Janssen Research & Development *

Clinical Protocol

Protocol Title
A Randomized, Placebo-controlled, Double-blind, Multicenter Study to Assess the Efficacy and Safety of Nipocalimab in Adults with Primary Sjogren's Syndrome (pSS)

Protocol 80202135SJS2001; Phase 2
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).

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

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 3	20 July 2022
Amendment 2	04 February 2022
Amendment 1	26 May 2021
Original Protocol	26 March 2021

Amendment 3 (20 July 2022)

Overall Rationale for the Amendment: Key laboratory supplies required for the Erythrocyte Sedimentation Rate (ESR) test that meet European Union (EU) CE marking requirements for laboratory tests are no longer commercially available. Therefore, the inclusion criterion (number 8) and secondary endpoint (Sjögren's Syndrome Responder Index [SSRI] response) that depend on ESR have been revised. In addition, a new secondary endpoint (Sjögren's Tool for Assessing Response [STAR]) was added, for which the European Medicines Agency (EMA) issued a letter of support (EMADOC-1700519818-746443) on 15 March 2022. Finally, minor clarifying changes to enhance the safety and scientific rigor of the study are also included in this amendment.

The changes made to the clinical protocol 80202135SJS2001 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 previous protocol amendments are listed in Section 10.13 Appendix 13: Protocol Amendment History.

Section Number and Name	Description of Change	Brief Rationale
1.1.Synopsis Objectives and Endpoints, Statistical Methods; 3. Objectives and Endpoints; 9.4.3. Secondary Endpoints; 9.4.4. Exploratory Endpoints	Added a new secondary endpoint (STAR) and moved a secondary endpoint (SSRI) to an exploratory endpoint.	To enhance scientific rigor by including the new, more rigorously developed endpoint (STAR), which has received a letter of support from EMA, while the SSRI becomes an exploratory endpoint because an appropriate CE marked ESR kit is no longer available.
5.1. Inclusion Criteria, Criterion 8; Section 8. Study Assessments and Procedures	Removed ESR and clarified associated text.	To comply with the Regulation (EU) 2017/746 of the European Parliament and the Council on In Vitro Medical Devices (IVDR), as key laboratory supplies required for an appropriate ESR test that meet EU CE marking requirements are no longer commercially available.
1.1. Synopsis Objectives and Endpoints; 9.4.5. Other Analyses	Moved ESR from a clinical biomarker secondary endpoint to a pharmacodynamic exploratory endpoint.	ESR test results from an appropriate CE marked source are no longer commercially available.
2.1. Study Rationale; 8.1.9. STAR; 11. References	Added content to support the addition of the new secondary endpoint (STAR).	To enhance scientific rigor, by including the STAR, a new, more rigorously developed endpoint is included based on support from EMA.
2. Introduction; 2.2. Background; 2.3.1. Risks for Study Participation, Table 3	Revised text to align with new information from ongoing or completed clinical studies.	To align with the most recent IB for nipocalimab.

Section Number and Name	Description of Change	Brief Rationale
2.3.1. Risks for Study Participation, Table 3; 5.2. Exclusion Criteria, Criterion 39; 5.3. Lifestyle Considerations, Criterion 7	Changed the allowed timeframe for a participant to receive a live vaccine.	To align with the Vaccine Recommendations and Guidelines of the Advisory Committee on Immunization Practices from the Centers for Disease Control and Prevention General Best Practice Guidelines for Altered Immunocompetence.
2.3.1 Risks for Study Participation, Table 3	Removed the risk of overdose.	To align with the most recent IB for nipocalimab.
1.1 Synopsis Benefit-risk Assessment	Added a summary of the benefit-risk assessment.	To align with the European Union Clinical Trial Regulation (EU CTR) requirements.
5.1 Inclusion Criteria, Criterion 2	Clarified the acceptable methods to confirm that participants meet the classification criteria for pSS.	To enhance the scientific rigor by clarifying eligibility criteria.
5.1. Inclusion Criteria, Criterion 11	Deleted criterion requiring participants to be male or female.	To enhance the scientific rigor by maximizing inclusivity of the study.
5.1. Inclusion Criteria, Criterion 15; 10.7. Contraceptive and Barrier Guidance	Added contraceptive and barrier guidance for male participants regarding intimate partners.	To clarify contraception guidance.
5.1. Inclusion Criteria, Criterion 17	Modified vaccination recommendations.	To clarify instructions to investigators regarding COVID-19 vaccines.
5.2. Exclusion Criteria, Criterion 7	Clarified that exclusion criterion may be evaluated and assessed by the investigator.	To clarify the instructions for investigators.
5.2. Exclusion Criteria, Criterion 20	Clarified the timeframe that would exclude participants with endothelial keratoplasty.	To clarify the period of exclusion for a medical procedure that may confound endpoint assessments.
5.2. Exclusion Criteria, Criterion 26; 6.8 Concomitant Therapy, Table 4	Clarified the timeframe for treatment with stable dosing prior to first administration of study intervention.	To enhance scientific rigor by standardizing guidance for medications that may confound disease assessment.
5.2. Exclusion Criteria, Criterion 30, Criterion 31	Criteria were similar; modified each for clarity.	To enhance scientific rigor by clarifying guidance for medications that may confound evaluation of study intervention.
5.2. Exclusion Criteria, Criterion 45	Clarified the timeframe for a participant with an infection requiring oral anti-infectives to be excluded from the study.	To clarify the period of exclusion for medical procedures that may confound endpoint assessments.
5.2. Exclusion Criteria, Criterion 50.	Clarified the COVID-19 infection exclusion.	To align with current company COVID-19 guidance.
5.3. Lifestyle Considerations, Criterion 5	Clarified that the investigators should determine the impact of the use of any wigs or hair attachments on disease assessment.	To enhance study inclusivity by allowing investigator discretion regarding wigs or hair attachments.
1.3. SoA Table 1, Efficacy Assessments	Clarified that participants must practice PerfO tests before baseline.	To provide instructions to investigators to ensure participants have stable PerfO performance at baseline.
1.3. SoA Table 1, Clinical Laboratory Tests	Clarified guidance for investigators as to how Sjogren's autoantibody panel may be performed.	To enhance the scientific rigor.

Section Number and Name	Description of Change	Brief Rationale
1.3. SoA Table 1, Clinical Pharmacology Assessments	Clarified the timeframe and that no pregnancy test required for the collection of the random nipocalimab concentration sample.	To decrease participant burden.
1.3. SoA Table 1, Pharmacogenomics, Footnote c; 1.3. SoA Table 2, Footnote b; 8.6.1. Evaluations; 8. Study Assessments and Procedures, Table 5; 10.8.2. Follow-up Assessments	Clarified the time window for collection of samples.	To decrease participant burden and provide flexibility in sample collection.
1.3. SoA Table 1 Footnote a	Clarified the screening timeframe.	To decrease participant burden and site burden.
5.5. Screen Failures	Clarified retesting procedure if a laboratory abnormality occurs.	To clarify guidance to increase flexibility of retesting.
6.8.7. Prohibited Therapies	Added live vaccines and clarified the use of any investigational intervention or use of an invasive medical device.	To align with the safety data in the most recent IB for nipocalimab.
6.8.7. Prohibited Therapies	Added instructions regarding monoclonal antibody therapies for COVID-19.	To clarify guidance for investigators regarding study conduct for participants who contract COVID-19 and require IV treatment.
8. Study Assessments and Procedures, Table 5	Modified the footnotes on the timing of assessments.	Clarify laboratory testing plans to enhance scientific rigor.
8.1.8. CRESS	Added a description of Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS).	Provide additional information to the study investigators and health authorities.
8.2. Exit Interviews	Modified description of exit interview.	To clarify the consent process for exit interviews.
8.4.1. Physical Examinations	Allowed investigator discretion in completing certain portions of the full physical examination.	To decrease participant burden and enhance scientific rigor by clarifying instructions for study investigators.
8.5.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information; 10.5.5 Procedures	Added text to clarify safety reporting.	To clarify instructions for study investigators.
8.5.3. Follow-up of Adverse Events and Serious Adverse Events; 10.5.4. Special Reporting Situations	Modified to clarify that pregnancy is a special reporting situation.	To align with sponsor reporting requirements and clarify instructions for study investigators.
8.9. Immunogenicity Assessments	Removed inaccurate text regarding PK sample storage.	To enhance scientific rigor by providing accurate content in Section 10.3.5 Long-Term Retention of Samples for Additional Future Research.
9.4.2. Primary Endpoint	Added text to the baseline hydroxychloroquine (HCQ) subgroup.	To enhance scientific rigor by clarifying the statistical plan.

Section Number and Name	Description of Change	Brief Rationale
10.1 Appendix 1 Abbreviations	Updated abbreviations table.	Aligned with changes to the rest of the protocol.
10.3.1. Regulatory and Ethical Considerations	Added text regarding protocol clarification communications.	To align with sponsor protocol template update.
10.3.4. Data Protection	Updated the text on Privacy of Personal Data based on the EU CTR.	Align with updated EU CTR requirements.
10.3.14. Study and Site Start and Closure	Changed the definition of the first act of recruitment.	To align with sponsor protocol template update.
10.11. Guidance on Study Conduct During the COVID-19 Pandemic (or Other Major Disruption)	Changed appendix title and added general text to include other major disruption, if needed in the future.	To clarify processes/procedures to follow when/if these types of events occur.
Throughout the protocol	Added territory(ies) to country(ies).	To align with sponsor protocol template update.
Throughout the protocol	The term “should” was replaced with “must” where the text has an intrinsic mandatory component.	To enhance scientific rigor by incorporation of clarifying edits where the text has an intrinsic mandatory component instead of a probability or expectation. To clarify the protocol by removing the need for investigators to infer probability or expectation.
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 Randomized, Placebo-controlled, Double-blind, Multicenter Study to Assess the Efficacy and Safety of Nipocalimab in Adults with Primary Sjogren's Syndrome (pSS)

DESCRIPTION OF COMPOUND

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

BENEFIT-RISK ASSESSMENT

Study 80202135SJS2001 is the first study of nipocalimab conducted in participants with pSS. Therefore, the benefit risk profile of nipocalimab in participants with pSS has not been established. The potential risks of exposure to nipocalimab based on its mechanism of action include the potential for increased risk for infection, reduced effectiveness of routine vaccines, activation of latent virus, clinical manifestations of hypoalbuminemia, infusion reaction, drug-drug interactions, and increased lipids. Mitigation strategies include the exclusion of participants at high risk of serious complications, close monitoring of participant safety, and to establish guidelines for participants' management (including monitoring of clinical laboratory tests and treatment discontinuation criteria), detailed review of permitted and prohibited concomitant medications, and comprehensive medical monitoring of safety data by the sponsor during the conduct of the studies. Comprehensive medical monitoring of safety data includes regular assessment of AEs and SAEs, vital signs, physical examination, and laboratory results.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of nipocalimab in participants with primary Sjogren's syndrome (pSS) versus placebo	**Primary endpoint:** • Change from baseline in Clinical European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (clinESSDAI) score at Week 24 **Secondary endpoints:** • Change from baseline in EULAR Sjögren Syndrome Patient Reported Index (ESSPRI) score at Week 24 • Improvement of ≥4 points from baseline in EULAR Sjögren Syndrome Disease Activity Index (ESSDAI) score (minimal clinically important improvement) at Week 24 • Improvement of ≥4 points from baseline in clinESSDAI score (minimal clinically important improvement) at Week 24 • ESSPRI response defined as a decrease of one point or a decrease of ≥15% from baseline (minimal clinically important improvement) at Week 24

Objectives	Endpoints
	• Disease response according to the Sjögren's Tool for Assessing Response (STAR) composite score at Week 24 • Improvement in disease activity level by ≥1 level in at least one clinESSDAI or ESSDAI domain (biological, hematological, cutaneous, constitutional, lymphadenopathy and lymphoma, and glandular) at Week 24 • Improvement from baseline in ≥3 of 5 composite of relevant endpoints for Sjogren's Syndrome (CRESS) categories at Week 24
Secondary	
Safety • To evaluate the safety of nipocalimab treatment versus placebo in participants with pSS	• Number and proportion of participants with treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), treatment-emergent serious adverse events (SAEs), and TEAEs leading to treatment discontinuations through end of study visit • Number and proportion of participants with clinically significant abnormalities in vital signs, and laboratory safety tests through end of study visit
Clinical Pharmacology • To evaluate the pharmacokinetics (PK) and immunogenicity of nipocalimab in participants with pSS	• Summary of serum concentrations of nipocalimab over time in participants receiving active study intervention • Incidence and titers of antibodies to nipocalimab (anti-drug antibodies [ADA] and neutralizing antibodies [NAb]) in participants receiving active study intervention
Clinical Biomarkers • To evaluate the effect of nipocalimab versus placebo on levels of serum biomarkers related to pSS	• Change from baseline in biomarkers, including but not limited to: CRP, total IgG, IgG1, IgG2, IgG3, IgG4, and autoantibodies (anti-Ro/SSA, anti-La/SSB, RF, and ANA)
Exploratory	
Clinical • To further evaluate the efficacy of nipocalimab in participants with pSS versus placebo	• Change from baseline in Physician Global Assessment of Disease Activity (PhGA) at Week 24 • Change from baseline in ESSPRI components over time through Week 24 • Change from baseline in DAS28 CRP over time through Week 24 in participants with at least 3 swollen and 3 tender joints at baseline

Objectives	Endpoints
	• Change from baseline in DAS28 CRP over time through Week 24 in participants with <3 swollen and 3 tender joints at baseline • Change in DAS28 CRP over time through Week 24 • Change from baseline in International Digit Symbol Substitution Test - Symbols (IDSSTS), Identification test, and Detection test scores over time through Week 24 • Sjogren's Syndrome Responder Index (SSRI) response defined as ≥20% improvement from baseline in at least two of five domains (fatigue, oral dryness, ocular dryness, unstimulated whole salivary flow, erythrocyte sedimentation rate) at Week 24 • SSRI response defined as ≥ 30% improvement from baseline in at least two of five domains (fatigue, oral dryness, ocular dryness, unstimulated whole salivary flow, and erythrocyte sedimentation rate [ESR]) over time through Week 24 • SSRI response defined as ≥ 30% improvement from baseline in at least three of five domains (fatigue, oral dryness, ocular dryness, unstimulated whole salivary flow, erythrocyte sedimentation rate) at Week 24
Patient Reported Outcomes (PROs) • To evaluate the effect of nipocalimab versus placebo on key pSS symptoms, impacts, and HRQoL	*Change from baseline over time through Week 24 in scores from the following PRO tools:* • HADS (Hospital Anxiety and Depression Scale) • Work Limitations Questionnaire (WLQ) • Sjogren's Symptoms (fatigue, ocular, oral and vaginal dryness as well as joint pain) • Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) questionnaire • Patient Global Impression of Severity (PGIS) of Sjögren's Syndrome • Patient Global Impression of Change (PGIC) in Sjögren's Syndrome • Short Form 36 (SF-36 v2) domains and summary scores for the physical component score (PCS) and mental component score (MCS)

Objectives	Endpoints
	• Patient's Global Assessment of Disease Activity (PtGA)
Pharmacodynamics • To explore the effects of nipocalimab on cellular, transcriptomic, and soluble biomarkers	• Total antibody (eg, IgG, IgM, IgA), IgG subclasses, and broader autoantibody profiling • Change in ESR and serum albumin levels • Serum biomarker measurements, for example, inflammatory proteins, complement, cytokines, and chemokines • Change in absolute number and frequency (eg, percent and absolute number of total leukocytes) of immune cell subsets in blood • Changes in gene expression profiles in blood (ribonucleic acid [RNA]) over time • Changes in autoantibody and soluble proteins in saliva and tears • Biopsy – changes in cellular infiltrates, soluble mediators of inflammation, and IgG levels by immunohistochemistry and other methods • Changes in gene expression profiles in the salivary gland tissue
Pharmacogenomics To explore genetic associations to response to nipocalimab	• Correlate treatment response with genetic polymorphisms
Digital Health To explore the effects of nipocalimab on physical activity and sleep measured by actigraphy	• Change from baseline in Actigraphy Watch collected continuous data on physical activity, mobility, and sleep over time
SICCA Signs	• Change from baseline in unstimulated salivary flow rate over time through Week 24 • Improvement from baseline in unstimulated salivary flow rate (especially participants with dryness and fatigue dominant phenotype) over time through Week 24 • Change from baseline in tear secretion amount using the Schirmer's Test over time through Week 24 • Change from baseline in frequency of use and the amount of artificial tears and/or saliva to treat dryness over time through Week 24 • Change from baseline in Ocular Surface Staining (OSS) at Week 24

Objectives	Endpoints
Steroid use	• Change from baseline in steroid use in comparison to mean doses between groups over time through Week 24

Hypothesis

The primary hypothesis of this study is that at least one of the two nipocalimab dose regimens is superior to placebo as measured by change from baseline in clinESSDAI at Week 24, in adult participants with moderately active pSS.

OVERALL DESIGN

This is a Phase 2, randomized, placebo-controlled, parallel, multicenter, double-blind interventional study in men and women between the ages of 18 to 75 years, inclusive, with active, autoantibody-positive pSS.

A placebo comparator (in addition to standard-of-care background therapy) will be used in this study through Week 22 to allow for blinded, placebo-controlled evaluation of the efficacy and safety of nipocalimab in participants with pSS.

At selected sites, an optional labial salivary gland biopsy substudy will be conducted to evaluate the molecular and histologic changes from baseline in participants with pSS. In addition, ocular surface staining (OSS) will be conducted at selected sites to assess the change in keratoconjunctivitis sicca (KCS) from baseline in participants with pSS.

Randomization will be carried out centrally using permuted block randomization, stratified by 1) baseline steroid use (Y/N), 2) anti-malarial use (Y/N), and 3) geographic region (eg, North America, Eastern Europe, Western Europe). Clinical and laboratory evidence of disease activity will be evaluated and assessed to verify that participants are meeting inclusion/exclusion criteria. The sites and sponsor will be blinded to treatment assignments and specified lab results following randomization.

Clinical and laboratory evidence of disease activity will be evaluated and assessed by a committee of the sponsor or designee to verify that participants are meeting inclusion/exclusion criteria and to ensure data quality and consistency.

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

The primary efficacy analysis will be performed after all participants have completed Week 24 efficacy assessments (or discontinued). A final database lock (DBL) is planned at Week 30 and includes 6 weeks of follow-up after the Final Efficacy Visit. An interim analysis committee will perform an early interim review of PD data in a small subset of approximately 30 participants that complete 8 weeks of study intervention and will perform a second interim review of available efficacy data of approximately 100 participants, or 67% at Week 24 to enable future study planning.

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

Key safety assessments include adverse event (AE)s, serious adverse event (SAE)s, adverse events of special interest (AESI), clinical laboratory parameters (hematology, chemistry, including lipid panel, and urinalysis), vital signs, systolic and diastolic blood pressures over time, and AEs temporally associated with infusion, including hypersensitivity reactions.

A final database lock (DBL) is planned at Week 30. The end of the study is defined as the last follow-up assessment (8 weeks after the last infusion of study intervention) for the last participant.

A Data Monitoring Committee (DMC) will be commissioned for safety reviews of this study. A separate interim analysis committee (IAC) will be commissioned for interim analysis of PD and efficacy data.

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

NUMBER OF PARTICIPANTS

A target of approximately 150 participants will be enrolled in this study. Participants will be randomly assigned into 3 treatment groups in a 1:1:1 ratio with 50 participants planned in each of the placebo, nipocalimab 5 mg/kg, and 15 mg/kg groups.

INTERVENTION GROUPS AND DURATION

The total duration of the study is up to 36 weeks and consists of 3 study periods: a ≤6-week screening period, a 24-week double blind treatment period, and an 6-week follow-up period (8 weeks post last study intervention administration).

Group 1: placebo IV every 2 weeks (q2w)

Participants will receive placebo IV q2w through Week 22.

Group 2: nipocalimab 5 mg/kg IV q2w

Participants will receive nipocalimab 5 mg/kg IV q2w through Week 22.

Group 3: nipocalimab 15 mg/kg IV q2w

Participants will receive nipocalimab 15 mg/kg IV q2w through Week 22.

EFFICACY EVALUATIONS

Investigator assessments and patient-reported outcomes (PROs) of efficacy include the following:

- ESSDAI/ClinESSDAI
- Joint count assessment
- Schirmer's Test
- Ocular Staining Score (OSS)
- Unstimulated Salivary Flow Test
- Physician's Global Assessment of Disease Activity (PhGA)
- International Digit Symbol Substitution Test - Symbols (IDSSTS)
- Detection Test
- Identification Test
- PRO measures to assess: ESSPRI, FACIT-Fatigue, Sjögren's Symptoms (SS), PGIS, PGIC, SF-36 v2, Hospital Anxiety and Depression Scale (HADS), WLQ, PtGA

PHARMACOKINETIC EVALUATIONS

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

IMMUNOGENICITY EVALUATIONS

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

PHARMACODYNAMIC AND BIOMARKER EVALUATIONS

Pharmacodynamic markers will be evaluated using blood, saliva and tear samples collected at visits as indicated in the SoA. Biomarker assessments will be made to examine the biological response to treatment and to identify biomarkers that are relevant to nipocalimab treatment response and/or pSS, where local regulations permit. Assessments will include the evaluation of relevant biomarkers in serum, plasma, whole blood, saliva, tears, peripheral blood mononuclear cells, and salivary gland biopsy samples (optional) collected as specified in the SoA where local regulations permit.

PHARMACOGENOMIC (DNA) EVALUATIONS

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

SAFETY EVALUATIONS

Key safety assessments include AEs, SAEs, AESI, laboratory parameters (hematology and chemistry, including lipid panel, and urinalysis), vital signs, systolic and diastolic blood pressures over time, and AEs temporally associated with infusion, including hypersensitivity reactions.

STATISTICAL METHODS

Sample Size Determination

The primary endpoint is change from baseline in clinESSDAI at Week 24. Based on a previous external study (abatacept study), the standard deviation (SD) of this endpoint was 6.4 to 6.6. Assuming a SD of 7, the power estimates for detecting a clinically meaningful improvement of 4 points at a 2-sided level of significance of 0.10 is 88.3% with a sample size of 50 participants per group.

Statistical Analyses

General Considerations

Simple descriptive summary statistics, such as n, mean, SD, median, IQ range, minimum, and maximum for continuous variables, and counts and percentages for discrete variables will be used to summarize most data. In addition, graphical data displays (eg, line plots) and participant listings may also be used to summarize/present the data.

The chi-squared test or Cochran-Mantel-Haenszel (CMH) test stratified by stratification factors will be used to compare categorical variables such as the proportion of participants responding to treatment, unless otherwise stated. In general, ANOVA with the stratification factors as independent variables will be used for analyzing continuous variables, unless otherwise stated. All statistical tests will be performed at α=0.10 (2-sided).

Efficacy analyses and study population summaries will be based on the Full Analysis Set, which is defined as all randomized participants who received at least one dose of study intervention, unless otherwise stated. Participants included in the efficacy analyses will be summarized according to their assigned intervention group regardless of whether or not they receive the assigned intervention.

Safety, PK and immunogenicity analyses will be based on the Safety Analysis Set, PK Analysis Set, and Immunogenicity Analysis Set, respectively.

Primary Endpoint

The primary endpoint is change from baseline in clinESSDAI score at Week 24. The primary estimand is defined as follows:

- Treatment:
  - Nipocalimab 5 mg/kg q2w in addition to standard of care through Week 22
  - Nipocalimab 15 mg/kg q2w in addition to standard of care through Week 22
  - Placebo q2w in addition to standard of care through Week 22

Standard of care includes symptomatic medications/procedures (including ophthalmic drops, artificial tears and saliva, punctum plugs, and secretagogues), and/or one immunomodulator (Table 4), with or without low-dose glucocorticosteroids (≤10 mg/day prednisone equivalent).

- Population: Participants with pSS
- Variable: Change from baseline in clinESSDAI at Week 24
- Intercurrent Events:
  - (1) Participants who experienced at least one of the following events will be considered Treatment Failures.
    - Discontinuation of study intervention prior to Week 24 for any reason
    - Initiation or increase medications for pSS
  - (2) Discontinuation of study intervention due to Coronavirus Disease 2019 (COVID-19) pandemic situation or confirmed COVID-19 infection

For both types of intercurrent events, hypothetical strategy which envisages that participants would not have these events will be used. Data from the time an intercurrent event occurred and onward will not be utilized.

- Population-level Summary: Difference in the means of the variable between treatment arms

The primary analysis will use MMRM with change from baseline in clinESSDAI at Week 24 as the dependent variable and baseline clinESSDAI, treatment, study visit, treatment by study visit interaction and stratification factors for randomization as independent variables. No missing data imputation will be performed explicitly. Comparisons will be carried out at a 2-sided 0.1 level of significance to evaluate the treatment difference between individual nipocalimab arms and placebo.

Given the hypothesis-generating nature of the study, no multiplicity control is planned.

The following sensitivity analyses will also be performed:

- Same analysis as the primary analysis but assume the participants with intercurrent event(s) to have 0 change from baseline. This analysis is corresponding to a supplementary estimand which is the same as the primary estimand but employs a composite strategy for the first type of intercurrent events (ie, Treatment Failures) assuming the worst outcome.
- Same analysis as the primary analysis but assume both types of intercurrent events have no impact on the treatment effect. Data points collected after intercurrent events will be included in the analysis. This analysis is corresponding to a treatment policy estimand.

