is acknowledged that previous treatment decisions could have been made based on evaluation of other measures that may be indicative of worsening disease (eg, elevations of inflammatory markers including but not limited to CRP and/or evidence of disease flare based on clinical imaging modalities including but not limited to CT and MRI). Under these circumstances, documentation of these specified measures of worsening disease activity can be accepted as evidence of IR to prior Advanced Therapies (bDMARD or tsDMARD). However, investigators should note that participants must meet protocol-specified criteria for active disease during the current screening period as described in Section 5.1 to be eligible for enrollment.

C. Have documentation available to the investigator that meets the following 2 requirements:

   7) Provide the dates and doses of the failed Advanced Therapies (bDMARD or tsDMARD).

   8) Documents that the participant had recurrence of disease activity despite Advanced Therapies (bDMARD or tsDMARD). Examples of acceptable documents include medical records, letter provided by a referring physician, or other “reason for referral” documents (eg, insurance authorization form).

10.11. Appendix 11: Protocol Amendment History

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

DOCUMENT HISTORY		
Document	**Country/Territory Affected**	**Date**
Amendment 3	All	xx October 2023
Amendment 2	All	27 September 2023
Amendment 1	All	7 September 2023
Original Protocol	All	28 March 2023

Amendment 2 (27 September 2023)

Overall Rationale for the Amendment: To address comments from EU CTR review.

The changes made to the clinical protocol 80202135ARA2002 as part of Protocol Amendment 2 are listed below, including the rationale of each change and a list of all applicable sections.

Section Number and Name	Description of Change	Brief Rationale
1.3. SoA; 8.2.5 Pregnancy Testing; Appendix 2: Clinical Laboratory Tests	Added the fact that pregnancy tests will be highly sensitive.	To address the comments from EU-CTR RFI.
5.1. Inclusion Criteria; Appendix 2: Clinical Laboratory Tests	Appendix 2, IC#17, IC#18, and IC#19 have been modified to increase the time of using a contraceptive (5 months instead of 70 days) after the end of treatment.	To address the comments from EU-CTR RFI.
5.2. Exclusion Criteria	EC#24 has been modified to update the exclusion criteria of participants with latent TB.	To address the comments from EU-CTR RFI.

Amendment 1 (7 September 2023)

Overall Rationale for the Amendment: To address comments from EU CTR review.

The changes made to the clinical protocol 80202135ARA2002 as part of Protocol Amendment 1 are listed below, including the rationale of each change and a list of all applicable sections.

Section Number and Name	Description of Change	Brief Rationale
1.3. SoA	A note was added to the SoA specifying that the chest X-ray is only needed if no chest radiograph done within the last 90 days before first administration of study intervention, and required for tuberculosis screening as per local standard procedures.	Further clarification in the SoA
2.1 Study Rationale	Updated a sentence describing the mechanism of action of anti-TNFα agents.	To correct an inadvertently incorrect description of the mechanism of action of anti-TNFα agents
1.1 Synopsis; 3. Objectives and	Added/updated tertiary or exploratory endpoints through Week 24.	To clarify the tertiary or exploratory endpoints.

Section Number and Name	Description of Change	Brief Rationale
Endpoints; 9.4.5.Tertiary or Exploratory Endpoints		
1.1 Synopsis; 4.1 Overall Design; 6.3 Measures to Minimize Bias: Randomization and Blinding; 9.5 Interim Analysis; 10.3.7 Committee Structure	Updated text to remove the optional interim analysis.	To remove the optional interim analysis.
4.3 Justification for Dose	Added further information from the completed Phase 2 RA study to support the proposed nipocalimab dosing.	To further clarify the selection of the dose.
5.1 Inclusion Criteria	Added a clarification that male participants should use an acceptable methods of contraception per local regulations during this study and for 90 days after the last dose of study intervention.	To clarify the contraceptive requirements.
5.1 Inclusion Criteria; 10.3.3. Informed Consent Process	Removed the option for a legally acceptable representative to sign the ICF.	To clarify the informed consent process.
5.1 Inclusion Criteria;	Added a requirement for male participants to use contraception during the study and for a period of 90 days after the last administration of study intervention.	To clarify the duration of time that male participants must use contraception.
5.2 Exclusion Criteria	Exclusion criteria 14 and 24 concerning malignancy and TB were updated.	To minimize the risks of immunosuppression with combination therapy.
7.1 Discontinuation off Study Intervention	Removed the exception for basal cell carcinoma	To further clarify the discontinuation criteria.
8.3.4. Regulatory Reporting Requirements for Serious Adverse Events and Anticipated Events	Added information on the appropriate reporting of safety information.	To clarify the sponsor responsibilities for safety reporting.
Appendix 2	Added text explaining that urine pregnancy kits will be provided for female participants to allow for monthly home testing after Week 24 until 70 days after the last dose of study intervention.	To allow for pregnancy testing after the last study visit.
Appendix 3	Added Section 10.3.4	To add a description of the recruitment process.
Appendix 3	Added a sentence to Section 10.3.8 to describe registration and disclosure of study results in accordance with EU CTR Annex IV.	To update the protocol with the publication policy of the trial data being uploaded to the CTIS database.
Appendix 5	Removed footnote (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	This footnote was removed as the potential of DDI between nipocalimab or certolizumab and contraceptives is low.

Section Number and Name	Description of Change	Brief Rationale
	hormonal contraception may interact with the study intervention.	
Appendix 10	Appendix 10 was added.	To define of inadequate response to previous DMARDs.

11. REFERENCES

Aletaha D, 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, 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.

Boleto G, Kanagaratnam L, Dramé M, Salmon JH. Safety of combination therapy with two bDMARDs in patients with rheumatoid arthritis: A systematic review and meta-analysis. 2019; Seminars in arthritis and rheumatism;49(1), 35–42.

Felson DT, 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, 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, Smolen JS, Wells G, et al. 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, Spitz P, Kraines RG, Holman HR. Measurement of patient outcomes in arthritis. Arthritis Rheum. 1980;23:137-145.

Hawley DJ, 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.

Kosinski M, 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.

Levey AS, Stevens LA, Schmid CH, et al. CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

Lin YJ, Anzaghe M, Schülke S. Update on the Pathomechanism, Diagnosis, and Treatment Options for Rheumatoid Arthritis. Cells. 2020;9(4):880.

Pope JE, 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, 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.

Rodriguez F, 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.]

Sampson HA, 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.

Smolen JS, Landewé RBM, Bijlsma JWJ et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020;79(6):685-699.

van Riel PL, 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.

Wells GA, 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.

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

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	05-Oct-2023 20:31:06 (GMT)	Document Approval