Other sensitivity analyses will be specified in the statistical analysis plan (SAP).

Secondary Endpoints

The following major secondary endpoints will be summarized by treatment group. For between group comparisons, p-values will be reported. However, no multiplicity control is planned.

- Change from baseline in ESSPRI score at Week 24
- Improvement of ≥4 points from baseline in ESSDAI (minimal clinically important improvement) at Week 24
- Improvement of ≥4 points from baseline in clinESSDAI score (minimal clinically important improvement) at Week 24
- ESSPRI response defined as a decrease of one point or a decrease of ≥15% from baseline (minimal clinically important improvement) at Week 24
- Disease response according to the STAR composite score at Week 24
- Improvement in disease activity level in at least one clinESSDAI or ESSDAI domain (biological, hematological, cutaneous, constitutional, lymphadenopathy and lymphoma, and glandular) at Week 24
- Improvement from baseline in ≥3 of 5 Composite of Relevant Endpoints for Sjogren's Syndrome (CRESS) categories at Week 24

Safety Endpoints

- **Adverse Events**

Any AE occurring at or after the initial administration of study intervention through the end of the study is considered to be treatment emergent. All reported treatment-emergent AEs, SAEs, and AESIs will be included in the analysis. For each AE, the proportion of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an AE, or who experience a severe or an SAE.

- **Clinical Laboratory Tests**

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

- **Vital Signs**

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

- **Weight**

Descriptive statistics of changes from baseline will be summarized at each scheduled time point.

Other Analyses

Pharmacokinetic Analyses

Serum nipocalimab concentrations over time will be summarized for each treatment group using descriptive statistics. Descriptive statistics will be calculated at each sampling timepoint.

If sufficient data are available, a population PK analysis using a nonlinear mixed-effects modeling approach will be used to characterize the disposition characteristics of nipocalimab. Details will be given in a population PK analysis plan, and the results of the population PK analysis will be presented in a separate technical report.

Immunogenicity Analyses

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

The incidence of neutralizing antibodies (NAbs) to nipocalimab will be summarized for participants who are positive for antibodies to nipocalimab and have samples evaluable for NAbs.

Biomarkers Analyses

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

Pharmacokinetic/Pharmacodynamic Analyses

If data permit, the relationship between serum concentrations of nipocalimab and the efficacy measures and/or relevant PD biomarkers/endpoints may be explored when appropriate. If any visual trend is observed, additional analysis may be conducted. Analyses results may be summarized in a separate technical report.

Pharmacogenomic Analyses

Genetic (deoxyribonucleic acid [DNA]) analyses may be conducted only in participants who sign the consent form to participate in the pharmacogenomic sampling. These analyses are considered exploratory and may be summarized in a separate technical report.

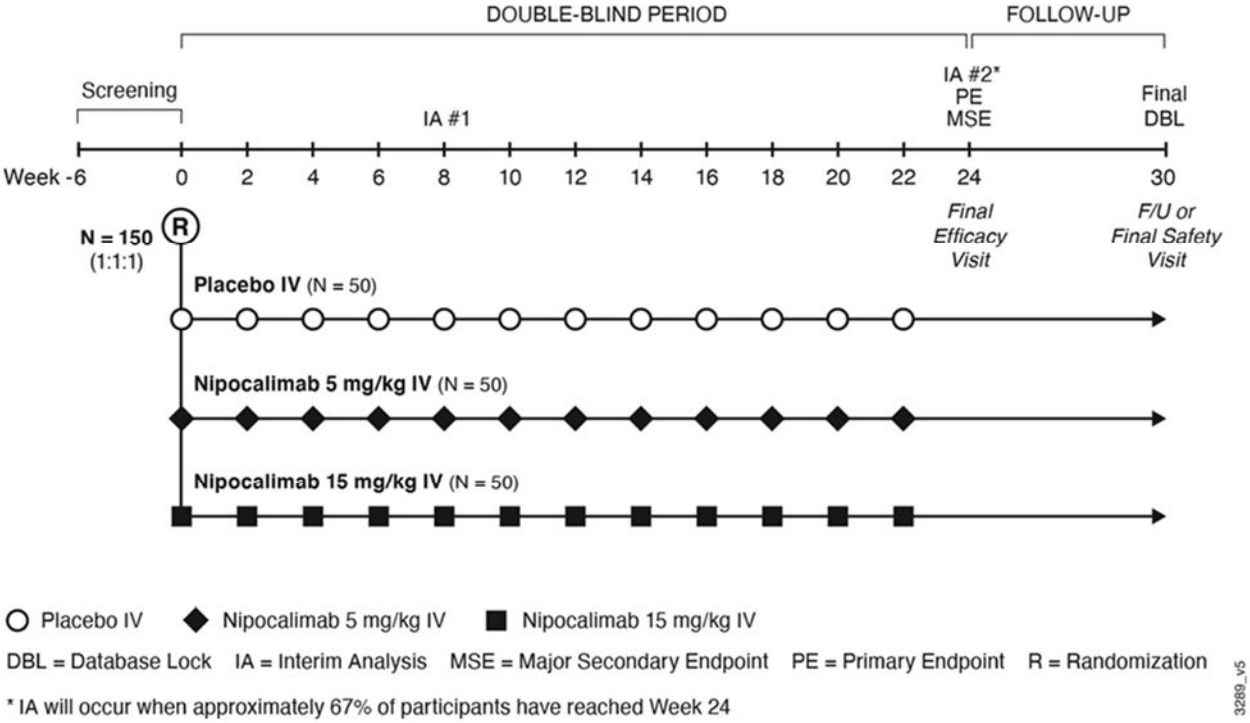
Digital Health - Actigraphy Analyses

The raw data sampled by the actigraphy watch sensors will be transformed into derived digital health endpoints, assessing the changes from baseline on physical activity, mobility and sleep parameters through Week 24. Endpoints include, but are not limited to, step count, activity count, sleep time, sleep efficiency, and percent mobile time.

Additional actigraphy endpoints may be derived using emerging algorithms. Associations between actigraphy endpoints and primary and secondary endpoints may be explored. All actigraphy-related analyses are considered exploratory and will be summarized in a separate technical report.

1.2. Schema

Figure 1: Schematic Overview of the Study



1.3. Schedule of Activities (SoA)

Table 1: 80202135SJS2001 SOA Screening through Week 12

									Notes:
Period	**Screening[a]**	**Placebo-controlled**							
Timeframe (Weeks)	**≤6**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	
Visit Window (days)		±3 days							
Study Procedure[b]									
Screening/Administrative									
Informed consent (ICF)	X								Must be signed prior to first study-related activity.
ICF for optional genetic research samples	X								
ICF for optional salivary gland biopsy substudy	X								Only for selected sites, if feasible
Demographics	X								
Review of Medical History	X								Will include detailed history of pSS manifestations and evaluations
Height	X								
Inclusion/exclusion criteria	X	X							At Week 0, criteria defined in Section 5.4 must also be met prior to randomization of a participant.
Review prestudy therapy	X								
Pre-planned surgery/procedure(s)	X								
pSS classification by 2016 ACR-EULAR Classification Criteria	X								
Peripheral blood smear	X								
HIV, HBV, HCV testing	X								Includes screening for HIV-1 and 2 antibodies, HBV, HBsAg, anti-HBc and anti-HBs, HCV antibodies.
12-lead ECG	X								
Chest X-ray (locally)	X								Chest radiograph within 3 months prior to the first administration of study intervention.
FSH	X								For female participants exhibiting amenorrhea for less than 12 months
Study Intervention Administration									
Randomization		X							
Administer study intervention by infusion		X	X	X	X	X	X	X	

Table 1: 80202135SJS2001 SOA Screening through Week 12									
									Notes:
Period	**Screening[a]**	**Placebo-controlled**							
Timeframe (Weeks)	**≤6**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	
Visit Window (days)		±3 days							
Study Procedure[b]									
Efficacy Assessments									
Patient-reported Outcomes (PRO)									
ESSPRI	X	X	X	X	X	X	X	X	Whenever possible, PRO assessments should always be conducted in the order as outlined here and in Section 8.
FACIT-Fatigue	X	X		X		X		X	
Sjögren's Symptoms	X	X		X		X		X	
Patient Global Impression of Severity (PGIS) Sjögren's Syndrome	X	X		X		X		X	
Patient Global Impression of Change (PGIC) Sjögren's Syndrome				X		X		X	
SF-36 v2	X	X		X		X		X	
Hospital Anxiety and Depression Scale (HADS)	X	X		X		X		X	
Work Limitations Questionnaire (WLQ)		X				X		X	
Patient's Global Assessment of Disease Activity (PtGA)	X	X		X		X		X	
Clinician-reported Outcome (ClinRO)									ClinRO portion to be completed by the same investigator/designee at each visit. Refer to Section 8 and Table 5 for the assessor assignments, permitted substitutions and the order of assessments.
Joint count assessment	X	X	X	X		X		X	
ClinESSDAI/ESSDAI	X	X	X	X		X		X	Carefully use the instructions accompanying the disease activity indices to ensure that the assessment avoids inappropriately assessing pSS activity as damage or damage as activity, in the context of the pSS history.
Schirmer's Test	X	X	X	X		X		X	Every effort should be made to perform this evaluation at approximately the same time of day at each visit. The test strips should be frozen for exploratory biomarker analyses.
Ocular Staining Score (OSS)		X							Performed on participants enrolled at selected sites only. OSS may be done ≤5 days in advance of study visit.
Unstimulated Salivary Flow Test	X	X	X	X		X		X	Every effort should be made to perform this evaluation at approximately the same time of day at each visit. The saliva

Table 1: 80202135SJS2001 SOA Screening through Week 12									
									Notes:
Period	**Screening[a]**	**Placebo-controlled**							
Timeframe (Weeks)	**≤6**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	
Visit Window (days)		±3 days							
Study Procedure[b]									
									collected should be saved and frozen for biomarker analyses.
Physician's Global Assessment of Disease Activity (PhGA)	X	X	X	X		X		X	The investigator should be blinded to all PRO results when completing the PhGA.
Performance Outcome assessments (PerfO)									
International Digit Symbol Substitution Test - Symbols (IDSSTS)	X	X	X	X	X	X	X	X	Familiarization with PerfO tests will occur during screening visit or Week 0. No data will be collected from the familiarization session. If the familiarization session is not completed at the screening visit, then it must be completed ≥15 minutes before the Week 0 PerfO tests and prior to any Week 0 assessments.
Detection Test	X	X	X	X	X	X	X	X	
Identification Test	X	X	X	X	X	X	X	X	
Safety Assessments									
Full physical examination	X								Details for full and targeted physical examinations are in Section 8.4.1
Targeted physical examination		X	X	X		X		X	
Vital signs	X	X	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	X	Needed for IV preparation (dose calculation)
Pregnancy test	X	X	X	X	X	X	X	X	For females of childbearing potential only
Infusion reaction evaluation		X	X	X	X	X	X	X	Participants will be observed at the study site for safety during and for 1 hour after the first 3 infusions (Week 0, Week 2, and Week 4); if no clinically relevant AEs related to the infusion are observed with the first 3 infusions, the post-infusion period may be reduced to 30 minutes post-infusion for the remaining intervention administrations.
Concomitant therapy	X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	
Clinical Laboratory Tests									
Hematology	X	X	X	X		X		X	
Serum chemistry	X	X	X	X		X		X	
Circulating Immune Complex (CIC)	X	X	X	X		X		X	
Lipid panel	X	X[e]		X[e]		X[e]		X[e]	Nonfasting lipid panel (at screening only) includes total cholesterol, HDL, LDL (calculated), VLDL, and triglycerides.

Table 1: 80202135SJS2001 SOA Screening through Week 12									
									Notes:
Period	**Screening[a]**	**Placebo-controlled**							
Timeframe (Weeks)	**≤6**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	
Visit Window (days)		±3 days							
Study Procedure[b]									
									Fasting lipid panel (at baseline, Week 4, Week 8, Week 12) includes total cholesterol, HDL, LDL (calculated), VLDL, and triglycerides. Fasting is recommended for at least 6 hours unless medically contraindicated.
Lipoprotein panel		X		X		X		X	Includes apolipoprotein-B, -A1, -A2, ratio of apolipoprotein B: A1 ratio, and lipoprotein-a
Sjogren's Autoantibody panel	X	X	X	X		X		X	Anti-Ro/SSA (may be performed locally during screening, as needed, when approved by the sponsor), anti-La/SSB, ANA, RF
Urine protein/creatinine ratio	X	X	X	X		X		X	
ESR (locally)	X	X	X	X		X		X	Performed at the site
CRP	X	X	X	X	X	X	X	X	Refers to the high sensitivity (hs)-CRP assay
Immunoglobulin (Ig) Profile	X	X	X	X		X		X	Includes total Ig isotypes, total IgG, and IgG subclasses
Urinalysis	X	X	X	X		X		X	Include microscopic analysis and dipstick
aPTT	X	X	X	X		X		X	
PT/INR	X	X						X	
C3, C4, CH50 (total complement)	X	X	X	X		X		X	
Other Autoantibody Profile	X								The profile includes among others, anti-Smith, anti-phospholipid, anti-dsDNA, and anti-nRNP
Cryoglobulins (locally, where feasible)	X	X[e]		X[e]		X[e]		X[e]	Participants should be in a fasting condition unless medically contraindicated (ie, no food or beverages [except water]) for at least 6 hours before blood is drawn for laboratory testing. See lab manual for additional details.
Serum globulin profile		X		X		X		X	Includes α-1 antitrypsin, sex hormone-binding globulin, α-1 acid glycoprotein, transferrin, retinol binding protein, thyroglobulin
Serum protein electrophoresis (SPEP)	X	X	X	X		X		X	with monoclonal gammopathy and light chain evaluation
Free light chains (Freelite) and free light chain ratio (kappa:lambda)	X	X	X	X		X		X	

Table 1: 80202135SJS2001 SOA Screening through Week 12									
									Notes:
Period	**Screening[a]**	**Placebo-controlled**							
Timeframe (Weeks)	**≤6**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	
Visit Window (days)		±3 days							
Study Procedure[b]									
Thyroid function panel	X							X	Includes TSH, total T4, free T4, free T3
D-dimer		X						X	
Clinical Pharmacology Assessments									
Serum nipocalimab concentration[c]		2X	2X	X		2X		2X	See footnote "c" for more details on Clinical Pharmacology assessments. *One random (other than the scheduled) nipocalimab concentration sample, will be collected from all participants any time between 3 to 7 days after the Week 0 or Week 2 visit. No pregnancy test required at this visit.
Random nipocalimab concentration sample[c]		←X*→							
Antibodies to nipocalimab[c]		X	X	X		X		X	
Biomarkers (where local regulations permit)[d]									
Plasma sample collection for complement	X	X	X	X		X			
Whole blood sample for RNA	X	X	X	X		X			
Whole blood sample for PBMC		X		X					
Serum biomarker profiling (eg, cytokine analysis, antibody profiling)	X	X	X	X		X			
Saliva for biomarker profiling	X	X	X	X		X			
Minor salivary gland biopsy (optional sub-study)	X								The time between the biopsy and Week 0 should be ≥11 days
Digital Health									
Actigraph data collection	X	X	X	X	X	X	X	X	Approximately 150 participants will be provided the option to wear an Actigraphy wrist-worn device during the study to collect continuous data on physical activity, mobility, and sleep.
Pharmacogenomics (DNA; where local regulations permit)									
Whole blood sample collection (optional)		X							The sample should be collected prior to dosing (either at screening or first study visit). When necessary, it is permitted to collect the sample (prior to administration of study intervention) at a later visit.

Abbreviations: ACR = American College of Rheumatology; ADA = anti-drug antibodies; AE = adverse events; aPTT = activated partial thromboplastin time; β-hCG = B-human chorionic gonadotropin; clinESSDAI = clinical EULAR Sjögren's syndrome disease activity index; ESSPRI = EULAR Sjogren's Syndrome Patient Reported Index; dsDNA = double stranded

deoxyribonucleic acid; ECG = electrocardiogram; ESSDAI = EULAR Sjögren's syndrome disease activity index; EULAR = European League Against Rheumatism; FACIT-Fatigue = Functional Assessment of Chronic Illness Therapy-Fatigue Scale; FSH = Follicle-stimulating Hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HDL=high-density lipoproteins; HIV = human immunodeficiency virus; ICF = Informed Consent Form; Ig = immunoglobulin; IV = intravenous; LDL=low-density lipoproteins; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic(s); RNA = ribonucleic acid; PT = Prothrombin time; RNP = ribonucleoprotein; SF-36 = Short Form 36-item; SoA = Schedule of Activities; SSA = Sjogren's syndrome-related antigen A; SSB = Sjogren's syndrome-related antigen B; UPCR = urine protein/creatinine ratio

a. The Screening visit must be performed no more than 6 weeks (+ 3 days if approved by the sponsor) prior to the randomization visit (Week 0).
b. Participants who discontinue study intervention administration and do not wish to continue the study should complete their Week 24 visit assessments at their next scheduled visit and should return 8 weeks after their last study intervention administration for the final safety visit. Participants who discontinue study intervention administration but do not withdraw from study participation should be encouraged to follow all subsequent study visits through Week 30. Week 24 may serve as the final safety follow-up visit if study intervention was stopped on or before Week 16, but a full physical examination should be performed along with the other Week 24 assessments.
c. (1) 2X means 2 samples 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 infusion) for all participants. The sample should be drawn from the opposite arm than the IV line. For all other visits, only a predose serum nipocalimab concentration sample will be collected.
   (2) For visits with study intervention administration, all blood samples for assessing predose nipocalimab concentration and antibodies to nipocalimab MUST be collected BEFORE the administration of the study intervention.
   (3) One random 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.
   (4) When both PK/ADA samples are collected, one sample (instead of 2) will be collected for both assays.
d. For visits with study intervention administration, all clinical laboratory test and biomarker samples on visits MUST be collected BEFORE the administration of the study intervention.
e. Fasting should be for at least 6 hours unless medically contraindicated.

Table 2: 80202135SJS2001 SOA Week 14 through Week 30								
								Notes:
Period	**Placebo-controlled**							
Timeframe (Weeks)	**14**	**16**	**18**	**20**	**22**	**24/Final Efficacy Visit**	**30 or Final Safety Follow-up Visit**	
Visit Window (days)	±3 days						±7 days	
Study Procedure[a]								
Study Intervention Administration								
Administer study intervention by infusion	X	X	X	X	X			
Efficacy Assessments								
Patient-reported Outcomes (PRO)								
ESSPRI	X	X	X	X	X	X		Whenever possible, PRO assessments should always be conducted in the order as outlined here and in Section 8.
FACIT-Fatigue		X		X		X		
Sjögren's Symptoms		X		X		X		
Patient Global Impression of Severity (PGIS) Sjögren's Syndrome		X		X		X		
Patient Global Impression of Change (PGIC) Sjögren's Syndrome		X		X		X		
SF-36 v2		X		X		X		
Hospital Anxiety and Depression Scale (HADS)		X		X		X		
Work Limitations Questionnaire (WLQ)						X		
Patient's Global Assessment of Disease Activity (PtGA)		X		X		X		
Exit Interview						X		Interviews to be conducted within 2 weeks of final treatment visit or upon early termination.
Clinician-reported Outcome (ClinRO)								ClinRO portion to be completed by the same investigator/designee at each visit. Refer to Section 8 and Table 5 for the assessor assignments, permitted substitutions, and the order of assessments.
Joint count assessment		X		X		X		
ClinESSDAI/ESSDAI		X		X		X		Carefully use the instructions accompanying the disease activity indices to ensure that the assessment avoids inappropriately assessing pSS activity as damage or damage as activity, in the context of the pSS history.

Table 2: 80202135SJS2001 SOA Week 14 through Week 30								
								Notes:
Period	**Placebo-controlled**							
Timeframe (Weeks)	**14**	**16**	**18**	**20**	**22**	**24/Final Efficacy Visit**	**30 or Final Safety Follow-up Visit**	
Visit Window (days)	±3 days						±7 days	
Study Procedure[a]								
Schirmer's Test		X		X		X	X	Every effort should be made to perform this evaluation at approximately the same time of day at each visit. The test strips should be frozen for exploratory biomarker analyses.
Ocular Staining Score (OSS)						X		Performed on participants enrolled at selected sites only. OSS may be done ≤5 days in advance of study visit.
Unstimulated Salivary Flow Test		X		X		X	X	Every effort should be made to perform this evaluation at approximately the same time of day at each visit. The saliva collected should be saved and frozen for biomarker analyses.
Physician's Global Assessment (PhGA)		X		X		X		The investigator should be blinded to all PRO results when completing the PhGA.
Performance Outcome assessments (PerfO)								
International Digit Symbol Substitution Test - Symbols (IDSSTS)	X	X	X	X	X	X		
Detection test	X	X	X	X	X	X		
Identification test	X	X	X	X	X	X		
Safety Assessments								
Full physical examination							X	Details for full and targeted physical examinations are in Section 8.4.1.
Target physical examination		X		X		X		
Vital signs	X	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	Needed for IV preparation (dose calculation)
Pregnancy test	X	X	X	X	X	X	X	For females of childbearing potential only.
Infusion reaction evaluation	X	X	X	X	X			Participants will be observed for safety during and for 1 hour after the first 3 infusions at the study site (Week 0, Week 2, and Week 4); if no clinically relevant AEs related to the infusion are observed with the first 3 infusions, the post-infusion period may be reduced to 30 minutes post-infusion for the remaining intervention administrations.
Concomitant therapy	X	X	X	X	X	X	X	

Table 2: 80202135SJS2001 SOA Week 14 through Week 30								
								Notes:
Period	**Placebo-controlled**							
Timeframe (Weeks)	**14**	**16**	**18**	**20**	**22**	**24/Final Efficacy Visit**	**30 or Final Safety Follow-up Visit**	
Visit Window (days)	±3 days						±7 days	
Study Procedure[a]								
Adverse events	X	X	X	X	X	X	X	
Clinical Laboratory Tests								
Hematology		X		X		X	X	
Serum chemistry		X		X		X	X	
Circulating Immune Complex (CIC)		X		X		X	X	
Lipid Panel						X[d]		Fasting lipid panel (at Week 24) includes total cholesterol, HDL, LDL (calculated), VLDL, and triglycerides.
Lipoprotein Panel						X	X	Includes apolipoprotein-B, -A1, -A2, ratio of apolipoprotein B: A1 ratio, and lipoprotein-a
Sjogren's Autoantibody panel		X		X		X	X	Anti-Ro/SSA, anti-La/SSB, ANA, RF
Urine protein/creatinine ratio		X		X		X	X	
ESR (locally)		X		X		X	X	Performed at the site
CRP		X		X		X	X	Refers to the hs-CRP assay
Immunoglobulin (Ig) Profile		X		X		X	X	Includes total Ig isotypes, total IgG, and IgG subclasses
Urinalysis		X		X		X	X	Include microscopic analysis and dipstick
aPTT		X		X		X	X	
PT/INR						X	X	
C3, C4, CH50 (total complement)		X		X		X	X	
Other Autoantibody Profile						X		This profile includes among others, anti-Smith, anti-phospholipid, anti-dsDNA, and anti-nRNP
Cryoglobulins (locally, where feasible)						X[d]		Participants should be in a fasting condition unless medically contraindicated (ie, no food or beverages [except water]) for at least 6 hours before blood is drawn for laboratory testing. See lab manual for details.

Table 2: 80202135SJS2001 SOA Week 14 through Week 30								
								Notes:
Period	**Placebo-controlled**							
Timeframe (Weeks)	**14**	**16**	**18**	**20**	**22**	**24/Final Efficacy Visit**	**30 or Final Safety Follow-up Visit**	
Visit Window (days)	±3 days						±7 days	
Study Procedure[a]								
Serum globulin profile						X	X	Includes a-1 antitrypsin, sex hormone-binding globulin, a-1 acid glycoprotein, transferrin, retinol binding protein, thyroglobulin
Serum protein electrophoresis (SPEP)		X		X		X	X	with monoclonal gammopathy and light chain evaluation
Free light chains (Freelite) and free light chain ratio (kappa:lambda)		X		X		X	X	
Thyroid function panel						X	X	Includes TSH, total T4, free T4, free T3
D-dimer						X	X	
Clinical Pharmacology Assessments								
Serum nipocalimab concentration[b]		X				X	X	See footnote "b" for details on PK and immunogenicity assessments.
Antibodies to nipocalimab[b]		X				X	X	
Biomarkers (where local regulations permit)[c]								
Plasma sample collection for complement		X				X	X	
Whole blood sample for RNA		X				X	X	
Whole blood sample for PBMC						X	X	
Serum biomarker profiling (eg, cytokine analysis, antibody profiling)		X				X	X	
Saliva for biomarker profiling		X				X	X	
Minor salivary gland biopsy (optional sub-study)						X		
Digital Health								
Actigraph data collection	X----------X							
Pharmacogenomics (DNA; where local regulations permit)								
Whole blood sample collection (optional)						X		

Abbreviations: ACR = American College of Rheumatology; ADA = anti-drug antibodies; AE = adverse events; aPTT = activated partial thromboplastin time; β-hCG = B-human chorionic gonadotropin; clinESSDAI = clinical EULAR Sjögren's syndrome disease activity index; ESSPRI = EULAR Sjogren's Syndrome Patient Reported Index; dsDNA = double stranded deoxyribonucleic acid; ECG = electrocardiogram; ESSDAI = EULAR Sjögren's syndrome disease activity index; EULAR = European League Against Rheumatism; FACIT-Fatigue =

Functional Assessment of Chronic Illness Therapy-Fatigue Scale; FSH = Follicle-stimulating Hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HDL=high-density lipoproteins; HIV = human immunodeficiency virus; ICF = Informed Consent Form; Ig = immunoglobulin; IV = intravenous; LDL=low-density lipoproteins; OSS = Ocular Staining Score; PBMC = peripheral blood mononuclear cells; PK = pharmacokinetic(s); PT = Prothrombin time; RNA = ribonucleic acid RNP = ribonucleoprotein; SF-36 = Short Form 36-item; SoA = Schedule of Activities; SSA = Sjogren's syndrome-related antigen A; SSB = Sjogren's syndrome-related antigen B; UPCR = urine protein/creatinine ratio;

a. Participants who discontinue study intervention administration and do not wish to continue the study should complete their Week 24 visit assessments at their next scheduled visit and should return 8 weeks after their last study intervention administration for the final safety visit. Participants who discontinue study intervention administration but do not withdraw from study participation should be encouraged to follow all subsequent study visits through Week 30. Week 24 may serve as the final safety follow-up visit if study intervention was stopped on or before Week 16, but a full physical examination should be performed along with the other Week 24 assessments.
b. (1) 2X means 2 samples 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 infusion) for all participants. The sample should be drawn from the opposite arm than the IV line. For all other visits, only a predose serum nipocalimab concentration sample will be collected.
   (2) For visits with study intervention administration, all blood samples for assessing predose nipocalimab concentration and antibodies to nipocalimab MUST be collected BEFORE the administration of the study intervention.
   (3) When both PK/ADA samples are collected, one sample (instead of 2) will be collected for both assays.
c. For visits with study intervention administration, all clinical laboratory test and biomarker samples on visits MUST be collected BEFORE the administration of the study intervention.
d. Fasting should be for at least 6 hours unless medically contraindicated.

2. INTRODUCTION

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

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

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

Since nipocalimab use results in a decrease in circulating IgG antibody concentrations, including pathogenic IgG antibody concentrations, and associated inflammatory pathways, this approach is felt useful to explore for the treatment of pSS.

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

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

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

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

2.1. Study Rationale

Sjogren's syndrome may occur alone (pSS) or with a comorbid autoimmune condition (secondary Sjogren's syndrome [sSS]), and disease severity can vary. Sjogren's syndrome is a chronic, progressive autoimmune disease of unclear etiology typically originating in exocrine glands and capable of affecting the function of almost any organ system in the body. Primary Sjogren's syndrome results from dysregulated humoral immunity characterized by abnormally high levels of IgG in the blood, the production of auto-reactive IgG, and abnormal B lymphocyte activity (Nocturne 2013). Patients with elevated levels of anti-Ro/SSA autoantibodies in circulation exhibit more severe end-organ involvement in the disease and require glucocorticoid or other immunosuppressive drugs more frequently. The estimated incidence of pSS is approximately 6.92 per 100,000 person-years, and its prevalence is approximately 60.8 per 100,000 persons (Qin 2015). The disease is observed with a ~10-fold greater prevalence in women, and usually appears during the 4th to 7th decade of life, though it can present in adolescent or young adult women and men and very rarely in children (Qin 2015).

Sjogren's syndrome is characterized by autoantibody production, inflammation, and lymphocytic infiltration of exocrine glands, including lacrimal and salivary glands, resulting in the formation of germinal center-like structures in these glands, where high affinity IgG autoantibodies are produced (Nocturne 2013). These circulating IgG autoantibodies and the immune complexes they form activate humoral and cellular immune processes, including the aberrant activation of local and circulating B cells and other immune cells which culminates in systemic tissue damage and local destruction of salivary, lacrimal, and other exocrine glands. Together, these processes lead to a variety of pSS symptoms, including xerostomia (dry mouth) and keratoconjunctivitis sicca (eye dryness), among others. Additional systemic or extraglandular manifestations may also occur, including fatigue, musculoskeletal symptoms, cutaneous lesions, and internal organ involvement (Section 2.1.1). Because the nipocalimab mechanism of action, specifically, blocking the binding site for IgG on FcRn, leads directly to increased IgG catabolism and a decrease in circulating IgG antibody concentrations, including pathogenic IgG antibody concentrations, and directly inhibits inflammatory cellular responses to these pathogenic IgG, nipocalimab may successfully treat pSS disease pathology and manifestations. Importantly, studies pursuing a similar approach for systemic lupus erythematosus, which is similarly mediated by autoantibodies (ie, anti-double stranded DNA, etc), are currently being initiated.

Systemic disease activity in pSS is evaluated using composite scores and patient reported outcomes. The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) which consists of 12 domains, 11 related to organ involvement and one biological domain reflecting B-cell activity, including elevated circulating IgG levels (Seror 2010). ClinESSDAI includes the same domains as the ESSDAI but excludes the biological domain (Seror 2016). The weightings of the remaining pSS disease domains of clinESSDAI were re-calculated, and the score has been psychometrically

validated against ESSDAI (Seror 2016). The statistical reliability and sensitivity of clinESSDAI to change in disease activity are similar to those of ESSDAI (Seror 2016). Multiple clinical studies of medications in pSS have utilized the ESSDAI in primary (ESSDAI only) or secondary (ESSDAI or clinESSDAI) endpoints almost uniformly with negative results. Multiple efforts have since then aimed to develop new tools for use in clinical studies, but none are validated as of this protocol submission. At least one such tool, the "Composite of Relevant Endpoints for Sjogren's Syndrome" (CRESS), incorporates measures of disease activity (clinESSDAI), symptoms (ESSPRI), glandular function and systemic inflammation to assess disease activity (Arends 2020). Similarly, the "Sjögren's Tool for Assessing Response" (STAR), incorporates identical measures as CRESS but was developed by different methods with unique definitions of improvement (Seror 2022). In summary, all of these endpoints have some degree of validation in the context of clinical studies, but none are registrationally accepted and all require further study to fully delineate their performance characteristics (eg, consistency, redundancy, relative sensitivity to change in disease status, and pSS disease domains). These challenges with disease assessment and endpoints in studies highlights the degree of unmet need in pSS, not just for therapeutics, but for rigorous clinical and experimental methods. To this end and in order to prepare for registrational clinical studies, this proof-of-concept study will evaluate a broad constellation of pSS endpoints. The mechanism of action of nipocalimab uniquely positions this study to comparatively evaluate multiple possible pSS endpoints.

2.1.1. Unmet Need in Sjogren's Syndrome

There is a high unmet need for new treatment options in pSS that are safe and effective, especially new therapies that demonstrate improved long-term efficacy (ie, induce and maintain sustained remission) over currently available therapies. In patients with pSS, the pathogenic autoantibodies and associated immune complexes that mediate pSS broadly induce inflammation and extra-glandular damage in diverse organs including the skin, joints, lungs, blood vessels, bone marrow, kidneys, central and peripheral nervous system, and lymphatic system, with overall approximately 70% of pSS patients experiencing extra-glandular manifestations (Both 2017). The standardized mortality ratio for pSS is 2.9 to 4.7, suggesting the disease impacts overall survival (Both 2017; Brito-Zeron 2016). Compared to healthy controls, these patients also carry ~5-fold higher risk of lymphoma, which is the extra-glandular SS manifestation associated with the highest mortality risk (Both 2017). Other serious extra-glandular complications associated with pSS occur more frequently, including skin rashes (23% to 67%), myalgia or myositis (~40%), articular inflammation (~50%), renal disease (~30%), neuropathy (~10%), and interstitial lung disease (~10% to 20%), with central nervous system involvement being less common (Both 2017). Patients with mild disease first experience dryness and fatigue, which can be present for years before a pSS diagnosis is made. The most common and disabling symptom experienced by patients with pSS is fatigue, occurring in up to 80% of individuals, with accompanying complaints of pain, depression, and anxiety. These symptoms together result in up to ~50% of working-age pSS patients being unable to work due to disability (Both 2017). Fatigue and systemic disease manifestations constitute the most commonly experienced morbidities in pSS patients.

The current medications comprising the standard of care in pSS can sometimes improve symptoms but do not alter the disease course or restore organ function. No therapy currently used in pSS has

been found in robust randomized placebo-controlled studies to be superior to placebo in treating this condition, and no disease-modifying anti-rheumatic drugs (DMARDs) are currently approved for pSS. This study is designed to test whether nipocalimab may mediate disease-modifying treatment effects in pSS with a favorable risk-benefit profile.

Study 80202135SJS2001 is a Phase 2 study designed to evaluate the efficacy and safety of nipocalimab in participants with pSS. This study will enroll a target of approximately 150 participants with a total duration of up to approximately 30 weeks.

An overview of the protocol design and supportive rationale is described in Section 4.

The clinical and scientific rationale in support of the overall development program is described in Section 2.1.

Relevant background information on the nonclinical and clinical development of nipocalimab is summarized in Section 2.2.

2.2. Background

Nonclinical Studies

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

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

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

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

Clinical Studies

Phase 1 Studies of IV Nipocalimab

Safety, PK, and PD data are available from 4 completed Phase 1 studies in healthy adult participants: a first-in-human (FIH) study of single ascending doses (SAD) up to 60 mg/kg and multiple ascending doses (MAD) up to 30 mg/kg weekly (MOM-M281-001), a single-dose infusion rate study (MOM-M281-007), a single-dose, dose-escalating study conducted in Japanese adults (MOM-M281-010), and a study to assess the drug-drug interaction (DDI) potential of nipocalimab with therapeutic IgG-based antibodies (MOM-M281-008).

Pharmacokinetic parameters for IV nipocalimab showed dose dependency and likely target mediated disposition. Across the SAD dose groups (0.3-60 mg/kg) maximum concentration (C_{max}) increased in a dose-proportional manner, whereas area under the concentration-time curve (AUC) increased in a greater than dose-proportional manner. Serum clearance (CL) decreased nearly 50% from 10 to 60 mg/kg while half-life ($t_{1/2}$) increased with increasing dose, from approximately 7.36 hours at 3 mg/kg to 32.2 hours at 60 mg/kg.

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

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

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

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

Phase 2 Studies of IV Nipocalimab

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

Consistent with its mechanism of action, nipocalimab produced dose-dependent, reversible decreases in mean total IgG values. Infusions of IV nipocalimab were generally safe and well-tolerated in this study with no deaths, discontinuations due to treatment-emergent AEs,

treatment-emergent AEs of Common Terminology Criteria for Adverse Events [CTCAE] ≥Grade 3, or adverse events of special interest (AESIs, infection or hypoalbuminemia ≥Grade 3). The overall incidence of treatment-emergent AEs was similar between the combined nipocalimab group (83.3%) and placebo group (78.6%). Three SAEs were reported during the study; an SAE of musculoskeletal pain was reported for one nipocalimab-treated patient (30 mg/kg q4w) and 2 SAEs (ischaemic stroke, myasthenia gravis) were reported in placebo-treated patients; none of the SAEs were considered by the investigator as related to the study intervention.

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

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

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

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

While a dose-dependent increase in the number of nipocalimab-treated patients with NAb was observed in gMG participants, NAb titers were low throughout the studies. Overall, IV administration of nipocalimab did not lead to a detectable clinically relevant immune response against nipocalimab. No definitive conclusions can be made regarding the impact of immunogenicity on PK due to the low sample sizes.

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

2.3. Benefit-Risk Assessment

Study 80202135SJS2001 is the first study conducted in participants with pSS. Therefore, the benefit-risk profile of nipocalimab in participants with pSS has not been established. The theoretical and potential risks of exposure to nipocalimab based on its mechanism of action are summarized in Table 3. More detailed information about the risks of nipocalimab may be found in the IB.

2.3.1. Risks for Study Participation

Table 3: Potential Risks for Nipocalimab

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Lack of clinical benefit/Clinical worsening of pSS	The benefit-risk of nipocalimab in treatment of pSS has not been established.	• During the study, participants will be permitted to continue treatment of pSS 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 protocol-prohibited medications including certain biologics (Sections 6.8.7 and 7.1). • Participants will be allowed to use glucocorticoids (GCs) as needed, although this may trigger a treatment failure (TF) if a high enough dose is required as detailed in Section 6.8.2.
Risks Due to Study Interventions		
Potential increased risk for infection due to decreased serum IgG concentrations	As predicted, based on its mechanism of action, 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 (Section 5.2). • Participants with serum IgG <6 g/L (<600 mg/dL) at screening will be excluded from the study. • Study intervention stopping criteria for profound hypogammaglobulinemia (confirmed serum total IgG <1 g/L [100 mg/dL]) and infections are included in Section 7.1. • All infections will be monitored closely and treatment-emergent infections meeting the AESI criteria must be reported to the sponsor within 24 hours (Section 8.5.6). • Participants who have had a live vaccine within 4 weeks before the first administration of study intervention, (or within 1 year of first administration of study

		intervention for bacilli Calmette-Guerin [BCG]), or have a known need to receive a live vaccine during the study, or within at least 8 weeks (including BCG) after the last dose of study intervention in this study are excluded from participation in the study (Section 5.2).
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 per routine local medical guidelines. • Non live vaccinations should be administered 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 or hepatitis B or C infections (Section 5.2). • Temporary and permanent study intervention stopping criteria for infections are included in Section 7.1. • Infections will be monitored closely; treatment-emergent infections meeting the AESIs criteria must be reported to the sponsor within 24 hours (Section 8.5.6).
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 should be reported as an AESI within 24 hours (Section 8.5.6) • Study intervention interruption rules for 3+ pedal edema, ascites, or pleural or pericardial effusions are included in the protocol (Section 7.1)

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. As of the data cutoff date of 28 April 2022, most infusion reactions have been mild or moderate in severity, and none have required hospitalization.	• Participants will be monitored for infusion reactions.
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 DDI study (MOM-M281-008) is completed as of the data cutoff date for the IB (28 April 2022). The DDI observed in this study was consistent with mechanism of action 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 drugs with both high protein binding rate (>95%) and narrow therapeutic index may lead to higher free drug concentrations which could increase the risk for potential toxicities. • Hydroxychloroquine (HCQ) may hypothetically reduce IgG lowering by nipocalimab.	• Participants who are on IgG Fc-containing protein therapeutics are excluded from the study (Section 5.2). • Participants treated with nipocalimab and who are on concomitant medications which have a high protein binding rate (>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. • A potential drug interaction of HCQ with nipocalimab on serum IgG concentration will be evaluated by an Interim Analysis Committee (IAC).
Increased lipids	• Elevations in total cholesterol and low-density lipoprotein (LDL) were reported recently with another experimental drug in the same pharmacological class of FcRn antagonists. • In the MOM-M281-001 and MOM-M281-004 studies, asymptomatic, dose dependent, reversible elevations in non-fasting mean total cholesterol were observed up to 25% of baseline. In both studies, elevations in total cholesterol appear to mirror the	• Participants with recent myocardial infarction (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, calculated LDL, HDL, VLDL, triglycerides) will be performed in the study.

	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.	• Lipid 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 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-treated groups and no nipocalimab-related developmental toxicity was identified. • As of 31 December 2020, one participant with intrauterine growth restriction and another with placental abruption have been reported from a study involving antenatal treatment of pregnant women at risk of EOS-HDFN.	• Pregnant women are excluded from this study and participants must agree to use highly effective methods of contraception (Sections 5.1 and 5.2). • Pregnancy tests are conducted throughout the study. Participants who become pregnant will be withdrawn and followed up until delivery or termination of pregnancy (Section 7.1).
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 Weeks 14 to 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	• Pregnant women are excluded from this study and participants must agree to use highly effective methods of contraception (Section 5.1 and 5.2). • Pregnancy tests are conducted throughout the study. Participants who become pregnant will be withdrawn and followed up until delivery or

	duration of low IgG in these infants is currently unknown. • As of 31-Dec-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.	termination of pregnancy (Section 7.1).
Risks Due to Study Procedures		
Labial salivary gland biopsy	Labial salivary gland biopsy for diagnosing and characterizing pSS syndrome can be standard of care and is therefore common in the course of pSS management. Complications of labial minor salivary gland may include infection or transient focal lip numbness for 2 to 3 months. No nipocalimab-specific risks are anticipated related to lip biopsy complications.	• The biopsy is a voluntary sub-study. Participants may decline participation in the biopsy sub-study intervention if it is not in their best interest or if they are not comfortable.

Abbreviations: AESI = adverse event of special interest; EOS-HDFN=early-onset severe hemolytic disease of the fetus and newborn; FcRn = neonatal Fc receptor; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IgG = immunoglobulin G; IV intravenous

2.3.2. Benefits for Study Participation

There is no established benefit to participants of receiving study intervention. There is evidence that inflammation through autoantibodies and IgG-antigen immune complexes plays an important role in the pathogenesis of pSS. Given the scientific rationale for FcRn blockade and that nipocalimab shows early signs of efficacy in an autoantibody-driven disease like gMG, nipocalimab may provide benefit in the treatment of pSS (Section 2.2). Participants in the study will also help in furthering development of this study intervention to treat pSS and increased understanding of pSS. Thus, the knowledge gained from this study has the potential to benefit many more patients suffering from pSS and thus offers potential public health benefits.

Participants may also experience some benefit from the 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

Study 80202135SJS2001 is the first study conducted in participants with pSS and the benefit-risk profile of nipocalimab in patients with pSS has not been established. However, the available results from nonclinical and clinical studies (Phase 1 and Phase 2 studies) with nipocalimab, the scientific and clinical rationale for blocking FcRn in pSS, and the measures taken to minimize the potential risks, support the potential benefit-risk balance for participants in this study.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of nipocalimab in participants with primary Sjogren's syndrome (pSS) versus placebo	**Primary endpoint:** • Change from baseline in Clinical European League Against Rheumatism Sjögren's Syndrome Disease Activity Index (clinESSDAI) score at Week 24 **Secondary endpoints:** • Change from baseline in EULAR Sjögren Syndrome Patient Reported Index (ESSPRI) score at Week 24 • Improvement of ≥4 points from baseline in EULAR Sjögren Syndrome Disease Activity Index (ESSDAI) score (minimal clinically important improvement) at Week 24 • Improvement of ≥4 points from baseline in clinESSDAI score (minimal clinically important improvement) at Week 24 • ESSPRI response defined as a decrease of one point or a decrease of ≥15% from baseline (minimal clinically important improvement) at Week 24 • Disease response according to the Sjögren's Tool for Assessing Response (STAR) composite score at Week 24 • Improvement in disease activity level by ≥1 level in at least one clinESSDAI or ESSDAI domain (biological, hematological, cutaneous, constitutional, lymphadenopathy and lymphoma, and glandular) at Week 24 • Improvement from baseline in ≥3 of 5 CRESS categories at Week 24
Secondary	
Safety • To evaluate the safety of nipocalimab treatment versus placebo in participants with pSS	• Number and proportion of participants with treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), treatment-emergent serious adverse events (SAEs), and TEAEs leading to treatment discontinuations through end of study visit • Number and proportion of participants with clinically significant abnormalities in vital signs, and laboratory safety tests through end of study visit

Objectives	Endpoints
Clinical Pharmacology	
• To evaluate the pharmacokinetics (PK) and immunogenicity of nipocalimab in participants with pSS	• Summary of serum concentrations of nipocalimab over time in participants receiving active study intervention • Incidence and titers of antibodies to nipocalimab (anti-drug antibodies [ADA] and neutralizing antibodies [NAb]) in participants receiving active study intervention
Clinical Biomarkers	
• To evaluate the effect of nipocalimab versus placebo on levels of serum biomarkers related to pSS	• Change from baseline in biomarkers, including but not limited to: CRP, total IgG, IgG1, IgG2, IgG3, IgG4, and autoantibodies (anti-Ro/SSA, anti-La/SSB, RF, and ANA)
Exploratory	
Clinical	
• To further evaluate the efficacy of nipocalimab in participants with pSS versus placebo	• Change from baseline in Physician Global Assessment of Disease Activity (PhGA) at Week 24 • Change from baseline in ESSPRI components over time through Week 24 • Change from baseline in DAS28 CRP over time through Week 24 in participants with at least 3 swollen and 3 tender joints at baseline • Change from baseline in DAS28 CRP over time through Week 24 in participants with <3 swollen and 3 tender joints at baseline • Change in DAS28 CRP over time through Week 24 • Change from baseline in International Digit Symbol Substitution Test - Symbols (IDSSTS), Identification test, and Detection test scores over time through Week 24 • Sjogren's Syndrome Responder Index (SSRI) response defined as ≥20% improvement from baseline in at least two of five domains (fatigue, oral dryness, ocular dryness, unstimulated whole salivary flow, erythrocyte sedimentation rate) at Week 24 • SSRI response defined as ≥ 30% improvement from baseline in at least two of five domains (fatigue, oral dryness, ocular dryness, unstimulated whole salivary flow, erythrocyte sedimentation rate) over time through Week 24

Objectives	Endpoints
	• SSRI response defined as ≥ 30% improvement from baseline in at least three of five domains (fatigue, oral dryness, ocular dryness, unstimulated whole salivary flow, and erythrocyte sedimentation rate) at Week 24
Patient Reported Outcomes (PROs) • To evaluate the effect of nipocalimab versus placebo on key pSS symptoms, impacts, and HRQoL.	*Change from baseline over time through Week 24 in scores from the following PRO tools:* • HADS (Hospital Anxiety and Depression Scale) • Work Limitations Questionnaire (WLQ) • Sjogren's Symptoms (fatigue, ocular, oral and vaginal dryness as well as joint pain) • Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) questionnaire • Patient Global Impression of Severity (PGIS) of Sjögren's Syndrome • Patient Global Impression of Change (PGIC) in Sjögren's Syndrome • Short Form 36 (SF-36 v2) domains and summary scores for the physical component score (PCS) and mental component score (MCS) • Patient's Global Assessment of Disease Activity (PtGA)
Pharmacodynamics • To explore the effects of nipocalimab on cellular, transcriptomic, and soluble biomarkers	• Total antibody (eg, IgG, IgM, IgA), IgG subclasses, and broader autoantibody profiling • Change in ESR and serum albumin levels • Serum biomarker measurements, for example, inflammatory proteins, complement, cytokines, and chemokines • Change in absolute number and frequency (percent of total leukocytes and parent populations) of immune cell subsets in blood • Changes in gene expression profiles in blood (ribonucleic acid [RNA]) over time • Changes in autoantibody and soluble proteins in saliva and tears

Objectives	Endpoints
	• Biopsy – changes in cellular infiltrates, soluble mediators of inflammation, and IgG levels by immunohistochemistry and other methods • Changes in gene expression profiles in the salivary gland tissue
Pharmacogenomics • To explore genetic associations to response to nipocalimab	• Correlate treatment response with genetic polymorphisms
Digital Health • To explore the effects of nipocalimab on physical activity and sleep measured by actigraphy	• Change from baseline in Actigraphy Watch collected continuous data on physical activity, mobility, and sleep over time
SICCA Signs	• Change from baseline in unstimulated salivary flow rate over time through Week 24 • Improvement from baseline in unstimulated salivary flow rate (especially participants with dryness and fatigue dominant phenotype) over time through Week 24 • Change from baseline in tear secretion amount using the Schirmer's Test over time through Week 24 • Change from baseline in frequency of use and the amount of artificial tears and/or saliva to treat dryness over time through Week 24 • Change from baseline in Ocular Surface Staining (OSS) at Week 24
Steroid use	• Change from baseline in steroid use in comparison to mean doses between groups over time through Week 24

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

HYPOTHESIS

The primary hypothesis of this study is that at least one of the two nipocalimab dose regimens is superior to placebo as measured by change from baseline in clinESSDAI at Week 24, in adult participants with moderately active pSS.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, randomized, placebo-controlled, parallel, multicenter, double-blind interventional study in men and women between the ages of 18 to 75 years, inclusive, with active, autoantibody-positive pSS.

The total duration of the study is up to 36 weeks and consists of 3 study periods: a ≤6-week screening period, a 24-week double blind treatment period, and a 6-week follow-up period (8 weeks post last study intervention administration).

A target of approximately 150 participants will be enrolled in this study. Participants will be randomly assigned into 3 treatment groups in a 1:1:1 ratio with 50 participants planned in each of the placebo, nipocalimab 5 mg/kg, and 15 mg/kg groups.

Group 1: placebo IV q2w

Participants will receive placebo IV q2w through Week 22.

Group 2: nipocalimab 5 mg/kg IV q2w

Participants will receive nipocalimab 5 mg/kg IV q2w through Week 22.

Group 3: nipocalimab 15 mg/kg IV q2w

Participants will receive nipocalimab 15 mg/kg IV q2w through Week 22.

A placebo comparator (in addition to standard of care background therapy) will be used in this study through Week 22 to allow for blinded, placebo-controlled evaluation of the efficacy and safety of nipocalimab in participants with pSS.

At selected sites, an optional labial salivary gland biopsy substudy will be conducted to evaluate the molecular and histologic changes from baseline in participants with pSS. In addition, ocular surface staining (OSS) will be conducted at selected sites to assess the change in keratoconjunctivitis sicca (KCS) from baseline in participants with pSS.

Randomization will be carried out centrally using permuted block randomization, stratified by 1) baseline steroid use (Y/N), 2) anti-malarial use (Y/N), and 3) geographic region (eg, North America, Eastern Europe, Western Europe). Clinical and laboratory evidence of disease activity will be evaluated and assessed to verify that participants are meeting inclusion/exclusion criteria. The sites and sponsor will be blinded to treatment assignments and specified lab results following randomization.

Clinical and laboratory evidence of disease activity will be evaluated and assessed by a committee of the sponsor or designee to verify that participants are meeting inclusion/exclusion criteria and to ensure data quality and consistency.

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

The primary efficacy analysis will be performed after all participants have completed Week 24 efficacy assessments (or discontinued). An interim analysis committee will perform an early interim review of PD data in a small subset of approximately 30 participants that complete 8 weeks of study intervention and will perform a second interim review of available efficacy data of approximately 100 participants, or 67% at Week 24 to enable future study planning.

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

Key safety assessments include AEs, SAEs, AESI, laboratory parameters (hematology and chemistry, including lipid panel, and urinalysis), vital signs, systolic and diastolic blood pressures over time, and AEs temporally associated with infusion, including hypersensitivity reactions.

A final database lock (DBL) is planned at Week 30 and includes 6 weeks of follow-up after the Final Efficacy Visit. The end of the study is defined as the last follow-up assessment (8 weeks after the last infusion of study intervention) for the last participant.

A Data Monitoring Committee (DMC) will be commissioned for safety reviews of this study. A separate interim analysis committee (IAC) will be commissioned for interim analysis of PD and efficacy data. Refer to Section 10.3.6 for details.

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

4.2. Scientific Rationale for Study Design

A double-blind, placebo-controlled study was selected where participants are randomized to nipocalimab or placebo in addition to the standard-of-care background therapy. Study designs with a true placebo comparator group are unethical for this serious disease condition. Therefore, placebo and experimental treatments will be added to standard-of-care, including glucocorticoids and permitted immunosuppressive drugs (Table 4). This is consistent with both the European League Against Rheumatism (EULAR; Ramos-Casals 2020) and the Sjögren's Syndrome Foundation (Carsons 2017) management guidelines for Sjogren’s syndrome.

Participants can enter on systemic glucocorticoid therapy; if so, must be on a stable dose at ≤10 mg/day of prednisone-equivalent for ≥4 weeks prior to study intervention.

The inclusion and exclusion criteria will be assessed prior to randomization. The assessment by the sponsor or designee will be the final determinant for allowing randomization.

Blinding, Control, Study Phase/Periods, Intervention Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active intervention. Randomization will be used to minimize bias in the assignment of participants to intervention groups, to increase the likelihood

that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention groups and to enhance the validity of statistical comparisons across intervention groups. Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints. Specific laboratory tests that may be unblinding (eg, nipocalimab concentrations, IgG, albumin, total protein, CICs, SPEP, autoantibody and complement 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 for screening or randomization purposes will be available to the investigator and study team. Given that albumin laboratory results are masked, the investigator will be notified if their participant meets the laboratory criteria for hypoalbuminemia <20 g/L (<2.0 g/dL). These AESI cases will be handled similarly to an SAE for reporting purposes and reviewed by the DMC as they occur.

Stratification is implemented to minimize the risk for baseline imbalance(s) across treatment arms on potentially confounding variables. Baseline imbalances of these factors could impact efficacy and/or safety assessments of nipocalimab versus placebo.

DNA and Biomarker Collection

Biomarker samples will be collected, where local regulations permit, to evaluate the humoral, cellular and molecular mechanism of nipocalimab, or to help to explain interindividual variability in clinical outcomes, or to help to identify population subgroups that respond differently to an intervention. Biomarkers will be analyzed in blood, saliva, and tear samples to evaluate disease activity and to assess PD markers associated with nipocalimab. Optional biopsy samples may be obtained in the minor salivary gland (inner lip) biopsy substudy from participants who meet additional inclusion criteria and provide specific consent. Biopsy samples will be analyzed to explore disease biomarkers and treatment effects at the tissue level. The goal of the biomarker analyses is to further define the mechanism of action of the FcRn blockade with nipocalimab in pSS and aid in evaluating the intervention-clinical response relationship.

Optional pharmacogenomic samples may be obtained, where local regulations permit, from participants only when specific consent is provided by signing the optional genetic research informed consent form (ICF). It is recognized that genetic and epigenetic 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, identify markers associated with disease susceptibility and prognosis, 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 for the identification of genetic and epigenetic factors that may influence the PK, PD, efficacy, safety, or tolerability of nipocalimab and to identify genetic factors associated with pSS or the response to nipocalimab treatment. Additional pharmacogenomic samples may be collected after exposure to nipocalimab or placebo. Epigenetic data from these samples may be compared with baseline samples to identify epigenetic changes that may associate with the disease or the treatment.

Biomarker and optional DNA samples may also be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies for pSS.

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.

Salivary Gland Biopsy Substudy

A labial salivary gland biopsy substudy will be conducted at selected sites with the established capability to perform the tissue collection and processing procedures. In participants that provide consent in the ICF, salivary gland biopsies will be performed before Week 0 and following Week 24 of the study to evaluate the effect of nipocalimab treatment on the molecular and cellular inflammation in the affected tissue. The biopsy procedure should be performed after all screening results are available and ≥11 days leading up to the Week 0 study visit to allow at least 1 week for healing prior to baseline study assessments. The end of study biopsy can be performed on the day of the Week 24 visit once all assessments have been completed or performed on any day in the following week. All glands within the biopsy site (typically 6 to 10 glands) will be collected. A standardized procedure detailed in the salivary gland biopsy manual will be applied for obtaining the glands. In addition to standardized focus scoring, exploratory analyses of salivary gland tissue may include immunohistochemistry (IHC), mRNA profiling, and potentially other methods in order to fully assess the mechanism of action of nipocalimab as well as the degree of change from baseline at the site of disease in patients with pSS treated with nipocalimab as compared to placebo.

4.2.1. Participant Input Into Design

An advisory board of patients with pSS was consulted on study designs for pSS studies. Participants provided insights on the protocol design, where they perceived barriers to participation and how the clinical study experience could be improved for patients. In particular, concerns were raised about some of the inclusion/exclusion criteria (optional biopsy requirement, steroid tapering) and patient-reported outcomes (PROs) convenience, time demand for visits, concerns with receiving placebo and worsening of their disease. These insights were taken into account in the protocol design.

New recruitment strategies were identified, including: providing sites with tools to help identify newly diagnosed patients in their referral network that could be a good fit for the study, providing more information about the placebo and standard-of-care requirement to explain its significance to potential participants, and providing more education to potential participants about the protocol design and the protections in place for participants of clinical studies.

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.

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

The total blood volume to be collected is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the American Red Cross standard limit for whole blood donation (approximately 450 mL every 8 weeks) and is, therefore, considered an acceptable amount of blood to be collected over this time. For more details regarding blood collection, see Section 8.

4.3. Justification for Dose

Nipocalimab was specifically engineered to bind to FcRn and block FcRn-mediated IgG recycling and redirects internalized IgG from early endosomes to lysosomes for catabolism. Dose-dependent lowering of circulating IgG/pathogenic antibodies has been demonstrated in prior Phase 1 and Phase 2 studies with nipocalimab. The reduction of endogenous pathogenic autoantibodies by nipocalimab is expected to be similar to the reduction of total IgG, thus total IgG levels were chosen as the PD biomarker for dose selection of nipocalimab. As it is unknown what percentage of IgG reduction will correlate with clinical efficacy, with total IgG lowering as a surrogate for the lowering of pathogenic antibodies, 2 target levels for dose ranging were identified. A maximum of 80% to 85% IgG lowering (on average between peaks and troughs) can be reached with nipocalimab due to the continued synthesis of endogenous IgG. Therefore, a dose regimen that can target 70% to 80% IgG lowering would be considered the higher dose regimen in this study. For the lower dose regimen, approximately 50% IgG lowering was considered low enough to be able to explore dose ranging while not being too low for patients to have the chance to achieve clinical efficacy.

The nipocalimab dose regimens selected for this Phase 2 study were based on 2 available studies including the Phase 1 FIH SAD/MAD study in healthy participants (MOM-M281-001) where single doses of nipocalimab up to 60 mg/kg and multiple doses up to 30 mg/kg weekly were evaluated and the Phase 2 study in generalized gMG (MOM-M281-004) where dosing regimens up to 60 mg/kg q2w were evaluated. Also contributing to the dose selection for this pSS study were the simulations from PK/PD/efficacy modeling for the Phase 3 gMG study based on the accumulated Phase 1 and Phase 2 gMG nipocalimab data as well as simulations for pSS based on an updated PK/receptor occupancy (RO)/PD model based on the FIH SAD/MAD data. For this Phase 2 study, 2 dose levels are planned to be explored: 5 mg/kg IV q2w and 15 mg/kg IV q2w, in order to achieve enough separation to be able to evaluate a range of exposure with the corresponding clinical response.

Dose Selection for gMG Phase 3

In the Phase 2 study in gMG participants (MOM-M281-004), rapid, dose-dependent IgG lowering was observed 1 week after the initial dose in all dose groups (5 mg/kg q4w, 30 mg/kg q4w, 60 mg/kg q2w, 60 mg/kg single dose), with maximal IgG lowering achieved at Week 2 in the 60 mg/kg single dose and q2w groups. Total IgG levels and pathogenic autoantibodies

(anti-acetylcholine receptor) were reduced to a similar degree over time and corresponded to observed dose-dependent improvements in Myasthenia Gravis Activities of Daily Living (MG-ADL) scores, suggesting a correlation between IgG lowering and MG-ADL scores.

To support the Phase 3 dose selection for gMG, population PK/PD/efficacy modeling analyses were conducted using data obtained from the nipocalimab Phase 1 and 2 studies to evaluate the relationship between PK, IgG lowering, and MG-ADL, in addition to other efficacy and safety endpoints (including serum albumin). The simulation results indicated that the q2w dosing interval would provide more sustained IgG lowering and MG-ADL reduction at all simulated dose levels when compared with the q4w dosing interval. Further, while modeling and simulation did suggest some numerical differences in the percent of IgG lowering and MG-ADL reduction between the 15 and 30 mg/kg q2w dosing regimens (the model-predicted mean IgG lowering is 73.8% versus 79.4%, respectively), the additional 5.6% IgG reduction with the 30 mg/kg q2w dose regimen would translate to only ~0.2 points additional MG-ADL improvement at steady-state trough when compared with 15 mg/kg q2w specifically given the PK/PD/efficacy simulations for gMG, thus the 15 mg/kg q2w maintenance dosing regimen was proposed for evaluation through the placebo-controlled portion of the planned Phase 3 study in participants with gMG (MOM-M28-011).

Dose Selection for pSS Phase 2

Additional 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 help the dose selection in patients with pSS. Nipocalimab PK and the interaction with FcRn, ie, receptor occupancy (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 two 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. Predicted PK and PD (eg, IgG lowering) profiles using this model were overall consistent with the observations from the Phase 2 MG study (MOM-M281-004) and Phase 2 EOS-HDFN study (MOM-M281-003), indicating a similar PK/PD relationship in healthy participants and these patient populations. A similar PK/PD relationship is expected for the pSS patient population since naturally generated pathogenic IgG autoantibodies and normal IgG would share similar disposition characteristics.

Pharmacokinetic/PD simulations for the pSS population were then performed using the aforementioned PK/RO/PD model and incorporating the typical pSS population body weight. Based on these simulations, the 5 and 15 mg/kg q2w dosing regimens were selected. The 5 mg/kg IV q2w dosing regimen is expected to maintain an average of 58% IgG reduction (65% and 49% IgG reduction peak and trough, respectively). The 15 mg/kg q2w dose regimen is predicted to achieve an average of 71% IgG reduction (77% and 64% IgG reduction peak and trough, respectively).

Safety Considerations

In terms of safety, the proposed dose regimen of 15 mg/kg or 5 mg/kg IV q2w starting from Week 0 is well below the PK exposure observed from 60 mg/kg q2w in the Phase 2 gMG study (MOM-M281-004) as well as the 45 mg/kg once weekly (QW) dose regimen being studied in pregnant women at high risk for EOS-HDFN (MOM-M281-003), which were both generally well-tolerated based on the currently available safety data. The dose regimens proposed for this study are expected to have less than 20% reduction in the mean albumin level and less than 20% elevation in the mean total cholesterol level. The magnitudes of albumin reduction and total cholesterol increase are expected to be less than those observed in prior studies with 30 mg/kg IV weekly (MOM-M281-001) or 60 mg/kg IV q2w (MOM-M281-004) dose regimens. Therefore, the proposed dose regimen in this Phase 2 study is expected to be safe and well-tolerated.

Dose Justification Summary

In conclusion, the 5 and 15 mg/kg q2w dose regimens were selected for this Phase 2 study in pSS to fully explore the dose range in this heterogenous population. The safety profile for these 2 dose regimens is expected to be consistent with what was previously observed, and the effect on albumin and total cholesterol are expected to be below that seen with the higher dose regimens studied previously.

4.4. End of Study Definition

End of Study Definition

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

Study Completion Definition

A participant will be considered to have completed the study if he or she has completed the study through Week 24 of the double-blind phase and the safety follow-up.

5. STUDY POPULATION

Screening for eligible participants will be performed within 6 weeks before administration of the study intervention. Refer to Section 5.5 for conditions under which the repeat 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.

The inclusion and exclusion criteria will be assessed prior to randomization of a participant. The sponsor (or designee) will make the final determinant for allowing randomization.

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 during Screening to be enrolled in the study:

Age

1. Criterion modified per Amendment 2.

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

Disease Characteristics

2. Criterion modified per Amendment 2.

   2.1 Criterion modified per Amendment 3.

   2.2 Meets classification criteria for primary pSS by the 2016 American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR; Shiboski, 2017) at the time of Screening (results either obtained during screening or documented in the participant's medical history are acceptable to fulfill these criteria for Schirmer's test, unstimulated salivary flow test, ocular staining score, or labial salivary gland biopsy), and was diagnosed with pSS no less than 26 weeks prior to screening.

3. If on oral glucocorticoid therapy, must be on a stable dose at ≤10 mg/day of prednisone-equivalent for ≥4 weeks prior to study intervention

4. Criterion modified per Amendment 2.

   4.1 At screening is seropositive for antibodies to pSS-associated antigen A (Ro/SSA)

5. Has residual salivary gland function as defined by unstimulated whole salivary flow >0.01 mL/min

6. Criterion deleted per Amendment 2.

7. Criterion modified per Amendment 2.

   7.1 Total clinESSDAI score ≥6, inclusive

8. Criterion modified per Amendment 2.

8.1 Criterion modified per Amendment 3.

8.2 Must demonstrate at least one of the following at screening:

- elevated inflammatory marker (ie, hs-CRP),

OR

- elevated rheumatoid factor (RF)

OR

- at least low activity in the hematological domain of ESSDAI

OR

- at least low activity in the biological domain of ESSDAI.

AND

At least low activity in at least one of the following ESSDAI domains: cutaneous, articular, glandular, constitutional, and lymphadenopathy.

Note (applicable to this entire eligibility criterion 8.2): Demonstrating at least low activity in both the biological and hematologic domains will satisfy this eligibility criterion.

9. Criterion modified per Amendment 2.

9.1 A score of ≥5 in at least one of the ESSPRI subcategories of dryness and/or fatigue

10. Schirmer's test ≥1 mm per 5 minutes, inclusive, in at least one eye

Sex and Contraceptive/Barrier Requirements
Contraceptive (birth control) use by men or women should 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 should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

11. Criterion deleted per Amendment 3.

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

13. Criteria modified per Amendment 1.

13.1 A woman must be (as defined in Section 10.7):

a. Not of childbearing potential

OR

b. Of childbearing potential and

- Practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study intervention and until 30 days after last dose - the end of relevant systemic exposure. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study intervention. Examples of highly effective methods of contraception are located in Section 10.7.
- If using oral hormonal contraceptives for birth control and receiving MMF/MPA, a woman must, in addition to the oral hormonal contraceptive, utilize a barrier method of birth control (eg, either an occlusive cap [diaphragm or cervical/vault caps] plus spermicidal foam/gel/film/cream/suppository if available in their locale) or their partner must agree to use a condom with spermicidal foam/gel/film/cream/suppository if available in their locale, during the study and for at least 30 days after receiving the last administration of study intervention

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

15. Criterion modified per Amendment 3.

15.1 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 at least 90 days after receiving the last administration of study intervention.

In addition, male participants with female partners who are of childbearing potential are to be highly encouraged to inform their partner to use highly effective contraception methods that result in a low failure rate (less than 1% per year).

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

Vaccination History

17. Criterion modified per Amendment 3.

    17.1 It is recommended to be up to date on all age-appropriate vaccinations prior to screening per routine local medical guidelines. It is strongly recommended that participants will have completed a locally-approved (or emergency use-authorized) Coronavirus Disease 2019 (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 standard of care for patients receiving immune-targeted therapy when determining an appropriate interval between vaccination and study enrollment (see Section 6.8.6 and Exclusion #39).

General

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

19. Must sign a separate ICF if he or she agrees to provide optional DNA samples for research where local regulations permit.

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

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

21. Must sign a separate ICF if he or she agrees to participate in optional salivary gland biopsy substudy. Refusal to give consent for the optional substudy does not exclude a participant from participation in the study.

22. Must be able to read and write.

5.2. Exclusion Criteria

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

Coexisting Medical Conditions or Past Medical History

1. Criterion modified per Amendment 2.

    1.1 Has a history of severe and/or uncontrolled, hepatic (eg, viral/alcoholic/autoimmune hepatitis/cirrhosis and/or metabolic liver disease), gastrointestinal, renal, pulmonary, cardiovascular, psychiatric, neurological, or musculoskeletal disorder, hypertension,

and/or any other medical or uncontrolled autoimmune disorder(s) (eg, diabetes mellitus) that might interfere with participant's full participation in the study, and/or might jeopardize the safety of the participant or the validity of the study results.

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

2. Has experienced MI, unstable ischemic heart disease, or stroke within 12 weeks of screening.

3. Has any confirmed or suspected clinical immunodeficiency syndrome not related to treatment of his/her pSS or has a family history of congenital or hereditary immunodeficiency unless confirmed absent in the participant.

4. Currently has a malignancy or has a history of malignancy within 3 years before screening (with the exception of localized basal cell carcinoma and/or squamous cell carcinoma skin cancer that has been adequately treated with no evidence of recurrence for at least 3 months [defined as a minimum of 12 weeks] before the first study intervention administration or cervical carcinoma in situ that has been treated with no evidence of recurrence for at least 3 months before the first study intervention administration).

5. Has known allergies, hypersensitivity, or intolerance to nipocalimab or its excipients (refer to the IB).

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

7. Criterion modified per Amendment 2.

   7.1 Criterion modified per Amendment 3.

   7.2 Has any unstable or progressive manifestation of pSS that is likely to warrant escalation in therapy beyond permitted background medications and/or has severely active pSS as evaluated and assessed by the investigator or sponsor.

8. Has a clinESSDAI pulmonary domain score >6.

9. Criterion modified per Amendment 2.

   9.1 Has Sjögren's Syndrome overlap syndromes where another confirmed autoimmune rheumatic or systemic inflammatory condition (ie, RA, SLE, scleroderma, IBD) is the primary diagnosis or has clinical manifestations that, in the opinion of the investigator, or the sponsor or sponsor's representative, are likely to interfere with the investigator's ability to assess pSS manifestations.

10. Diagnosis of any other non-SS sicca syndrome (eg, due to head and neck radiation, sarcoidosis, chronic graft-versus-host disease etc. according to the requirements in the 2016 EULAR/ACR primary Sjogren's Syndrome classification criteria).

11. Severe uncontrolled fibromyalgia causing significant symptoms or signs, including limiting fatigue, pain, generalized tenderness and/or cognitive dysfunction that would interfere with the investigator's ability to assess pSS activity and/or response to treatment is excluded. Active fibromyalgia requiring an escalation in medication within the 90 days prior to first study administration intervention to control symptoms is excluded. Participants with well controlled fibromyalgia and are on stable treatment for 90 days prior to randomization may otherwise be allowed.

12. Has taken opioid pain medications (any dose), not otherwise allowed elsewhere in this protocol, to treat pSS- or fibromyalgia-related symptoms within 8 weeks of screening.

13. Any history of non-Hodgkin's Lymphoma related to pSS.

14. Has any blasts or tumor cells noted on a peripheral blood smear at screening.

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

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

16. Is (anatomically or functionally) asplenic.

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

18. Criterion modified per Amendment 2.

    18.1 Prior history of refractive eye surgeries (including but not limited to laser assisted in situ keratomileusis, photorefractive keratectomy, and laser epithelial keratomileusis) within 3 years or less from screening.

19. Has had cataract surgery within 6 months prior to randomization and new installation of lacrimal punctal plugs within 4 weeks of randomization; however, patients with existing lacrimal punctal plugs may enroll and have these plugs replaced as necessary during the study).

20. Criterion modified per Amendment 3.

20.1 Has had a full-thickness corneal transplantation (penetrating keratoplasty); however, participants who have had endothelial keratoplasty ≥1 year prior to first administration of study intervention are not excluded.

21. Has a history of catastrophic anti-phospholipid syndrome (APS). Participants with a history of non-catastrophic APS must be adequately controlled with anticoagulation and/or anti-platelet therapy using medications permitted in this protocol and in accordance with local guidelines. The suitability of the participant to participate in the study must be discussed with the medical monitor and/or sponsor before the participant is randomized.

22. Criteria modified per Amendment 1.
22.1 Has a chest X-ray (radiograph) suggestive of interstitial lung disease and confirmed by review of medical records.

23. Criteria modified per Amendment 1.
23.1 Screening laboratory tests

a. Hemoglobin ≤8.0 g/dL
b. White blood cell count (WBCs) ≤3.0 × 10^3/μL, unless the leukopenia is due to pSS
c. Neutrophils ≤500/μL
d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations must be within 2 times the ULN range for the laboratory conducting the test
e. Direct (conjugated) bilirubin ≥1.0 mg/dL
f. Estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73 m^2
g. Serum total IgG <6 g/L (<600 mg/dL)

Concomitant or Previous Medical Therapies Received

24. Criterion modified per Amendment 2.

24.1 Prednisone-equivalent >10 mg/day alone, including immediate and extended-release oral formulations,

OR

Prednisone-equivalent at any dose, regardless of formulation, if concomitant with more than one immunosuppressive agent (eg, methotrexate, azathioprine, mycophenolic acid, mycophenolate mofetil, leflunomide, systemic cyclosporine A)

OR

Use of pulse glucocorticoids (prednisone equivalent >125 mg per day) within 90 days prior to randomization.

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

26. Criterion modified per Amendment 3.

26.1 Medications known to cause dry mouth AND that in the judgement of the investigator or sponsor would compromise the validity of the study results, including medications which have been dose-adjusted in less than 4 weeks prior to screening AND cannot be maintained throughout the study at the dose(s) in use at screening. The use of such medications that are required standard of care for non-pSS-related conditions AND have been used at stable doses for ≥4 weeks prior to screening AND ≥10 weeks before first administration of study intervention AND are anticipated to remain at stable dosing throughout the study may be permitted and may NOT preclude participation in the study.

27. Use of topical ophthalmic glucocorticoid agent(s) within the previous 8 weeks prior to first administration of study intervention.

28. Initiation of any antimalarial (eg, hydroxychloroquine) or any immunosuppressive (methotrexate, azathioprine, mycophenolic acid, mycophenolate mofetil, leflunomide) within the 12 weeks prior to first administration of study intervention, or adjustment of dosing of these agents within 8 weeks of first study intervention. See Table 4 for maximal allowed doses.

29. Is currently using other IgG Fc-conjugated therapeutic agents, including factor or enzyme replacement therapy, not specifically included or allowed in other criteria.

30. Criterion modified per Amendment 3.

30.1 Has received any B cell depleting drug (eg, rituximab, anti-BAFF monoclonal antibody).

31. Criterion modified per Amendment 3.

31.1 Has received a single B cell-targeting (but nondepleting) therapy within 3 months of screening; or received more than 1 previous B cell-targeting therapy, within 6 months prior to screening.

32. Eculizumab or any anti-C5 agents within 6 months prior to screening.

33. Criterion modified per Amendment 2.

33.1 Use of biologic medications within the past 90 days, or 5 half-lives prior to first administration of study intervention, whichever is greater. Examples include, anti-tumor necrosis factor (TNF) medication (eg, infliximab, golimumab, certolizumab pegol,

etanercept, CT-P13, and adalimumab), other biologic medications (eg, tocilizumab, alefacept, efalizumab, natalizumab, abatacept, anakinra, brodalumab, secukinumab, ixekizumab), or agents whose mechanism of action targets interleukin (IL)-1, IL-2, IL-6, IL-17, cytotoxic T-lymphocyte-associated protein (CTLA)-4 or other T cell-inhibitors, or interferon pathways (eg, anifrolumab), or exogenous IL-2 therapy, within the past 90 days, or 5 half-lives prior to first administration of the study intervention, whichever is greater.

34. Has received topical cream/ointment preparations of cyclosporine A, high potency topical glucocorticoids (eg, World Health Organization [WHO] Classification, Group I to III), or other topical immunomodulatory agents (such as tacrolimus, pimecrolimus) covering a body surface area (BSA) of >20% within 4 weeks prior to first administration of study intervention.

35. Has received adrenocorticotropic hormone (ACTH) administered by injection within 1 month prior to the first administration of study intervention.

36. Has received epidural, IV, IM, intra-articular (IA), intrabursal, or intralesional administration of glucocorticoids within 6 weeks prior to the first administration of study intervention.

37. Has comorbidities (other than pSS, eg, asthma, chronic obstructive pulmonary disease) which have required 3 or more courses of systemic glucocorticoids within the previous 12 months.

38. Has received plasmapheresis, immunoadsorption therapy, or intravenous immunoglobulin (IVIg) within 6 months prior to screening.

39. Criterion modified per Amendment 2.

    39.1 Criterion modified per Amendment 3.

    39.2 Has received a live vaccine within 4 weeks before the first administration of study intervention, or has a known need to receive a live vaccine during the study or within at least 8 weeks (including BCG) after the last administration of study intervention in this study.

40. 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.

41. Criterion modified per Amendment 2.

41.1 Has taken any disallowed therapies with the indicated time periods as noted in Section 6.8.7 before the planned first administration of study intervention, unless otherwise specified elsewhere in the protocol.

Prior/Concurrent Clinical Study Experience

42. Criterion modified per Amendment 2.

42.1 Has received an investigational antibody or biologic therapy (other than those listed elsewhere in this section) within 6 months prior to the first administration of study intervention, or received any other investigational therapy, including an investigational medical device, or new investigational agent within 3 months or 5 half-lives (whichever is longer) prior to the first administration of study intervention or is currently enrolled in another study using an investigational intervention or procedure.

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

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

Infections or Predisposition to Infections

45. Criterion modified per Amendment 2.

45.1 Criterion modified per Amendment 3.

45.2 Has a severe infection (eg, pneumonia, tuberculosis, biliary tract infection, diverticulitis, *Clostridioides difficile* infection, cytomegalovirus, pneumocystosis, 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 re-screened after the 8-week exclusionary period has passed. Any participant with an infection requiring oral anti-infectives (eg, sinusitis, bronchitis, uncomplicated urinary tract infection) within 4 weeks prior to or during screening will be excluded.

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

47. History of being human immunodeficiency virus (HIV)1 or HIV2 antibody-positive, or tests positive for HIV at screening.

48. Is seropositive for hepatitis B virus (HBV) infection (Section 10.9).

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

    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

    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.

50. Criterion modified per Amendment 3:

    50.1 COVID-19 infection:

    During the 6 weeks prior to baseline, has had **any** of the following (regardless of vaccination status):

    (a) confirmed SARS-CoV-2 infection (test positive), **OR**

    (b) suspected SARS-CoV-2 infection (clinical features of COVID-19 without documented test results), **OR**

    (c) close contact with a person with known or suspected SARS-CoV-2 infection

    Exception: may be included with a documented negative result for a validated SARS-CoV-2 test:

    - obtained at least 2 weeks after conditions (a), (b), (c) above (timed from resolution of key clinical features if present, eg, fever, cough, dyspnea)

    AND

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

    NOTE on COVID-related exclusion:

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

and in accordance with current regulations/guidance from authorities/standards of care.

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

Other Exclusions

51. A current diagnosis of anxiety and/or depression, according to DSM-V, unless the condition(s) have been on well-controlled and on stable therapy for at least 3 months prior to screening and is managed with an intervention or therapy that can be maintained throughout the study.

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

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

54. Criterion modified per Amendment 2.

    54.1 Has any condition for which, in the opinion of the investigator or the sponsor or sponsor's representative, 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.

55. Is unwilling or unable to undergo multiple venipunctures because of poor tolerability or lack of easy venous access or has/or requires a central venous catheter.

56. Has a history of active granulomatous infection, including histoplasmosis or coccidioidomycosis, prior to screening.

57. Has received a bacille Calmette-Guerin vaccine (BCG) vaccination within 12 months before first administration of study intervention.

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

5.3. Lifestyle Considerations

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

1. Refer to Section 6.8.7 for details regarding prohibited and restricted therapy during the study.

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

3. Agree to avoid excess exposure to natural or artificial (tanning beds, phototherapy, etc) sunlight. In addition, it is advised that participants maintain their typical use of sun protective measures (such as a hat, sunglasses, protective clothing, sunscreen). The time period for this requirement is from the start of screening until the last dose of study intervention has been received.

4. Skin concealers or topical tan preparations or nonpermanent tattoos should be avoided within 48 hours before a study visit due to their potential to obscure skin disease activity.

5. Criterion modified per Amendment 3.

   5.1 Participants should avoid use of any wigs or hair attachments that in the opinion of the investigator will interfere with disease activity assessment or that cannot be readily removed for scalp examination.

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

7. Criterion modified per Amendment 3.

   7.1 Must agree not to receive a live vaccine (including BCG) during the study and for 8 weeks after receiving the last dose of study intervention.

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

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

10. Tobacco products and medical marijuana use is discouraged but not prohibited. Because marijuana can affect concentration and mentation, the participant must refrain from marijuana use on the day of the visit prior to completing of the PROs and salivary flow tests. For a similar reason, tobacco products must not be used for at least 2 hours prior to salivary flow tests.

5.4. Randomization Criteria

Prior to randomization and first administration of study intervention, participants must meet the following criteria in order to be randomized:

1. No acute exacerbation of pSS requiring augmentation of therapy or hospitalization since the Screening visit.

2. Results for the following tests performed at Week 0 must meet inclusion criteria: The ESSPRI, Schirmer's and Unstimulated salivary flow.

3. Confirm that the history and testing results obtained at screening meet all inclusion and exclusion criteria.

5.5. Screen Failures

Participant Identification, Enrollment, and Screening Logs

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

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

Retesting

Retesting of abnormal laboratory values for safety, total IgG, complement, anti-Ro/SSA, autoantibodies, or CBC/differential that may lead to exclusion will be allowed once. Retesting can occur at an unscheduled visit during the screening phase, as long as this is done within the specified screening window of up to 6 weeks. In such cases, the first abnormal test result will not constitute a screen failure. If a laboratory abnormality occurs, the site is encouraged to wait for all laboratory tests to be completed to ensure other laboratory tests do not need to be repeated. Participants who have laboratory values that do not meet entry criteria following the retest or do not meet disease activity inclusion criteria following the repeat procedure are to be deemed screen failures. A screening laboratory test(s) analyzed by the central laboratory may be repeated more than once in the event of suspected error in sample collection or analysis as long as the result is obtained within the screening period.

Rescreening

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened one time after discussion with the sponsor representative or their designee.

Rescreened participants are assigned a new participant number, undergo the informed consent process, and then start a new screening phase.

5.6. Criteria for Temporarily Delaying Administration of Study Intervention

Guidelines for study intervention administration affected by the COVID-19 pandemic are found in Section 10.11. Criteria for temporary discontinuation of study intervention are described in Section 7.1.2.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Intervention(s) Administered

Participants in the study will be on protocol-permitted standard of care treatment (Section 6.8), supplied by the clinical study site.

In addition to remaining on the standard of care treatment noted above, approximately 150 participants will be randomized in a 1:1:1 ratio with 50 participants planned in each of the placebo, nipocalimab 5 mg/kg, and 15 mg/kg groups.

- **Group 1: placebo IV q2w:** Participants will receive placebo IV q2w through Week 22.
- **Group 2: nipocalimab 5 mg/kg IV q2w:** Participants will receive nipocalimab 5 mg/kg IV q2w through Week 22.
- **Group 3: nipocalimab 15 mg/kg IV q2w:** Participants will receive nipocalimab 15 mg/kg IV q2w through Week 22.

Participants will remain on their assigned treatment through Week 22. All participants will receive a planned total of 12 IV infusions over a 22-week period.

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

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

Nipocalimab will be manufactured and provided under the responsibility of the sponsor. Excipients include sodium phosphate, sodium chloride, trehalose, polysorbate 80, and water for injection. Placebo will be a commercially available saline solution. Placebo will be centrally sourced and provided under the responsibility of the sponsor where required under local regulations. Nipocalimab and the centrally sourced and supplied placebo are designated as Investigation Medicinal Product (IMP). In the United States (US), a site-sourced and locally-sourced saline placebo option will be available in addition to the centrally-sourced placebo. These site and locally sourced commercial saline for placebo are designated as Non-Investigational Medicinal Product (nIMP) per US Food and Drug Administration (FDA) regulations.

Detailed instructions on the administration of study intervention will be provided in the Site Investigational Product Procedures Manual and IPPI.

Guidelines for study intervention administration affected by the COVID-19 pandemic are found in Section 10.11.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

For nipocalimab IV administrations, the study intervention is supplied as a sterile solution in a single-use glass vial containing 20 mL at a concentration of 30 mg/mL. Saline will be used as placebo. Study intervention will be prepared for IV administration based on the instructions provided to clinical sites in the IPPI by the unblinded pharmacist(s) or designee.

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

Refer to the site IPPI for additional guidance on study intervention preparation, handling, and storage.

Accountability

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

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

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

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

Study intervention must be dispensed under the supervision of the investigator or a qualified member of the study-site personnel or by a hospital/clinic pharmacist. Study intervention will be 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 Site Investigational Product Procedures Manual (SIPPM).

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Permuted block central randomization will be implemented in this study using an Interactive Web Response System (IWRS). Approximately 150 participants will be randomly assigned in a 1:1:1 ratio to 1 of 3 intervention groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor; however, the sponsor will not be privy to the actual randomization schedule. The randomization will be balanced by using randomly permuted blocks with the following stratification factors:

Randomization will be carried out centrally using permuted block randomization, stratified by

- baseline steroid use (Y/N),
- anti-malarial use (Y/N), and
- geographic region (eg, North America, Eastern Europe, Western Europe).

The IWRS will assign a unique intervention code, which will dictate the intervention assignment and matching study intervention kit for the participant. The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

Blinding

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

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

Data that may potentially unblind the intervention assignment (ie, study intervention serum concentrations, anti-nipocalimab antibodies, intervention allocation, or other specific laboratory data [eg, IgG levels, complement C3 and C4, serum albumin levels, SPEP, and selected autoantibody levels]) 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 masking/segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of DBL and unblinding. If the investigator has a sufficient concern for safety that local laboratory samples are drawn to check the level of any masked laboratory assessments, the medical monitor or sponsor should be notified immediately. The participant may be required to be discontinued from study intervention.

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

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

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

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

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

6.4. Study Intervention Compliance

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

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

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

6.5. Dose Modification

Dose modification is not applicable in this study.

6.6. Treatment of Overdose

For this study, any dose of nipocalimab in excess of the intended dose by 10% at a single dosing visit specified in this protocol will be considered an overdose. The sponsor does not recommend specific treatment for an overdose.

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

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

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

There are no provisions for continued access to study intervention after the end of this proof-of-concept study. The benefit-risk data and final safe and efficacious dose of nipocalimab in pSS from this study will not be available until after final study data are reported, making it unethical to continue participants on further blinded treatment after the study.

6.8. Concomitant Therapy

Detailed information of prestudy topical and systemic therapies for pSS-related symptoms and disease manifestations, including dosage and frequency of administration must be recorded for past history. Other prestudy therapies administered at the time of screening or up to 90 days before first dose of study intervention, whichever is longer, must be recorded at screening. For any therapies that were discontinued, the reason for discontinuation (eg, non-response, loss of response, intolerance, safety concern, improvement in disease,) should be documented.

Concomitant pSS therapies (and non-pSS concomitant therapies) and associated dosing regimens must be recorded throughout the study beginning with screening through the final safety follow-up visit after the last dose of study intervention.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; 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 eCRF. Recorded information will include a description of the type of therapy, duration of use, dosing 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.

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.

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

Every reasonable effort should be made to keep concomitant medications stable and to avoid introducing non-protocol medications for pSS disease activity through the final safety visit or as specified in the following sections. Dose stabilization of all concomitant medications is required prior to randomization. All medications must meet study protocol guidelines (Sections 5.1 and 5.2 and Table 4, which outline permitted concomitant medication use and dose stabilization requirements prior to randomization and during the blinded study period). Any changes in concomitant therapy regimens must be recorded. If necessary, a concomitant medication may be reduced or temporarily discontinued because of abnormal laboratory values, safety and tolerability issues, concurrent illness, or the performance of a surgical procedure, but the change and reason for the medication change should be clearly documented in the eCRF and in the participant's medical record. Adjustments in concomitant therapies that do not comply with the study protocol guidelines may cause a participant to be considered a treatment failure for the primary and secondary endpoints through Week 24.

During the entire study, investigators should consider whether increases in permitted background therapy due to increased pSS disease activity warrant discontinuation of study intervention. If protocol-prohibited immunosuppressants (such as cyclosporine or tacrolimus), biologics (such as belimumab or rituximab), cytotoxic agents (such as cyclophosphamide), IV glucocorticoids, or average daily doses of oral prednisone-equivalent >10 mg are initiated for severe, progressive, or unstable pSS disease activity, the participant should be considered for discontinuation from study intervention (Section 7.1). This should be discussed with the medical monitor and/or sponsor.

Table 4: Permitted Concomitant Medication Use and Dose Stabilization Requirements Prior to Randomization; Protocol Requirements for Permitted Concomitant pSS Medications

Permitted Concomitant Medications for pSS[a]	Stabilization Period Prior to First Administration of Study Intervention	Maximum Allowable Dose	
		Study Entry	During Study
Antimalarials (chloroquine, hydroxychloroquine, or quinacrine)	Treated with stable dosing for ≥12 weeks	≤250 mg/day chloroquine (≤3 mg/kg/day) ≤500 mg/day hydroxychloroquine (≤7 mg/kg/day) ≤100 mg/day quinacrine Initiation of new antimalarial treatment is not permitted through Week 24.	
Oral glucocorticoids[b]	If currently in use, must have been treated for ≥6 weeks with stable dosing ≥4 weeks. If not currently using oral glucocorticoids, must not have received them for ≥6 weeks	Stable dosing equivalent to average daily dose of ≤10 mg prednisone equivalent New start or dose increase is not permitted through Week 24 except as outlined in Section 6.8.2. Any initiation or dosing changes and its indication must be documented in concomitant medications	
Oral opioid analgesics, only as required for non-pSS or non-fibromyalgia-related acute pain. Tramadol is an exception to this rule.	Not permitted within 2 weeks of Screening, nor at any time between Screening and Randomization.	Not permitted	• ≤20 mg/day oxycodone equivalent for ≤7 days per indication, and ≤21 days cumulative through Week 24. • Any use and its indication must be documented in concomitant medications.
Tramadol	Treated with stable dosing >90 days.	≤150 mg/day	≤150 mg/day. May not be used (ie, must be held) for 8 hours prior to joint assessment. The pattern of use must be documented at each study visit. Dosing adjustment (new start or any change) is not permitted through Week 24, except as follows. • For non-pSS indications: may use as needed at total doses ≤150 mg/day. • For pSS-related, non-fibromyalgia-related pain, may use as needed at total doses ≤150 mg/day. • For fibromyalgia symptoms, must use at a consistent, stable dose (even if intermittent) ≤150 mg/day.

Table 4: Permitted Concomitant Medication Use and Dose Stabilization Requirements Prior to Randomization; Protocol Requirements for Permitted Concomitant pSS Medications

Permitted Concomitant Medications for pSS[a]	Stabilization Period Prior to First Administration of Study Intervention	Maximum Allowable Dose	
		Study Entry	During Study
Systemic NSAIDs and other non-opioid analgesics	At least 2 weeks	• No more than the usual marketed doses approved in the country/territory where the study is being conducted. • Notable changes in dosing must be recorded in concomitant medications. • NSAIDs used 'as needed' may not be taken (ie, must be held) for >12 hours for immediate-release preparations, or >24 hours for extended-release preparations prior to assessments on study visit days, and may not be used on study visit days until after all assessments have been completed, if possible. If withholding NSAIDs in this manner is not tolerable, NSAIDs should be used in a consistent dose and manner for all study visits through Week 24.	
Oral antihistamines	Treated with stable dosing for ≥10 weeks and ≥4 weeks before screening. MUST remain at stable dosing throughout the Week 24 visit.	Stable dosing no more than the usual marketed doses approved in the country/territory where the study is being conducted.	• May not be used (ie, must be held) for 12 hours prior to any unstimulated whole salivary flow test, Schirmer's test or OSS. • Other than the above must remain on stable dosing through Week 24.
Artificial saliva and other non-pharmacologic salivary stimulants or suppressants (eg, dried fruit slices, maltose lozenges, xylitol gum or candy, regular, sugar-less or sugar-free gum or hard candies, artificial saliva sprays or drops, tobacco products, marijuana)	N/A	No more than the usual marketed doses approved/permitted or in the country/territory where the study is being conducted	May not be used (ie, must be held) for 2 hours prior to any unstimulated whole salivary flow test. Marijuana products may not be used at any time on the day of the study visit prior to any unstimulated whole salivary flow test.
Selective serotonin reuptake inhibitor or other agent with anti-cholinergic activity, or other agent known to cause dry mouth, which is required	Treated with stable dosing for ≥10 weeks and ≥4 weeks before screening. If safe in the judgement of the investigator, should remain	No more than the usual marketed doses approved in the country/territory	• No more than the usual marketed doses approved in the country/territory where the study is being conducted • Medications should be taken at consistent times of day throughout the study and/or at each study visit, except if otherwise specified elsewhere in this protocol

Table 4: Permitted Concomitant Medication Use and Dose Stabilization Requirements Prior to Randomization; Protocol Requirements for Permitted Concomitant pSS Medications

Permitted Concomitant Medications for pSS[a]	Stabilization Period Prior to First Administration of Study Intervention	Maximum Allowable Dose	
		Study Entry	During Study
standard of care for a non-pSS comorbidity.	at stable dosing through the Week 24 visit.	where the study is being conducted	Dose adjustments required or consistent with standard of care are permitted but must be documented
Topical ophthalmic agents NSAIDs, artificial tears, autologous serum, antihistamines, diquafasol, rebamipide	Treated with stable dosing for ≥4 weeks.	No more than the usual marketed doses approved in the country/territory where the study is being conducted	• All topical ophthalmic topical agents must not be used for at least 12 hours prior to Schirmer's test or OSS. • Stable dosing no more than the daily dose in use on the day of first administration of study intervention. Notable changes in dosing of any of these agents to be recorded in concomitant medications.
Cyclosporin or lifitegrast		≤2 drops per day per eye	
Oral muscarinic agents:	Treated with stable dosing for ≥8 weeks.		• May not be used (ie, must be held) 48 hours prior to any salivary flow test and at least 12 hours prior to Schirmer's test or OSS. • Dose adjustment (increase) is not allowed through Week 24.
cevimeline		≤90 mg/day	≤90 mg/day
pilocarpine		≤20 mg/day	≤20 mg/day
Non-biologic immunomodulators:	Treated for ≥12 weeks prior to randomization, with stable dosing for ≥8 weeks.		Stable dosing through Week 24. Initiation of a new immunomodulator is not permitted through Week 24.
Mycophenolate mofetil		≤2 g/day	
Mycophenolic acid		≤1.5 g/day	
Azathioprine/6-mercaptopurine		≤2 mg/kg/day (up to 100 mg/day for participants weighing ≤50 kg)	

Table 4: Permitted Concomitant Medication Use and Dose Stabilization Requirements Prior to Randomization; Protocol Requirements for Permitted Concomitant pSS Medications

Permitted Concomitant Medications for pSS[a]	Stabilization Period Prior to First Administration of Study Intervention	Maximum Allowable Dose	
		Study Entry	During Study
Methotrexate (MTX)[c]		≤25 mg/week, oral; ≤25 mg/Week IM or SC	
Leflunomide		≤20 mg/day	

a. Permitted concomitant medications are not supplied by the sponsor.
b. Between Weeks 12 and 24, participants requiring average daily doses of glucocorticoids for pSS disease activity that exceed their baseline dose at Week 0 will be categorized as treatment failures. While these participants will be permitted to remain in the study, the investigator must consider whether glucocorticoid dose increases to an average daily dose ≥60 mg prednisone or equivalent for more than 10 consecutive days or whether a requirement for multiple rescues with glucocorticoid therapy between Weeks 12 and 24 should result in discontinuation of study intervention administration.
c. It is recommended that all participants taking MTX in this study receive concomitant folate or folinic acid. Participants receiving concomitant folate or folinic acid should have been treated with stable dosing for ≥6 weeks before the first dose of study intervention. Guidelines for dose adjustment in the event of MTX toxicity are included in the Trial Center File.

Abbreviations: IM=intramuscular; NSAID=nonsteroidal anti-inflammatory drug; SC=subcutaneous; pSS= primary Sjogren's Syndrome

6.8.1. Antimalarial Medications

Stable treatment with HCQ, chloroquine, or quinacrine is permitted through Week 30 as shown in Table 4. It is not permitted to introduce or adjust dosing of antimalarials through Week 24; however, if necessary, one antimalarial may be substituted for another at an equivalent or lower dose. Antimalarials produced by a licensed compounding pharmacy (eg, quinacrine) in the country/territory of administration and using pharmaceutical grade components are allowed. It is recommended that participants receiving antimalarials receive screening for retinal toxicity according to local guidelines.

6.8.2. Glucocorticoid Therapy

Participants likely to require multiple courses of systemic glucocorticoids for reasons other than pSS (eg, history of uncontrolled asthma, uncontrolled chronic obstructive pulmonary disease, etc) should be excluded from study participation. However, participants may receive a short course (10 days or less) of oral glucocorticoids for reasons such as prophylactic therapy before surgery (stress-dose glucocorticoids), therapy for certain infections, acute exacerbation of asthma or chronic obstructive pulmonary disease, or other condition (eg, contact dermatitis) not related to increased pSS disease activity. Dosage, duration, and reason for glucocorticoid use in these instances must be documented.

Unnecessary changes in glucocorticoid dose are discouraged, and any dose adjustments are recommended to be made in small amounts. Changes in glucocorticoid dosing other than those described in this section of the protocol are allowed only for medical necessity. The degree and timing of any unspecified glucocorticoid adjustments should be carefully considered as this may have a significant impact on the study results and upon continuation of study intervention.

Oral Glucocorticoids

Participants who are receiving this medication at screening and must be on a stable dose equivalent to an average daily dose of no more than 10 mg/day prednisone (or equivalent), for at least 4 weeks prior to the first administration of study intervention. Participants receiving this medication at screening must have been receiving this medication for at least 6 weeks prior to randomization. Increases for any reason will trigger treatment failure (TF) rules.

A summary of allowed glucocorticoid dosing at randomization and changes during the study are shown in Table 4.

Epidural, Intravenous, Intramuscular, Intra-articular, Intrabursal injection, and Intralesional Glucocorticoids

Use of pulse glucocorticoids (prednisone equivalent >125 mg per day) within 90 days prior to randomization is exclusionary.

Epidural, IV, and IM glucocorticoids should not be used during the study or within 6 weeks prior to randomization. Parenteral administration of glucocorticoids is not permitted during the study.

Adrenocorticotropic hormone (ACTH) administered by injection is not allowed within 1 month prior to randomization and throughout the study.

Rectal Administration

Rectal administration of glucocorticoids, if necessary, should be short-term and topical preparations should be used.

Inhalation Glucocorticoids

Glucocorticoids administered by bronchial or nasal inhalation for treatment for conditions other than pSS may be given as needed.

6.8.3. Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) and other regularly administered analgesics should not be adjusted for at least 2 weeks prior to the first administration of the study intervention and through Week 24, and they may be changed only if the participant develops adverse reactions. Participants are permitted to receive the usual marketed doses approved in the country/territory in which the study is being conducted. Use of NSAIDs, including aspirin or selective cyclooxygenase-2 (COX-2) inhibitors, and other analgesics (including injectable NSAIDs, analgesics or other pain-relieving agents) that are not consistent with 'stable dosing' as defined in Table 4, may be permitted on an 'as needed' basis if used consistent with the guidance in Table 4. Participants using NSAIDS 'as needed' in specific cases (eg, prior to physical activity) may be considered stable but these situations should be discussed with the medical monitor or sponsor prior to enrollment into the study. Generally, NSAIDs must not be used for ≥12 hours for immediate release preparations or ≥24 hours for extended-release preparations, prior to study assessments (Table 4).

6.8.4. Non-biologic Immunomodulators

Stable dosing of non-biologic immunomodulators as described in Table 4 is required in those subjects on those medications at screening. No other immunomodulators are permitted during the study. A reduction in immunomodulators is allowed only if the participant develops unacceptable adverse reactions, with the implication that this may affect interpretation of the participant's clinical data. There should be no additions of a new immunomodulator to the existing treatment regimen.

Increases in baseline dose of immunomodulators will trigger TF rules.

6.8.5. Topical Medications

Regular use of topical medications is permitted consistent with Table 4. and Section 6.8.7. "As needed" use of topical NSAIDs, analgesics, or other pain-relieving agents such as capsaicin is permitted. 'As needed' use of topical glucocorticoids is permitted if involving a limited BSA (≤20%). Do not use on study visit days until after PRO and joint assessments have been completed.

6.8.6. Vaccinations (including COVID-19)

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

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

6.8.7. Prohibited Therapies

Use of biologics included in this Section is prohibited for 5 half-lives or 90 days prior to the first administration of study intervention, whichever is greater, unless specified elsewhere in the protocol. The use of small molecule therapies listed in this Section is prohibited for 14 days prior to screening, unless otherwise specified elsewhere in this protocol. Use of additional immunosuppressants or immunomodulators will trigger TF rules. Use of additional immunosuppressants or immunomodulators, other than those explicitly allowed in the inclusion/exclusion criteria (Sections 5.1 and 5.2) are prohibited.

Use of a mAb specifically approved for treatment of COVID-19 infections, including emergency use-authorized mAbs for COVID-19 per local regulations, may be permitted for participants who medically require it. Because concomitant exposure to nipocalimab may reduce the efficacy of anti-COVID-19 mAbs, study intervention must be withheld upon administration of anti-COVID-19 mAbs. It is unknown how long nipocalimab has to be stopped to minimize its effect on the efficacy of anti-COVID-19 mAbs. The resumption of the study intervention may be considered for participants who have recovered from COVID-19 and must be discussed with the sponsor's medical monitor.

Prohibited therapies include, but are not limited to, the following:

Biologics:

- Other Fc-conjugated therapeutic agents, including factor or enzyme replacement therapy, not specifically included in other criteria
- B cell-depleting therapy or B cell- or lymphocyte-targeted therapies used to treat autoimmune disease (including but not limited to obinutuzumab, belimumab, rituximab, other anti-CD20 agents, anti-CD22 [epratuzumab], anti-CD52 [alemtuzumab], B lymphocyte stimulator [BLyS]-receptor fusion protein [BR3] [eg, atacicept], anti-B-cell activating factor [BAFF] [eg, tabalumab])
- Anti-interferon medication (eg, anifrolumab)
- Anti-TNF medication (eg, infliximab, golimumab, certolizumab pegol, etanercept, CT-P13, and adalimumab)
- T-cell inhibitors (eg, alefacept, abatacept)

- Complement inhibitors (eg, eculizumab)
- Inhibitors of interleukins, including anti-IL-1 (eg, canakinumab, anakinra), anti-IL-6 (eg, tocilizumab), and anti-IL-17 (eg, brodalumab, secukinumab, and ixekizumab)
- Interleukin-2 inhibitors or exogenous IL-2 therapy
- Other biologics including but not limited to: natalizumab

Small molecules:

- Prednisone >10 mg/day
- Ophthalmic glucocorticosteroids
- Parenteral glucocorticosteroids
- Cyclosporine A or its derivatives (oral or topical ointment/cream preparations) except for ophthalmic use
- Use of cytotoxic drugs within 3 months prior to first administration of study intervention (or 6 months for IV) is prohibited, including but not limited to, cyclophosphamide, chlorambucil, nitrogen mustard, or other alkylating agents
- Calcineurin inhibitors (eg, tacrolimus, pimecrolimus, or sirolimus)
- JAK inhibitors (eg, tofacitinib, baricitinib)
- Toll-like receptor inhibitors are prohibited within 5 half-lives prior to screening.
- Thalidomide or lenalidomide
- Dapsone
- Adrenocorticotropic hormone (ACTH) by injection
- Epidural, IV and IM glucocorticoids
- Topical preparations of any of the therapies noted here, unless specifically allowed, are prohibited
- Other systemic immunomodulatory agents (eg, mizoribine) not listed elsewhere are prohibited within 5 half-lives prior to screening.

Other Therapies:

- Medications known to cause dry mouth, including but not limited to antihistamines (oral), selective serotonin reuptake inhibitors or other anxiolytics or anti-depressants, anti-psychotics, anti-seizure medications, anti-hypertensive medications, anti-nausea medications, anti-diarrheal medications, and diuretics, UNLESS the medication(s) are required, standard of care treatments for non-pSS comorbidities AND can be safely maintained at stable dosing throughout the study, including at screening, as judged by the investigator. Dose adjustments required or consistent with standard-of-care are permitted but must be documented
- Opioid analgesic medications, EXCEPT within the parameters outlined in Table 4.
- IVIg (EC #38 for washout details).

- Plasmapheresis (EC #38 for washout details).
- Plasma exchange (EC #38 for washout details).

Use of other therapies are also prohibited as noted below:

- Any investigational intervention (including investigational vaccines) or use of an invasive investigational medical device unless specifically allowed elsewhere in this protocol.
- Live vaccines
- The use of complementary therapies (eg, herbs, ointments, traditional Chinese medicine, acupuncture) that have the potential to activate or inhibit the immune system is prohibited (see Section 5.2). In addition, use of complementary therapies that have the potential to interact with antithrombotic agents is prohibited in those taking antithrombotic agents.

The use of other complementary therapies is strongly discouraged; in individual cases, use may be permitted following discussion with the study sponsor and/or medical monitor.

Sulfa-based antibiotics, where reasonable and necessary, are allowed but should generally be avoided.

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

- The participant withdraws consent to receive study intervention
- The participant becomes pregnant
- A participant develops infections with life-threatening consequences and requiring urgent interventions
- A participant develops an infection that is unresponsive or worsening while on anti-infective therapy, requiring IV antibiotic, antifungal, or antiviral interventions
- The investigator believes that for safety reasons or tolerability reasons it is in the best interest of the participant to discontinue study intervention
- The participant has serum total IgG <1 g/L (100 mg/dL).
- The participant develops a severe allergic reaction related to the study intervention (eg, anaphylaxis as per Sampson's criteria [Section 10.12]).

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

- Persistent inadequate response or worsening of pSS, the medical monitor or designee should be consulted for possible discontinuation of study intervention.

- If the participant initiates treatment with prohibited therapies for pSS, the medical monitor or designee should be notified for possible discontinuation of study intervention (Section 6.8.7).
- The participant develops a serious infection, including but not limited to sepsis or pneumonia.
- Note: Any serious infection should be discussed with the medical monitor or designee and study intervention should be withheld until the clinical assessment is complete.
- The participant develops a severe infusion reaction.

If a participant permanently discontinues study intervention for any reason before the end of the double-blind phase they may continue in the study. Participants who discontinue study intervention administration but do not withdraw from study participation should be encouraged to follow all subsequent study visits through Week 30. Week 24 may serve as the final safety follow-up visit if study intervention was stopped on or before Week 16, but a full physical examination should be performed along with the other Week 24 assessments. Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant. Additional participants may be entered to ensure the protocol-specified number of participants complete the study.

If the participant wishes to discontinue the study, then the final efficacy and safety follow-up visit assessments should be obtained as specified in the SoA (Section 1.3 or as noted in Footnote b of the SoA.

7.1.1. Liver Chemistry Stopping Criteria

Discontinuation of study intervention for abnormal liver tests is required by the investigator when a participant meets 1 of the conditions outlined in Section 10.8 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. Temporary Discontinuation

Interruption of study intervention administration should be considered for the following AEs:

- If a participant develops a severe or medically significant but not immediately life-threatening infection requiring IV anti-infective or operative/invasive intervention and requiring hospitalization or prolongation of existing hospitalization, the investigator may elect to withhold study intervention until the clinical scenario clarifies whether the infection is improving or getting worse, in which case the participant may be permanently discontinued from the study intervention (Section 7.1).
- If a participant develops clinical manifestations of hypoalbuminemia including 3+ pedal edema, ascites, or pleural or pericardial effusions.

The decision to continue treatment or withhold additional doses of study intervention will be made by the investigator. The investigator must inform the medical monitor if a temporary discontinuation of the study intervention occurs in a participant.

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Lost to follow-up
- Withdrawal of consent
- Death

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent, 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 as local regulations permit.

Prior to a participant withdrawing consent for follow-up, the investigator must offer the participant an opportunity for 1 of the alternative reduced follow-up mechanisms described below. Participants will not be allowed to continue to receive study intervention if reduced follow up is in place, but other study evaluations should continue as much as possible. Withdrawal of consent must be an infrequent occurrence in clinical studies (Rodriguez 2015), therefore, prior to the start of the study the sponsor and the investigator must discuss and reach a clear understanding of what constitutes withdrawal of consent in the context of the available reduced follow-up mechanisms listed.

Circumstances for Reduced Follow-up

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

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

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

7.2.1. Withdrawal From the Use of Research Samples

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

- The collected samples will be retained and used in accordance with the participant's original separate informed consent for optional research samples.

- The participant may withdraw consent for optional research samples, in which case the samples will be destroyed, and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study-site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study-site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the 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 Section 10.3.5). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF and in the separate ICF for optional research samples.

7.3. Lost to Follow-up

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

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

- The study-site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant's last known mailing address,

or local equivalent methods). These contact attempts should be documented in the participant's medical records.

- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

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

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The SoA (Section 1.3) summarizes the frequency and timing of efficacy, PK, immunogenicity, PD, biomarker, pharmacogenomic, and safety measurements applicable to this study. The timing and order of assessments, tests, and study procedures is critical. **Study assessments, tests, and procedures should be performed in the following order detailed in Table 5 by the appropriate staff.** Every effort should be made to complete the PROs before any other assessment is completed or laboratory samples are collected. However, variation in the order of items 'a' through 'd' in Table 5 may not constitute a protocol deviation, but item 'b' must precede item 'd'. For a given participant, every effort should be made to perform all tests at approximately the same time of day and by the same assessor at each study visit.

Table 5: Study Assessment and Procedure Order and Performing Staff

Order	Performing staff	Study Procedure, as ordered
1.	PI-designated, fully and appropriately trained site staff	a. PROs b. Unstimulated salivary flow test (must precede item d) c. Collection of samples for all laboratory tests, including cryoglobulins*, and PK tests (except post-infusion PK samples – see below) that will be collected at the study site d. After the fasting samples are collected and if desired, may consume non-SICCA medications (on fasting days) and eat and/or drink (regardless of fasting status) e. Cognitive tests f. Vital signs
2.	The PI or investigator-designated assessor (refer to Section 8.1)	g. Schirmer's test h. Physical exam including Joint count assessments i. (ClinESSDAI systems review and information collection will occur throughout the visit) j. PhGA
3.	PI-designated, fully and appropriately trained site staff	k. Study intervention administration l. Blood collection for PK (45 minutes ±15 minutes post-infusion when appropriate; see SoA and Section 8.6)
*4.	Ophthalmologist or Optometrist trained in OSS Appropriately equipped and trained laboratory personnel	†OSS Blood collection for cryoglobulin test (if NOT performed at the study site, where feasible)

Table 5: Study Assessment and Procedure Order and Performing Staff

*The timing of OSS performance and blood collection for cryoglobulins (locally, where feasible) may be performed on either (i) the day of, or (ii) on any day ≤5 days preceding study intervention administration, but should be done consistently for a given participant, with the following associated instructions:

i) On the day of IP administration: OSS should occur after the procedures in rows 1-3 outlined above. SICCA medications may be taken upon completion of OSS.

ii) On any day ≤5 days prior to IP administration: OSS and blood collection for cryoglobulins may occur on different days, or in any order on the same day. Medication restrictions apply to OSS. Fasting conditions apply for cryoglobulin testing. See Section 1.3 and the lab manual.

†OSS must be performed prior to SICCA medications. If OSS and Schirmer's test are performed on the same day, Schirmer's test must be performed ≥15 minutes prior to OSS. Please refer to Section 6.8.7 for medication restrictions.

All visit-specific PRO assessments should be conducted/completed in the order of study procedures as noted in Table 5 to prevent influencing participant perceptions. All PROs should be completed independently by study participants, in the following sequence: ESSPRI, FACIT-Fatigue, Sjogren's Symptoms, PGIS, PGIC, SF-36, HADS, WLQ, and PtGA. Refer to the PRO completion guidelines in the study manual for instructions on the administration of the PROs. Clinician-reported Outcome (ClinRO) assessments should be performed by the investigator or an adequately trained assessor (Section 8.1). Schirmer's test should be performed at approximately the same time of day at each study visit for each participant. If Schirmer's test and OSS are performed on the same day, the Schirmer's test must occur at least 15 minutes before the OSS.

Laboratory samples: All samples (including for safety, efficacy, and PD/biomarkers) must be obtained prior to study intervention, except for some samples for PK analysis, which will be obtained after study intervention administration (Section 1.3 and Section 8.6).

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

Screening Phase

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

Women of childbearing potential must have a negative urine pregnancy (β-hGH) test result at screening and a negative urine pregnancy test result at each visit and before any study intervention administration. Participants (as described in Section 5.1, Inclusion Criterion 13 and Section 5.2) must be reminded that they are required to use a highly effective method of contraception during

the study and must continue taking such precautions for 12 weeks after receiving the last dose of study intervention. The method(s) of contraception used by each participant must be documented.

All screening evaluations establishing participant eligibility will be performed and reviewed by the investigator before a participant can be randomized. Participants must have received approval for study randomization following assessment of inclusion and exclusion criteria. Details of the data assessment process will be provided in a separate manual. Participants must have received approval for study randomization following assessment of inclusion and exclusion criteria by sponsor or designee. The Sponsor or designee will assign randomization.

In order to be eligible for randomization, a participant must, during screening, have both a positive anti-Ro/SSA IgG test and at least 1 laboratory result that meets inclusion criterion 8.2 (see Section 5.1).

Blood Sample Collection

The total blood volume to be collected from each participant will be approximately 932 mL over the full duration of the study.

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

Sample Collection and Handling

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

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

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

Study-Specific Materials

The investigator will be provided with the following supplies:

- pSS Study Outcome Measures Quick Reference Guide
- Investigator Site File (including study protocol and nipocalimab IB)
- Study SIPPM and IPPI
- Sample ICFs
- Laboratory manual and laboratory kits
- IWRS Manual
- eCRF completion instructions

- Electronic ClinRO and/or PRO equipment (tablet device questionnaires, completion instructions)
- Salivary gland biopsy manual for substudy sites only
- Actigraphy watch and instructions for use
- Patient recruitment materials
- Procedural Manual for major adverse cardiovascular events (MACE) Adjudication

8.1. Efficacy Assessments

All efficacy evaluations and clinROs, including joint assessments, should be performed consistently by the same study investigator or sub investigator at every visit for each individual participant to achieve comparable measures over time. The investigator or investigator-designated assessor must be a rheumatologist or physician with other equivalent subspecialty training (eg, clinical allergy/immunology) and expertise in the clinical evaluation and management of pSS and other rheumatologic diseases (eg, SLE, RA, etc). Exceptions to this requirement must be approved by the sponsor. It is required that the investigator or investigator-designated assessor identify an appropriate backup in case the designated assessor is unavailable. If a rheumatologist or similarly trained expert is not available, a backup assessor should perform the assessments, including the joint assessment. The backup assessor(s) should be a similarly trained physician-colleague or very experienced health care provider with expertise in rheumatologic examinations generally, and at least 1 year of experience in scoring these instruments specifically. The Ocular Assessor for the OSS should be a qualified ophthalmologist or optometrist, and the OSS should be performed by the same Ocular Assessor at specified visits for a given participant. A similarly qualified backup Ocular Assessor should be identified in case the designated assessor is unavailable. The sponsor must approve any investigator-designated assessor and any backup assessors.

All study investigators, designated physicians, and other sponsor-approved assessors must complete all study-required trainings (online or video or any other format) and all associated examinations in order to obtain certification. All required trainings and certifications must be completed prior to participants entering screening at the sites. If there is a change in assessors at the sites, the new investigator, designated physician or other sponsor-approved assessor must complete all required trainings and certification prior to performing any efficacy assessment.

Independent data review by the sponsor or sponsor-designated independent reviewer(s) will be performed throughout the study for key assessments (eg, joint count assessment).

8.1.1. ClinESSDAI/ESSDAI

The Clinical EULAR Sjogren's Syndrome Disease Activity Index (clinESSDAI) is a validated tool used in clinical studies to measure the systemic disease activity in patients with Sjogren's syndrome. The clinESSDAI includes 11 domains divided into 3-4 activity levels, where zero represents no activity and low, medium, and high scores can vary in numerical value depending on the domain. A minimal clinically important improvement in clinESSDAI is defined as a decrease of at least 4 points in the composite clinESSDAI score. The ESSDAI is a disease activity index from which the clinESSDAI was derived. The ESSDAI differs from clinESSDAI by

inclusion of the biological domain, which includes B-cell biomarkers, such as, elevated gamma-globulin or IgG serum levels, low complement levels, the presence of cryoglobulinaemia new onset low serum IgG levels, and/or of a monoclonal gammopathy. Exclusion of the biological domain in the ESSDAI through use of the clinESSDAI is appropriate in circumstances involving a therapeutic intervention that targets the B cell-IgG axis, such as nipocalimab, which might result in collinearity between biomarkers and laboratory-based disease outcome measures, or with composite disease measures that include such laboratory values in the disease activity scoring. The Biological Domain components will include blinded lab values and will be determined separately from other ClinESSDAI domains and blinded after the Week 0 study visit. Please refer to Section 10.6 and the pSS Study Outcome Measures Quick Reference Guide for more information.

8.1.2. Joint Count Assessments

Joint assessments will be performed at visits indicated in the SoA (Section 1.3). To be considered as exhibiting pSS activity, an affected joint must be tender and demonstrate at least 1 additional sign of inflammation (eg, observed swelling such as edema or effusion) on physical examination as determined by the joint assessor. Each of 28 joints will be evaluated for pSS activity, observed as tenderness and swelling due to inflammation.

8.1.3. Schirmer's Test

The Schirmer's test determines whether a pSS participant produces enough tears to keep their eyes moist and healthy. To perform this non-invasive test, a piece of filter paper is placed inside the lateral corner of the lower eyelids, which are gently held closed for 5 minutes without the use of anesthesia. The Schirmer's test should be done at approximately the same time at each visit for a given participant. The amount of wetting (moisture) on the paper reflects the relative level of tear production and determines the severity of dry eye. A normal level of tear production is considered to be >10 millimeters (mm) of tears on the paper. Requirements for obtaining from topical ophthalmic agents are outlined in Table 4. The Schirmer's test should precede the OSS evaluation if they occur on the same day.

8.1.4. Unstimulated Salivary Flow Test

The unstimulated whole salivary flow rate is a relatively simple test that assesses basal saliva production. Some residual salivary function (defined as unstimulated salivary flow rate >0.01 mL/min) is required for inclusion in the study and will be assessed at screening and randomization. The unstimulated salivary flow measurement is carried out over a period of 15 minutes, as recommended (Navazesh 2008). The test should be carried out at approximately the same time at each visit, preferably in the morning hours after at least a 2-hour fasting period (includes refraining from chewing gum or hard candies/lozenges, use of artificial saliva, drinking water or any other oral to start of the test. Participants should be asked to swallow their saliva once or expectorate before the start of the test and then to spit into a pre-weighed tube for 15 minutes. The collection tube is re-weighed, and the volume of saliva is calculated using the specific gravity for water (1 g/mL). The flow rate for normal, unstimulated saliva is 0.25 to 0.4 mL/minute. A resting flow rate between 0.1 and 0.25 mL/min is considered low and < 0.1 is considered very low.

8.1.5. SICCA Ocular Staining Score

The SICCA ocular staining score is a quantitative, simplified method of grading keratoconjunctivitis sicca-related changes (KCS) ocular damage in patients with or without pSS as described by Whitcher, et al. Utilizing Lissamine Green dye for the conjunctivae and fluorescein for the corneas, ophthalmologists or optometrists, experienced in the evaluation and management of KCS use a slit lamp to grade the corneas and conjunctivae of each eye based on the type, severity, and location of dye staining. The OSS gives equal numerical weight to corneal and conjunctival involvement and is easily applied in clinical practice. Each eye receives its own numeric score ranging from 0 to 12. This procedure will only be performed on participants at selected sites and may be done ≤5 days in advance of study visit.

8.1.6. Physician's Global Assessment of Disease Activity

The PhGA (Divi 2015) independent of participants' assessment is recorded on a visual analog scale (VAS) with responses ranging from 0 to 100 mm, with the anchors "No Sjogren's Syndrome Activity" (0) at one end of the scale and "Extremely Active Sjogren's Syndrome" (100 mm) at the opposite end of the scale. Disease activity can range from 0 representing no disease activity, 100 mm representing the most extremely active disease. The baseline measurement for the PhGA is defined as the closest measurement taken prior to the initiation of the Week 0 administration. To score the PhGA, the investigator should be blinded to all the PRO assessments for a given participant from the same day the PhGA is performed, but the investigator should review the PhGA completed by the investigator for that participant on the prior study visit.

No worsening in PhGA defined as no significant deterioration (<10% increase from baseline) using a VAS (Divi 2015).

8.1.7. Patient-reported Outcomes

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

The PRO instrument must be available for regulators and for IRB/ERC submissions, therefore the PRO instrument or screen shots need to be attached to the protocol or provided in a companion manual with the instruments that will be submitted with the protocol.

The PRO and AE data will not be reconciled with one another.

8.1.7.1. ESSPRI

The European League Against Rheumatism (EULAR) Sjögren's Syndrome Patient-Reported Index (ESSPRI) is a patient-reported assessment of the severity of dryness, fatigue, and pain associated with primary Sjögren's Syndrome (Seror 2011). Patients are asked to rate the severity of dryness, fatigue and pain over the past 2 weeks on a numeric rating scale (NRS), ranging from 0 "No symptoms (dryness, fatigue or pain)" to 10 "maximal imaginable (dryness, fatigue, pain)". A global score, calculated as the mean of the 3 domain scores, ranges from 0 to 10, with higher scores reflecting greater (worse) symptom severity. Measurement properties, evaluated in a sample of patients with pSS (n= 395), were found to be adequate (Seror 2015). A threshold for a minimum

clinically important improvement was found to be a reduction of 1 point on the 0-10 NRS or 15% from baseline (Seror 2016).

8.1.7.2. Functional Assessment of Chronic Illness Therapy-Fatigue

The FACIT-fatigue version 4.0 is a 13-item questionnaire formatted for participant self-administration that assesses patient-reported fatigue and its impact upon daily activities and function over the past 7 days. Participants will be asked to answer each question using a 5-point Likert-type scale (0=Not at all; 1=A little bit; 2=Somewhat; 3=Quite a bit; and 4=Very much). The interpretation of FACIT-Fatigue score is such that a higher score indicates less fatigue, with a range of possible scores of 0-52, with 0 being the worst possible score and 52 the best. The FACIT-Fatigue can generally be completed in 5 minutes (Cella 2002; Lai 2011; Yellen 1997).

8.1.7.3. Sjogren's Symptoms

For assessment of Sjogren's symptoms, participants will be asked to report the worst severity of their ocular, oral, and vaginal dryness and joint pain over the past 7 days on a 0 to 10 numeric rating scale, with the left anchor indicating "No [specific symptom]" and the right anchor, "Severe [specific symptom]". The items are scored individually, with higher scores reflecting greater symptom severity. The administration frequency is described in the SoA (Section 1.3).

8.1.7.4. Patient Global Impression of Severity Sjogren's Syndrome

The Patient Global Impression of Severity Sjogren's Syndrome (PGIS) is a 1-item questionnaire based on the clinical global impression scale developed by Guy (1976), designed to assess a patient's impression of the severity of their health condition. The PGIS asks the participant to select the one response, ranging from 1- 'No Symptoms' to 5- 'Very Severe', that best describes the overall severity of their pSS.

The PGIS will be used as an anchor in a mixed methods analysis to determine meaningful change thresholds for the study PROs.

8.1.7.5. Patient Global Impression of Change Sjogren's Syndrome

The Patient Global Impression of Change Sjogren's Syndrome (PGIC) is a patient-reported measure of perceived change in their health condition following a study intervention. The PGIC assesses the extent to which a person's health condition has improved or worsened since the start of their treatment using a scale ranging from 1=Very much improved to 7=Very much worse (4=No change). The instructions ask the participant to select the one response that best describes the overall change in their pSS since treatment was initiated (Guy 1976).

The PGIC will also serve as an anchor measure to explore clinically meaningful change thresholds for the other PRO measures included in the study.

8.1.7.6. Short Form Health Survey 36 Standard (4-week recall)

The Short Form Health Survey 36 Standard (SF-36) version 2 is a participant self-administered, 36-item questionnaire measuring HRQoL. The recall period for all items is the past 4 weeks. The SF-36 version 2 Standard includes 8 domains that measure physical functioning, role limitations

due to physical health problems, bodily pain, general health, vitality social functioning, role limitations due to emotional problems and mental health. The 8 domains can be aggregated into 2 summary scales that reflect physical and mental health: a PCS and an MCS. Responses to all items are rated on a 3-, 5- or 6-point Likert scale. The SF-36 version 2 Standard can generally be completed in 5-10 minutes (Quality Metric 2011).

These scales are scored from 0 to 100 with higher scores indicating better health. Another algorithm yields 2 summary scores, the PCS and MCS. These summary scores are also scaled with higher scores indicating better health (Ware 1994). The concepts measured by the SF-36 are not specific to any age, disease, or treatment group, allowing comparison of relative burden of different diseases and the relative benefit of different treatments.

8.1.7.7. Hospital Anxiety and Depression Scale

The HADS is a 14-item instrument developed to detect states of anxiety and depression. The items are divided into 2 subscales: 1 for anxiety (HADS-A) and 1 for depression (HADS-D; Zigmond 1983). Each subscale score ranges from 0 to 21. Scores ≥8 identify mild cases, scores 11 to 15 identify moderate cases, and scores ≥16 identify severe cases (Snaith 2003).

8.1.7.8. Work Limitations Questionnaire

The Work Limitations Questionnaire (WLQ) is a 25-item self-report questionnaire that asks respondents to rate their level of difficulty or ability to perform specific job demands to assess health-related work productivity loss (Lerner 2001). The 25 items are aggregated into 4 scales: time management, physical demands, mental-interpersonal, and output. Scale scores range from 0 (limited none of the time) to 100 (limited all of the time) and represent the reported amount of time in the prior 2 weeks that respondents were limited on-the-job. Using an algorithm, WLQ scale scores can be converted into an estimate of productivity loss (or gain).

8.1.7.9. Patient's Global Assessment of Disease Activity

The Patient's Global Assessment of Disease Activity (PtGA) is a single item that asks participants to rate the current status of their pSS on a 0-100 mm visual analog scale (VAS), with responses ranging from 0 (Very well) to 100 (Very poor). The PtGA will be used to calculate the DAS28 composite index.

8.1.8. CRESS

The CRESS is a composite index that consists of 5 items (systemic disease activity, patient reported symptoms, salivary gland function, tear gland function, and serological activity) designed to assess treatment efficacy in patients with pSS. Assessments of these items include: clinESSDAI, ESSPRI, Schirmer's test or ocular staining score, unstimulated whole salivary flow or salivary gland ultrasonography, and rheumatoid factor or immunoglobin G level. (Arends 2021)

8.1.9. STAR

The STAR composite disease activity score assesses disease features of pSS and is designed to be an efficacy endpoint in randomized clinical trials. The candidate STAR includes 5 domains

(systemic activity, patient-reported outcome, lachrymal gland function, salivary gland function, and biological), each with a different weighting. Assessments of these domains (with weighting in parentheses) include: clinESSDAI (3), ESSPRI (3), Schirmer's test or ocular staining score (1), unstimulated whole salivary flow or ultrasound (1), and serum immunoglobin G level or rheumatoid factor (1). A candidate STAR response is defined as a composite STAR score of ≥5 points. Other thresholds for defining STAR response will also be analyzed, as appropriate. (Seror 2022)

8.2. Exit Interviews

In this study, qualitative interviews will be conducted with patients within two weeks of the final treatment visit (Week 24) or upon early termination. Informed consent for the exit interviews will be obtained as part of the study ICF, and interviews will be conducted with consenting participants by an external vendor. The objectives of this interview study are to assess the patient experience with treatment, treatment satisfaction, and what constitutes a clinically meaningful change from the patient perspective. Evaluation of potential AEs will be conducted at the time of the interview. The trained interviewer, from the vendor, will record any potential AE per the pharmaco-vigilance process and report them to the site within 24 hours of the completed interview. Sites will then evaluate the reported event(s) for AEs/SAEs based on procedures described in Section 8.5). It is estimated that the interviews will last approximately 60 minutes. The interviews will be audio recorded, transcribed, and analyzed, as appropriate.

8.3. Performance Outcome Assessments (PerfO)

8.3.1. International Digit Symbol Substitution Test -Symptoms

The IDSSTS is a brief, commonly used, and universally understood cognitive function test that requires a participant to match symbols to numbers according to a key provided. The participant copies the symbol into spaces below a row of numbers. The number of correct symbols within the allowed time (3 minutes) constitutes the score.

8.3.2. Detection (DET; Psychomotor Function)

The Detection test is a measure of psychomotor function and uses a well-validated simple reaction time paradigm with playing card stimuli. In this test, the playing cards all depict the same joker. The subject is asked to press the Yes key as soon as the card in the center of the screen turns face up. The software measures the speed and accuracy of each response. The duration of the test is 3 minutes.

8.3.3. Identification Test (IDN; Attention)

The Identification test is a measure of visual attention and uses a well-validated choice reaction time paradigm with playing card stimuli. In this test, the playing cards are all either red or black jokers. The subject is asked whether the card displayed in the center of the screen is red. The subject responds by pressing the Yes key when the joker card is red and No when it is black. The software measures the speed and accuracy of each response. The duration of the test is 3 minutes.

8.4. Safety Assessments

Details regarding the DMC are provided in Committees Structure in Section 10.3.6.

Adverse events will be reported and followed by the investigator as specified in Section 8.5 and Section 10.5.

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

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

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

8.4.1. Physical Examinations

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

The full physical examination will be performed at screening and the Week 30/Final safety follow-up visit, including the head and neck, chest, abdomen, and extremities, as well as including examinations based on the participant's medical history and manifestations of pSS (eg, sicca symptoms, neuropathies, arthritis). The full physical examination may include breast, anorectal and/or genitalia examination when relevant, per the judgement of the investigator.

A targeted physical examination, performed at visits not specified for full physical exams, based on the participant's pSS history and manifestations should also include evaluation of signs or symptoms of infection.

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

Height and Weight

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

8.4.2. Vital Signs

Temperature, pulse/heart rate, respiratory rate, and blood pressure will be assessed as specified in the SoA (Section 1.3).

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

If feasible, 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).

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

8.4.3. Electrocardiograms

A 12-lead electrocardiogram (ECG) will be performed at screening.

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.

8.4.4. Clinical Safety Laboratory Assessments

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

The following tests panels will be performed by the central laboratory (see Section 10.2) unless otherwise specified or approved by the medical monitor or designee:

- Hematology assessments
- Blood chemistry assessments
- Urine assessments
- Coagulation assessment
- Serology assessment (screening only)
- Lipid panel assessments

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

8.4.5. Pregnancy Testing

A urine pregnancy test (b-hCG) will be conducted at screening for women of childbearing potential only. Urine pregnancy testing will be conducted at each dosing visit prior to dose administration for women of childbearing potential only (performed locally), see definition in Section 10.7. Additional urine pregnancy tests may be performed, if applicable, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time

during the participation in the study. Additional local serum pregnancy testing is allowed if mandated by local regulations or at the investigator's discretion.

8.4.6. Concomitant Medication Review

Concomitant medications will be reviewed at each visit.

8.4.7. Adverse Events Temporally Associated with Infusion

Observation time after each 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 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.

8.4.8. Infusion Reactions

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

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

8.4.9. Hypersensitivity Reactions

Before any administration of study intervention at the study site, appropriately trained personnel and medications (eg, antihistamines, injectable epinephrine) must be available to treat hypersensitivity reactions, including anaphylaxis. All participants must be observed carefully for signs and symptoms of a hypersensitivity reaction (eg, urticaria, pruritis, angioedema, wheezing, dyspnea, or hypotension). Potential cases of anaphylaxis should be assessed according to Sampson's Criteria (Section 10.12; Sampson 2006).

In the case of a severe allergic reaction (eg, anaphylaxis), SC aqueous epinephrine, corticosteroids, respiratory assistance, and other proper resuscitative measures are essential and must be available when study intervention is being administered. Participants who experience severe adverse reactions related to an infusion should be considered to discontinue from further study intervention administrations.

8.4.10. Infections

Investigators are required to evaluate participants for any signs or symptoms of infection at scheduled visits. Study intervention administration should not be given to a participant with a clinically significant, active infection. If a participant develops a serious infection, including but not limited to sepsis or pneumonia, discontinuation of study intervention must be considered

(Section 7.1). Any serious infection should be discussed with the medical monitor or designee, and study intervention should be withheld until the clinical assessment is complete.

8.4.11. Increased Lipids

Lipids levels are routinely monitored in participants throughout the study.

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

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

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, and PQC, 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 PQC can be found in Section 10.5.

8.5.1. 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.

Serious Adverse Events

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

Serious adverse events, including those spontaneously reported to the investigator within the final safety visit after the last dose of study intervention, must be reported. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

A possible Hy's law Case is defined by the occurrence of ALT/AST ≥3×ULN, ALP <2×ULN together with Tbili ≥2×ULN or INR >1.5 (if measured). Any possible Hy's Law case is considered

an important medical event and should be reported to the sponsor within 24 hours, even before all other possible causes of liver injury have been excluded.

Selected events, including potential MACE, will undergo adjudication by an Event Adjudication Committee (EAC). For such events, investigators will be asked to provide a specific package of information for evaluation. Further details will be provided in the "Procedural Manual for MACE Adjudication."

Information regarding SAEs will be transmitted to the sponsor using the SAE Form and Safety Report Form of the eCRF, 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. 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.

8.5.2. Method of Detecting Adverse Events and Serious Adverse Events

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

8.5.3. Follow-up of Adverse Events and Serious Adverse Events

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

Adverse events, and the special reporting situation of pregnancy, will be followed by the investigator as specified in Section 10.5.

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

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all SUSARs. The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

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

- Worsening or flares related to pSS

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 intervention group than in the control group and the sponsor concludes there is a reasonable possibility that the drug under investigation caused the anticipated event.

The plan for monitoring and analyzing the anticipated 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.

8.5.5. 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, see Section 7.1.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required (Section 10.7).

8.5.6. Adverse Events of Special Interest

Treatment-emergent adverse events associated with the following situations are considered as AESIs:

1. Infections that are severe or require IV anti-infective or operative/invasive intervention.
2. Hypoalbuminemia with albumin <20 g/L (<2.0 g/dL); applicable to participants who have albumin >20 g/L at previous assessments. Those who enter with <20 g/L and stay below this level should not be reported as an AESI. Those who enter with an albumin > 20 g/L or those who enter with albumin <20g/L and then have an increase in albumin >20 g/L which subsequently decreases to <20 g/L should be reported as an AESI.

These AEs occurring after the first study intervention administration(s) in participants in this clinical study must be reported by the investigator to the sponsor or designee within 24 hours after being made aware of the event, according to the procedures in Section 10.5 for SAEs. These events are to be considered serious only if they meet the definition of an SAE.

8.6. Pharmacokinetics

Serum samples will be used to evaluate the PK of nipocalimab as well as the immunogenicity of nipocalimab (antibodies to nipocalimab). Serum collected for PK and immunogenicity analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during

or after the study period. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

8.6.1. Evaluations

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

Serum samples will also be collected at the final visit from participants who terminate study participation early. At visits where PK and immunogenicity will be evaluated, 1 blood draw of sufficient volume can be used. Each sample will be split into 3 aliquots (1 aliquot for serum nipocalimab concentration, 1 aliquot for antibodies to study intervention, and 1 aliquot as a back-up). Samples must be collected before study intervention administration at visits when a study intervention administration is scheduled. At Weeks 0, 2, 8, and 12, a blood sample before study intervention administration 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 3 to 7 days after the Week 0 or Week 2 visit other than the scheduled samples.

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 biologic samples can be found in the Laboratory Manual.

8.6.2. Analytical Procedures

Pharmacokinetics

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

8.6.3. Pharmacokinetic Parameters and Evaluations

Parameters

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

8.7. Genetics and Pharmacogenomics

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

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

The optional pharmacogenomic samples may be analyzed for identification of genetic and epigenetic factors that may be associated with the disease and/or the response to the treatments. This research may consist of the analysis of one or more candidate genes, or the analysis of genetic and epigenetic markers throughout the genome, or analysis of the entire genome (as appropriate) in relation to the disease and the treatments. Whole blood samples of approximately 6 mL will be collected for the genetic and pharmacogenomics analyses.

8.8. Biomarkers

Biomarker assessments will be made to examine the biologic response to treatment and to identify biomarkers that are relevant to nipocalimab treatment response and/or pSS, where local regulations permit. Assessments (detailed below) will include the evaluation of relevant biomarkers in serum, plasma, whole blood, saliva, tears, peripheral blood mononuclear cells, and salivary gland biopsy samples (optional) 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 but is not limited to the following objectives:

1. To understand the serologic, cellular, and molecular effects of nipocalimab.

2. To understand pSS pathogenesis.

3. To understand why individual participants may respond differently to nipocalimab.

4. To understand the impact of treatment with nipocalimab on salivary gland tissue and peripheral inflammation.

5. To develop biomarkers to identify pSS populations that may be responsive or non-responsive to treatment with nipocalimab.

Instructions for the collection and shipment of biomarker samples will be found in the Laboratory Manual.

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.

8.8.1. Pharmacodynamics

Samples for the analysis of PD biomarkers will be collected from all participants. Serum level of total IgG and albumin will be measured to assess the PD effect of nipocalimab. Different subclasses of IgG (IgG1, IgG2, IgG3, IgG4), IgA, IgM, IgE, and CICs may also be evaluated using separate assays. The relationship between PD effects and clinical responses may be assessed.

8.8.2. Serum and Plasma Biomarkers

Blood samples will be collected from all participants for serum and plasma-based biomarker analyses, where local regulations permit. Serum and plasma may be analyzed for levels of circulating proteins, autoantibodies (eg, ANA, anti-dsDNA, anti-Smith, anti-Ro/SSA, anti-La/SSB, anti-RNP, and anti-phospholipid antibodies, see Section 10.2 for further details), and other inflammation-related molecules and/or disease-associated serologies relevant to pSS pathogenesis and nipocalimab treatment.

8.8.3. Whole Blood Gene Expression Profile

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

8.8.4. Peripheral Blood Mononuclear Cells

If operationally feasible, whole blood will 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 in response to nipocalimab treatment and/or related to pSS pathogenesis. These analyses may not be performed if cryopreserved PBMC samples do not meet the quality or quantity standard required for the assessments

8.8.5. Saliva and Tear Biomarkers

Saliva and tears will be collected from all participants at the times specified in the SoA (Section 1.3). Saliva may be used for functional assessments and frozen for subsequent analysis of autoantibodies, proteins and other inflammation-related molecules relevant to pSS pathogenesis and nipocalimab therapy. Tears will be collected from frozen Schirmer's filter strips through elution techniques and may be analyzed for levels of autoantibodies, proteins and other inflammation-related molecules relevant to pSS pathogenesis and nipocalimab therapy.

8.8.6. Tissue Biomarkers

Salivary gland biopsy samples will be collected from all participants who consent to this optional substudy at the times specified in the SoA (Section 1.3). Tissue samples may be analyzed for levels of proteins, RNA transcripts, and other inflammation-related molecules and/or soluble factors relevant to pSS pathogenesis and nipocalimab therapy. Protein and gene expression may be measured at higher resolution in various immune cell populations isolated from these biopsy samples as permitted by relevant and advancing technologies that may enable single cell analyses. The biopsy samples may also be used in additional analyses including but not limited to histologic and immunohistochemical assessment of disease and healing.

8.9. Immunogenicity Assessments

Antibodies to nipocalimab will be evaluated in serum samples collected from all participants according to the SoA (Section 1.3). Additionally, serum samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.

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

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 concentrations to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study intervention(s).

8.10. Medical Resource Utilization and Health Economics

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

8.11. Digital Health – Actigraphy Measurements

Actigraphy, a non-invasive method of monitoring human rest/activity patterns, will be performed using a wrist-worn actigraphy watch. Only accelerometry measurements will be collected from actigraphy watches, with the data utilized to assess physical activity, mobility, and sleep parameters. Participants at selected sites will be provided the option to wear a single actigraphy watch at screening with instructions for use. Participants will be asked to continuously wear the watch on the non-dominant wrist from screening until Week 24, and bring the watch to each visit,

during which the data from the watch may be downloaded, as necessary. Sites and participants will not have access to data generated from the use of the watch. All actigraphy watches will be collected from participants at their respective Week 24 visit.

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.

Data will be summarized using descriptive statistics. Continuous variables will be summarized using the number of observations, mean, SD, coefficient of variation, median, interquartile range and range as appropriate, unless otherwise specified. Categorical values will be summarized using the number of observations and percentages as appropriate.

9.1. Statistical Hypotheses

The hypothesis is at least one of the two nipocalimab dose regimens is superior to placebo as measured by change from baseline in clinESSDAI at Week 24.

The testing will be performed at a 2-sided significance level of 0.1. No multiplicity control is planned.

9.2. Sample Size Determination

The primary endpoint is change from baseline in clinESSDAI at Week 24. Based on a previous external study (abatacept study), the standard deviation (SD) of this endpoint was 6.4 to 6.6. Assuming a SD of 7, the power estimates for detecting a clinically meaningful improvement of 4 points (or 3 points) at a 2-sided level of significance of 0.10 are listed in Table 6.

Table 6: Power to Detect a Treatment Difference in change form baseline in clinESSDAI at Week 24

Sample size per arm	Power	
	Between group difference = 4	Between group difference = 3
50	88.3%	68.6%

9.3. Populations for Analysis Sets

For purposes of analysis, the following populations are defined:

Analysis Sets	Description
Enrolled	All participants who sign the ICF.
Full Analysis Set (FAS)	The full analysis set (FAS) includes all randomized participants who received at least 1 dose (partial or complete) of any study intervention.
Safety	The safety analysis set includes all randomized participants who received at least 1 dose (partial or complete) of any study intervention.

Analysis Sets	Description
Pharmacokinetics (PK) Analysis Set	The PK analysis set is defined as all randomized participants who received at least 1 complete dose of nipocalimab and have at least 1 valid post-dose blood sample drawn for PK analysis.
Immunogenicity Analysis Set	The immunogenicity analysis set is defined as all randomized participants who received at least 1 dose (partial or complete) of nipocalimab and have appropriate samples for ADA detection.
Pharmacodynamic (PD) Analysis Set	The PD analysis set is defined as participants who received at least 1 dose (partial or complete) of nipocalimab and have at least 1 valid post-dose blood sample drawn for PD analysis.

Note: Additional details, as needed, will be described in the SAP.

9.4. Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to 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

Simple descriptive summary statistics, such as n, mean, SD, median, IQ range, minimum, and maximum for continuous variables, and counts and percentages for discrete variables will be used to summarize most data. In addition, graphical data displays (eg, line plots) and participant listings may also be used to summarize/present the data.

The chi-squared test or Cochran-Mantel-Haenszel (CMH) test stratified by stratification factors will be used to compare categorical variables such as the proportion of participants responding to treatment, unless otherwise stated. In general, ANOVA with the stratification factors as independent variables will be used for analyzing continuous variables, unless otherwise stated. All statistical tests will be performed at α=0.10 (2-sided).

Efficacy analyses and study population summaries will be based on the Full Analysis Set, which is defined as all randomized participants who received at least one dose of study intervention, unless otherwise stated. Participants included in the efficacy analyses will be summarized according to their assigned intervention group regardless of whether or not they receive the assigned intervention.

Safety, PK, and immunogenicity analyses will be based on the Safety Analysis Set, PK Analysis Set and immunogenicity analysis set, respectively.

9.4.2. Primary Endpoint

The primary endpoint is change from baseline in clinESSDAI score at Week 24. The primary estimand is defined as follows:

- Treatment:

- Nipocalimab 5 mg/kg q2w in addition to standard of care through Week 22
- Nipocalimab 15 mg/kg q2w in addition to standard of care through Week 22
- Placebo q2w in addition to standard of care through Week 22

Standard of care includes symptomatic medications/procedures (including ophthalmic drops, artificial tears and saliva, punctum plugs, and secretagogues), and/or one immunomodulator (Table 4), with or without low-dose glucocorticosteroids (≤10 mg/day prednisone equivalent).

- Population: Men and women between the ages of 18 to 75 years, inclusive with active, autoantibody-positive pSS
- Variable: Change from baseline in clinESSDAI at Week 24
- Intercurrent Events:
  - (1) Participants who experienced at least one of the following events will be considered Treatment Failures.
    - Discontinuation of study intervention prior to Week 24 for any reason
    - Initiation or increase medications for pSS
  - (2) Discontinuation of study intervention due to COVID-19 or confirmed COVID-19 pandemic situation or confirmed COVID-19 infection

For both types of intercurrent events, hypothetical strategy which envisages that participants would not have these events will be used. Note: Data from the time an intercurrent event occurred and onward will not utilized.

- Population-level Summary: Difference in the means of the variable (ie, change from baseline in clinESSDAI at Week 24) between treatment arms

The primary analysis will use MMRM with an unstructured variance-covariance structure and change from baseline in clinESSDAI at Week 24 as the dependent variable and baseline clinESSDAI, treatment, study visit, treatment by study visit interaction and stratification factors for randomization as independent variables. An alternative covariance structure may be used if there is a convergence issue. No missing data imputation will be performed explicitly. Comparisons will be carried out at a 2-sided 0.1 level of significance to evaluate the treatment difference between individual nipocalimab arms and placebo.

Given the hypothesis generating nature of the study, no multiplicity control is planned.

The following sensitivity analyses will also be performed:

- Same analysis as the primary analysis but assume the participants with intercurrent event(s) to have 0 change from baseline. This analysis is corresponding to a supplementary estimand which is the same as the primary estimand but employs a composite strategy for the first type of intercurrent events (ie, Treatment Failures) assuming the worst outcome.

- Same analysis as the primary analysis but assume both types of intercurrent events have no impact on the treatment effect. Data points collected after intercurrent events will be included in the analysis. This analysis is corresponding to a treatment policy estimand.

Other sensitivity analyses will be specified in the SAP.

To evaluate the robustness of the primary analysis, subgroup analysis based on demographics, baseline characteristics, disease severity, and baseline medications will be performed. Some of the subgroups that will be pre-defined include, but are not limited to:

- Age (≤ 65, > 65)
- Race (White, Black, Other)
- Gender (M, F)
- Region (North America, Eastern Europe, Western Europe, Other)
- Weight (≤ median, > median)
- Baseline HCQ (or other anti-malarial drug) use (Yes, No),
- Baseline oral corticosteroid use (Yes, No),
- Baseline immunomodulator use (Yes, No)
- Disease duration at baseline (≤ median, > median)
- Baseline ClinESSDAI total score (≤ median, > median)
- Baseline ClinESSDAI domain scores (≤ median, > median)
- Baseline ESSPRI total score (≤ median, > median)
- Baseline ESSPRI domain scores (≤ median, > median)
- Baseline glandular function (≤ median, > median)
- Baseline IgG (≤ median, > median)
- Baseline autoantibody levels (≤ median, > median)
- Baseline CRP levels (≤ median, > median)
- Baseline ESR levels (≤ median, > median)

As supportive analysis, the primary endpoint may also be analyzed at various times, such as Weeks 12 and 16, in addition to the Week 24 analysis.

9.4.3. Secondary Endpoints

The following major secondary endpoints will be summarized by treatment group. For between group comparisons, p-values will be reported. However, no multiplicity control is planned.

- Change from baseline in ESSPRI score at Week 24
- Improvement of ≥4 points from baseline in ESSDAI (minimal clinically important improvement) at Week 24

- Improvement of ≥4 points from baseline in clinESSDAI score (minimal clinically important improvement) at Week 24
- ESSPRI response defined as a decrease of one point or a decrease of ≥15% from baseline (minimal clinically important improvement) at Week 24
- Disease response according to the STAR composite score at Week 24
- Improvement in disease activity level by ≥1 level in at least one clinESSDAI or ESSDAI domain (biological, hematological, cutaneous, constitutional, lymphadenopathy and lymphoma, and glandular) at Week 24
- Improvement from baseline in ≥3 of 5 CRESS categories at Week 24

Secondary endpoints may be analyzed at various times, such as Weeks 12 and 16, in addition to the Week 24 analysis.

9.4.3.1. Pharmacokinetic Analyses

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

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

9.4.3.2. Immunogenicity Analyses

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

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

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

9.4.3.3. Safety Analyses

All safety analyses will be based on the safety analysis set based on actual intervention received, unless otherwise specified.

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE occurring at or after the initial administration of study intervention is considered to be treatment emergent. If the event occurs on the day of the initial administration of study intervention, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the AE onset time is missing and the AE onset date is the same as the infusion date, the missing time will be imputed with the time of the infusion. If the event date is recorded as partial or completely missing, then the event will be considered to be treatment emergent unless it is known to be prior to the first administration of study intervention based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

Summaries, listings, datasets, or participant narratives may be provided, as appropriate, for those participants who die, who discontinue intervention due to an AE, or who experience a severe or an SAE.

Listings of all participants with MACE (non-fatal myocardial infarction, stroke, and cardiovascular death) will be provided.

Clinical Laboratory Tests

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

Vital Signs

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

Weight

Descriptive statistics of changes from baseline will be summarized at each scheduled time point.

9.4.4. Exploratory Endpoints

The following exploratory endpoints will be summarized by treatment group. Nominal p-values may be reported at selected visit(s) for descriptive purposes.

Clinical Endpoints:

- Change from baseline in PhGA overtime through Week 24
- Change from baseline in ESSPRI components over time through Week 24
- Change from baseline in DAS28 CRP over time through Week 24 in participants with at least 3 swollen and 3 tender joints at baseline
- Change from baseline in DAS28 CRP over time through Week 24 in participants with <3 swollen and 3 tender joints at baseline
- Change from baseline in DAS28 CRP over time through Week 24
- Change from baseline in IDSSTS, Identification test, and Detection test scores over time through Week 24
- SSRI response defined as ≥20% improvement from baseline in at least two of five domains (fatigue, oral dryness, ocular dryness, unstimulated whole salivary flow, and erythrocyte sedimentation rate) at Week 24
- SSRI response defined as ≥ 30% improvement from baseline in at least two of five domains (fatigue, oral dryness, ocular dryness, unstimulated whole salivary flow, and erythrocyte sedimentation rate) over time through Week 24
- SSRI response defined as ≥ 30% improvement from baseline in at least three of five domains (fatigue, oral dryness, ocular dryness, unstimulated whole salivary flow, and erythrocyte sedimentation rate) at Week 24

PRO Endpoints:

Change from baseline over time through Week 24 in scores for the following endpoints:

- HADS
- WLQ
- Sjögren's Symptoms (fatigue, ocular, oral, and vaginal dryness as well as joint pain)
- FACIT-Fatigue questionnaire
- PGIS of Sjögren's Syndrome
- PGIC in Sjögren's Syndrome
- SF-36 v2 domains and PCS and MCS summary scores
- PtGA

SICCA Signs Symptoms Endpoints:

- Change from baseline in unstimulated salivary flow rate over time through Week 24
- Improvement from baseline in salivary unstimulated flow rate (especially participants with dryness and fatigue dominant phenotype) over time through Week 24
- Change from baseline in tear secretion amount using the Schirmer's Test over time through Week 24

- Change from baseline in frequency of use and the amount of artificial tears and/or saliva to treat dryness over time through Week 24
- Change from baseline in Ocular Surface Staining (OSS) at Week 24

Steroid Use Endpoints:

- Change from baseline in steroid use in comparison to mean doses between groups over time through Week 24

9.4.5. Other Analyses

Biomarkers Analyses

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

Some pharmacodynamic endpoints are:

- Total antibody (eg, IgG, IgM, IgA), IgG subclasses, and broader autoantibody profiling
- Change in ESR and serum albumin levels
- Serum biomarker measurements, for example, inflammatory proteins, complement, cytokines, and chemokines
- Change in absolute number and frequency (percent of total leukocytes) of immune cell subsets in blood
- Changes in gene expression profiles in blood (ribonucleic acid [RNA]) over time
- Changes in autoantibody and soluble proteins in saliva and tears
- Biopsy – changes in cellular infiltrates, soluble mediators of inflammation, and IgG levels by immunohistochemistry and other methods.
- Changes in gene expression profiles in the salivary gland tissue

Change in biomarkers including, but not limited to, CRP, ESR, total IgG, IgG1, IgG2, IgG3, IgG4, and autoantibodies (anti-Ro/SSA, anti La/SSB, RF, and ANA) over time may be summarized by treatment group. Associations between baseline levels and changes from baseline in select biomarkers and clinical response may be explored. Results of biomarker analyses will be documented in a separate technical report.

Planned biomarker analyses may be deferred if emerging study data show no likelihood of providing useful scientific information or insufficient number of samples are available for analyses. 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.

Pharmacokinetic/Pharmacodynamic Analyses

If data permit, the relationship between serum concentrations of nipocalimab and the efficacy measures and/or relevant PD biomarkers/endpoints may be explored when appropriate. If any visual trend is observed, additional analysis may be conducted. Analyses results will be documented 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. DNA samples will be used for research related to nipocalimab and/or pSS. They may also be used to develop tests/assays related to nipocalimab and/or pSS. Pharmacogenomic 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. Correlation between treatment response and genetic polymorphisms will be explored. Analyses results will be documented in a separate technical report.

Digital Health – Actigraphy Analyses

The raw data sampled by the actigraphy watch sensors will be transformed into derived digital health endpoints, assessing the changes from baseline on physical activity, mobility and sleep parameters through Week 24. Endpoints include, but are not limited to, step count, activity count, sleep time, sleep efficiency, and percent mobile time.

Additional actigraphy endpoints may be derived using emerging algorithms. Associations between actigraphy endpoints and primary and secondary endpoints may be explored. All actigraphy-related analyses are considered exploratory and will be summarized in a separate technical report.

9.5. Interim Analysis

9.5.1. Week 8 Interim Analysis

An interim analysis (IA) will be performed when the first 30 participants reach Week 8 to evaluate nipocalimab PK and the impact on IgG lowering by nipocalimab with and without concomitant HCQ use. An independent Interim Analysis Committee (IAC), including a limited number of internal members who are not otherwise involved in the conduct of the study, will be unblinded to perform this analysis. Recommendations based on the IA results will be specified in the charter. The recommendation is non-binding. Further details will be specified in the IA SAP/Charter.

Based on these data the IAC may recommend to continue as planned, or adjust randomization if not all dose levels are appropriate to continue. The recommendation is non-binding. Further details will be specified in the IAC SAP/Charter.

9.5.2. Week 24 Interim Analysis (67% participants)

A second IA will be performed at the time when 67% of the participants completed Week 24. The purpose of the IA is to trigger the preparation of the Phase 3 study. The result of the IA will have

no impact of the conduct on this current study. The same independent IAC mentioned in Section 9.5.1, of which the members are not otherwise involved in the conduct of the study will be used to carry out the IA.

Selected efficacy endpoints will be used for the interim efficacy evaluations. Summaries and/or analyses of PK, biomarker data, ie, total IgG, autoantibody and albumin levels may also be evaluated, if available. Additional data available at the time of the interim analysis (eg, secondary endpoints, other time points) may also be considered.

The IAC will review the unblinded interim efficacy data and make recommendations regarding the continuation of the study. The recommendation is non-binding. Refer to Committee Structure in Section 10.3.6 for further information on the IAC.

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

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

ACR	American College of Rheumatology
ACTH	adrenocorticotropic hormone
ADA	anti-drug antibodies
AE	adverse event
AESI	Adverse events if special interest
ALT	Alanine aminotransferase
APS	anti-phospholipid syndrome
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AZA	Azathioprine
BCG	Bacille Calmette-guerin
B-hCG	B-human chorionic gonadotropin
BSA	body surface area
CIC	Circulating immune complexes
ClinRO	clinician-reported outcome
Cmax	maximum concentration
COVID-19	Coronavirus Disease 2019
CRESS	Composite of Relevant Endpoints in Sjögren's Syndrome
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
DBL	database lock
DDI	drug-drug interaction
DMC	Data Monitoring Committee
dsDNA	double stranded deoxyribonucleic acid
DSM-V	Diagnostic and Statistical Manual of Mental Disorders (5th edition)
ECG	Electrocardiogram
eCRF	electronic case report form
eDC	electronic data capture
EMA	European Medicines Agency
ESR	erythrocyte sedimentation rate
ESSPRI	EULAR Sjögren Syndrome Patient Reported Index
EU CTR	European Union Clinical Trial Regulations
EULAR	European League Against Rheumatism
FACIT	Functional Assessment of Chronic Illness Therapy
FcRn	neonatal fragment crystallizable receptor
FDA	Food and Drug Administration
FIH	first-in-human
FOIA	Freedom of Information Act
FSH	follicle stimulating hormone
GC	Glucocorticoid
GCP	Good Clinical Practice
gMG	generalized myasthenia gravis
HADS	Hospital Anxiety and Depression Scale
HBV	hepatitis B virus
HBC	hepatitis C virus
HCQ	hydroxychloroquine
HBsAg	hepatitis B surface antigen
HDFN	hemolytic disease of the fetus and newborn
HIV	human immunodeficiency virus
HRQol	health-related quality of life
HRT	hormonal replacement therapy
IA	Interim analysis
IAC	Interim Analysis Committee

IB	Investigator's Brochure
ICE	intercurrent event
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IL	Interleukin
IM	Intramuscular
IMP	Investigational Medicinal Product
INR	international normalized ratio
IPPI	Investigational Product Preparation and Administration Instructions
IR	Infrared
IRB	Institutional Review Board
IV	Intravenous
IWRS	interactive web response system
mAb	monoclonal antibody
MACE	major adverse cardiovascular events
MAD	multiple ascending doses
MCS	mental component summary
MedDRA	Medical Dictionary for Regulatory Activities
MG-ADL	Myasthenia Gravis Activities of Daily Living
MMRM	Mixed-Effect Model Repeated Measure model
MPA	mycophenolic acid
MTX	Methotrexate
NAb	neutralizing antibodies
NRS	Numeric Rating Scale
NSAID	nonsteroidal anti-inflammatory drug
PBMC	peripheral Blood Mononuclear Cells
PCS	physical component summary
PD	pharmacodynamic(s)
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PhGA	Physician's Global Assessment
PK	pharmacokinetic(s)
PQC	product quality complaint
PRO	patient-reported outcome
q2w	every 2 weeks
q4w	every 4 weeks
RA	rheumatoid arthritis
RBC	red blood cell
RNA	ribonucleic acid
RO	receptor occupancy
SAD	single ascending doses
SAE	serious adverse event
SAP	statistical analysis plan
SF-36	Short Form 36-Item
SIPPM	Site Investigational Product Procedures Manual
SLE	systemic lupus erythematosus
SoA	Schedule of Activities
SSA	sjögren's-syndrome-related antigen A
SSB	sjögren's-syndrome-related antigen B
SSRI	Sjögren's Syndrome Responder Index
STAR	Sjögren's Tool for Assessing Response
SUSAR	suspected unexpected serious adverse reaction
TF	treatment failure
TNF	tumor necrosis factor
ULN	upper limit of normal

US	United States
VAS	Visual analog scale
wAIHA	warm autoimmune hemolytic anemia
WHO	World Health Organization

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the central laboratory, unless otherwise indicated:

Protocol-Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td rowspan="2">Hematology</td><td>Platelet count
Red blood cell count
Hemoglobin
Hematocrit</td><td><u>RBC Indices:</u>
Mean Corpuscular Volume (MCV)
Mean Corpuscular Hemoglobin (MCH)
% Reticulocytes</td><td><u>White Blood Cell (WBC) count with Differential:</u>
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td colspan="3">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.</td></tr>
<tr><td rowspan="2">Clinical Chemistry</td><td colspan="2">Sodium
Potassium
Chloride
Calcium
Phosphate
Bicarbonate
Blood urea nitrogen (BUN)
Creatinine
Glucose
Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic
Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic
Gamma-glutamyltransferase (GGT)</td><td>Total bilirubin (reflex test for direct bilirubin if abnormally elevated)
Alkaline phosphatase
Creatine phosphokinase (CPK)
Lactic acid dehydrogenase (LDH)
Uric acid
Albumin (blinded)
Total protein
Magnesium</td></tr>
<tr><td colspan="3">Note: Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 10.8. Potential Hy's Law case reporting requirements are defined in Section 8.5.1.</td></tr>
<tr><td rowspan="2">Lipid Panel</td><td colspan="3">Total cholesterol
HDL
LDL [calculated]
VLDL [calculated]
Triglycerides</td></tr>
<tr><td colspan="3">Note: Under fasting conditions except at Screening</td></tr>
</table>

<table>
<tr><td rowspan="2">Routine Urinalysis</td><td><u>Urinalysis</u>
Specific gravity
pH
Glucose
Protein
Blood
Ketones
Bilirubin
Urobilinogen
Nitrite
Leukocyte esterase</td><td><u>Sediment</u>
Red blood cells
White blood cells
Epithelial cells
Crystals
Casts
Bacteria</td></tr>
<tr><td colspan="2">Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, and urobilinogen will be determined using a conventional urinalysis with dipstick and evaluation.

In the microscopic examination, red blood cells, white blood cells, epithelial cells, crystals, casts, and bacteria will be measured but other observations may also be reported by the laboratory. Crystals, casts and bacteria will only be reported if they are present.</td></tr>
<tr><td>Other Tests</td><td colspan="2">• Urine Pregnancy Testing for women of childbearing potential only
• CRP
• FSH
• TSH, total T4, free T4, free T3
• ESR (performed at the site by Westergren method)
• Serology (HIV antibody, hepatitis B surface antigen [HBsAg], Hepatitis B surface antibody [anti-HBs], Hepatitis B core antibody [anti-HBc], Hepatitis C virus antibody, and HBV DNA, screening only)
• Coagulation (prothrombin time [PT], partial thromboplastin time [PTT], INR)
• Anti-nuclear antibodies, rheumatoid factor
• Anti-double stranded DNA
• Complement – C3, C4, CH50 (total complement)
• Other autoantibody profile, including but not limited to anti-Smith, anti-nRNP antibodies (screening only)
• Other autoantibody profile includes but is not limited to:
  • Anti-phospholipid antibodies (including but not limited to the following: anti-cardiolipin immunoglobulin [Ig]G and IgM and anti-β2 glycoprotein Ig G and IgM
  • Autoantibody profile (including but not limited to the following: anti-Sjogren's syndrome related antigen A (anti-Ro/SSA), anti-Sjogren's syndrome related antigen B (anti-La/SSB), and RF. Note: Anti-Ro/SSA may be performed locally during screening, as needed.
• Circulating immune complexes (CIC)
• Immunoglobulin profile (total IgG, IgG1, IgG2, IgG3, IgG4)
• Immunoglobulin Isotype (IgA, IgM, and IgE)</td></tr>
</table>

	• Serum protein electrophoresis • Free light chains (Freelite) • Urine protein/creatine ration (UPCR) • Cryoglobulin (arranged locally, and under fasting conditions except at Screening, where feasible; Collection requirements: collection tube and transfer device must be pre-warmed to 37C, and the sample must be maintained at 37C after collection until centrifugation is completed). See lab manual for details. Under fasting conditions except at Screening. • Includes apolipoprotein-B, -A1, -A2, ratio of apolipoprotein B:A1, and lipoprotein-a • Serum globulin profile (α-1 antitrypsin, sex hormone-binding globulin, α-1 acid glycoprotein, transferrin, retinol binding protein, thyroglobulin)
	Note: ESR (Westergren method) Reference Ranges Males <50 years of age: 0-15 Males ≥50 years of age: 0-20 Females <50 years of age: 0-20 Females ≥50 years of age: 0-30 (Tishkowski 2021)
	Note: hs-CRP Reference Range: 0-3 mg/L, inclusive (Person, 2003)

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 Good Clinical Practice (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 protocol clarification communication (PCC) may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, Local Trial Managers (LTMs), Clinical Trial Managers (CTMs), and/or Contract Research Organizations (CROs) who will ensure that the PCC explanations are followed by the investigators.

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

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

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for 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) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, 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 Pre-study Documentation

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

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

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

- Completed investigator financial disclosure forms from all sub-investigators
- Documentation of sub-investigator 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 4.2.2, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.2.

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

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

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

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

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

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

10.3.4. Data Protection

Privacy of Personal Data

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

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

The informed consent obtained from the participant (or his or her legally acceptable representative) includes information about, and where required per applicable regulations, explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. The informed consent also provides information to address the lawful transfer of the data to other entities and to other countries/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 DNA, PD, biomarker, PK, and immunogenicity research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

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

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

10.3.6. Committees Structure

Data Monitoring Committee

A joint Data Monitoring Committee (DMC, with other Phase 2 Immunology studies on nipocalimab) will be established to monitor data on an ongoing basis. This committee will consist of at least 2 medical experts in the relevant therapeutic area and at least one statistician; committee membership responsibilities, authorities, and procedures will be documented in its charter. The committee will meet periodically to review interim data through the Week 30 final DBL. For the scheduled safety reviews, the DMC will make a recommendation to the sponsor whether the study should continue, be modified, or stopped for safety concerns.

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

Interim Analysis Committee

An internal unblinded IAC will be established to review interim data. This committee will consist of physicians, statisticians, clinical pharmacologists and pharmacometricians unaffiliated with the study; committee membership responsibilities, authorities, and procedures will be documented in its charter. The committee will meet periodically to review the interim analysis data (Week 8 and Week 24, as specified in Section 9.5). The IAC will also review IgG and autoantibody levels for approximately 30 participants that complete 8 weeks of study intervention to ensure IgG and autoantibody levels are decreasing as expected. After the review of the Week 8 interim data, the IAC will make recommendations regarding the continuation of the study.

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

10.3.7. Publication Policy/Dissemination of Clinical Study Data

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

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

The results of the study will be reported in a 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, biomarker, or digital health 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 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 existence of, and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

10.3.8. Data Quality Assurance

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's 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 will review 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.

10.3.9. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in 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.

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.

10.3.10. Source Documents

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

The author of an entry in the source documents should 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 trial participants into source records cannot be overridden by site staff or investigators.

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

Information collected at unscheduled visits should be documented as described for scheduled visits. The minimum source documentation requirements for Sections 5.1 and 5.2 that specify a need for documented medical history are as follows:

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

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

An eSource system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. 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.

10.3.11. Monitoring

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

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

10.3.12. On-Site Audits

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

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

10.3.13. Record Retention

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

10.3.14. Study and Site Start and Closure

First Act of Recruitment

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

Study/Site Termination

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

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

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

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

10.4. Appendix 4: 2016 ACR/EULAR Classification Criteria

ACR/EULAR Classification Criteria 2016

American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjogren's syndrome (1)

The classification of primary Sjogren's syndrome applies to any individual who

- meets the inclusion criteria with a positive response to at least one question below - Section 1
- does not have any of the conditions listed as exclusion criteria† - Section 2
- has a score of ≥ 4 when the weights from the 5 criteria items are summed - Section 3

Section 1 - At least one positive response required to apply the classification criteria:

Symptom	Y/N
Have you had daily, persistent, troublesome dry eyes for more than 3 months?	___Y ___N
Do you have a recurrent sensation of sand or gravel in the eyes?	___Y ___N
Do you use tear substitutes more than 3 times a day?	___Y ___N
Have you had a daily feeling of dry mouth for more than 3 months?	___Y ___N
Do you frequently drink liquids to aid in swallowing dry food? or in whom there is suspicion of Sjogren's syndrome (SS) from the European League Against Rheumatism SS Disease Activity Index questionnaire (at least 1 domain with a positive item).	___Y ___N

-OR-

Is primary Sjogren's Syndrome suspected based on at least 1 positive item/domain on the ESSDAI?	___Y ___N

Section 2 - All responses below must be No to apply primary Sjogren's syndrome criteria:

† Exclusion criteria include prior diagnosis of any of the following conditions, which would exclude diagnosis of SS and participation in SS studies or therapeutic trials because of overlapping clinical features or interference with criteria tests.

Condition	Y/N
History of head and neck radiation treatment	___Y ___N
Active hepatitis C infection (with confirmation by polymerase chain reaction)	___Y ___N
AIDS	___Y ___N
Sarcoidosis	___Y ___N
Amyloidosis	___Y ___N

Graft-versus-host disease	___Y ___N
IgG4-related disease	___Y ___N

(1) Shiboski c, Shiboski S, Seror et al. 2016 ACR/EULAR Classification Criteria for Primary Sjogren's Syndrome. Arthritis Rheum 2017; 69: 35-45.

ACR/EULAR Classification Criteria 2016 (cont'd)

ACR/EULAR Classification Criteria 2016 for primary Sjogren's Syndrome - Inclusion Criteria

Section 3 - The classification of primary Sjogren's syndrome applies if the total score of criteria met from the list below is ≥ 4 when the weights are summed:

Criteria Items	Weight/ Score	
Labial salivary gland with focal lymphocytic sialadenitis and focus score of ≥ 1 foci/4 mm^2 ‡	3	Document in source for entry into eCRF
Anti-SSA/Ro positive	3	
Ocular Staining Score ≥ 5 (or van Bijsterveld score ≥ 4) in at least 1 eye §	1	
Schirmer's test ≤ 5 mm/5 minutes in at least 1 eye §	1	
Unstimulated whole saliva flow rate ≤0.1 ml/minute § #	1	
Total Score		

‡ The histopathologic examination should be performed by a pathologist with expertise in the diagnosis of focal lymphocytic sialadenitis and focus score count, using the protocol described by Daniels et al **(2)**.

§ Patients who are normally taking anticholinergic drugs should be evaluated for objective signs of salivary hypofunction and ocular dryness after a sufficient interval without these medications in order for these components to be a valid measure of oral and ocular dryness.

¶ Ocular Staining Score described by Whitcher et al **(3)**; van Bijsterveld score described by van Bijsterveld **(4)**.

Unstimulated whole saliva flow rate measurement described by Navazesh and Kumar **(5)**.

(2) Daniels TE, Cox D, Shiboski CH, Schiodt M, Wu A, Lanfranchi H, et al. Associations between salivary gland histopathologic diagnoses and phenotypic features of Sjögren's syndrome among1,726 registry participants. Arthritis Rheum 2011;63:2021–30.

(3) Whitcher JP, Shiboski CH, Shiboski SC, Heidenreich AM, Kitagawa K, Zhang S, et al. A simplified quantitative method for assessing keratoconjunctivitis sicca from the Sjögren's Syndrome International Registry. Am J Ophthalmol 2010;149:405–15.

(4) Van Bijsterveld OP. Diagnostic tests in the Sicca syndrome. Arch Ophthalmol 1969;82:10–4.

(5) Navazesh M, Kumar SK, University of Southern California School of Dentistry. Measuring salivary flow: challenges and opportunities. J Am Dent Assoc 2008;139 Suppl:35S–40S.

10.5. Appendix 5: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.5.1. 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 Conference 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 8.5.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last AE recording).

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 should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

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

Unlisted (Unexpected) Adverse Event/Reference Safety Information

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

10.5.2. Attribution Definitions

Assessment of Causality

The causal relationship to study intervention is determined 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.

10.5.3. 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).

10.5.4. Special Reporting Situations

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

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

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

10.5.5. 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 16 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.

Disease progression should not be recorded as an AE or SAE term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the SAE definition (refer to Section 10.5.1).

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. 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.

10.5.6. 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.

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.

10.5.7. 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.

10.6. Appendix 6: Clinical EULAR Sjögren's Syndrome Disease Activity Index

Clinical EULAR Sjögren's syndrome disease activity index (ClinESSDAI)[1,2]

Note: ClinESSDAI domain weights for each activity level are indicated below

Constitutional domain

Domain	Activity level	Description
Constitutional	No = 0	Absence of the following symptoms
Exclusion of fever of infectious origin and voluntary weight loss	Low = 4	Mild or intermittent fever (37.5°-38.5°C) / night sweats and/or involuntary weight loss of 5 - 10% of body weight
	Moderate = 8	Severe fever (>38.5°C) / night sweats and/or involuntary weight loss of >10% of body weight

Lymphadenopathy and lymphoma domain

Domain	Activity level	Description
Lymphadenopathy and lymphoma	No = 0	Absence of the following features
Exclusion of infection	Low = 4	Lymphadenopathy ≥1 cm in any nodal region or ≥2 cm in inguinal region
	Moderate = 8	Lymphadenopathy ≥2 cm in any nodal region or ≥3 cm in inguinal region, and/or splenomegaly (clinically palpable or assessed by imaging)
	High = 12	Current malignant B-cell proliferative disorder

Glandular domain

Domain	Activity level	Description
Glandular	No = 0	Absence of glandular swelling
Exclusion of stone or infection	Low =2	Small glandular swelling with enlarged parotid (≤3 cm), or limited submandibular (≤2 cm) or lachrymal swelling (≤1 cm)
	Moderate = 4	Major glandular swelling with enlarged parotid (>3 cm), or important submandibular (>2 cm) or lachrymal swelling (>1 cm)

Articular domain

Domain	Activity level	Description
Articular	No = 0	Absence of currently active articular involvement
Exclusion of osteoarthritis	Low = 3	Arthralgias in hands, wrists, ankles and feet accompanied by morning stiffness (>30 min)
	Moderate = 6	1 – 5 joints (of 28 total count) with synovitis
	High = 9	≥6 joints (of 28 total count) with synovitis

Cutaneous domain

Domain	Activity level	Description
Cutaneous	No = 0	Absence of currently active cutaneous involvement
Rate as "No activity" stable long-lasting features related to damage	Low =3	Erythema multiforma
	Moderate = 6	Limited cutaneous vasculitis, including urticarial vasculitis, or purpura limited to feet and ankle, or subacute cutaneous lupus
	High = 9	Diffuse cutaneous vasculitis, including urticarial vasculitis, or diffuse purpura, or ulcers related to vasculitis

Pulmonary domain

Domain	Activity level	Description
Pulmonary	No = 0	Absence of currently active pulmonary involvement
Rate as "No activity" stable long-lasting features related to damage, or respiratory involvement not	Low = 6	Persistent cough **due to** bronchial involvement with no radiographic abnormalities on radiography Or radiological or HRCT evidence of interstitial lung disease with: no breathlessness and normal lung function test
	Moderate = 12	Moderately active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath on exercise (NHYA II) or abnormal lung function tests restricted to: 70% >DL_{CO}≥ 40% or 80%>FVC≥60%

related to the disease (tobacco use etc.)	High = 18	Highly active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath at rest (NHYA III, IV) or with abnormal lung function tests: DL_{CO}<40% or FVC<60%

HRCT: high-resolution computed tomography; NYHA: New York Heart Association; FVC: Forced Vital Capacity

Renal domain

Domain	Activity level	Description
Renal *Rate as "No activity" stable long-lasting features related to damage and renal involvement not related to the disease. If biopsy has been performed, please rate activity based on histological features first*	No = 0	Absence of currently active renal involvement with proteinuria<0.5 g/day, no haematuria, no leucocyturia, no acidosis, or long-lasting stable proteinuria due to damage
	Low = 6	Evidence of mild active renal involvement, limited to tubular acidosis without renal failure or glomerular involvement with proteinuria (between 0.5 and 1 g/day) and without haematuria or renal failure (GFR ≥60 mL/min)
	Moderate = 12	Moderately active renal involvement, such as tubular acidosis with renal failure (GFR <60 mL/min) or glomerular involvement with proteinuria between 1 and 1.5 g/day and without haematuria or renal failure (GFR ≥60 mL/min) or histological evidence of extra-membranous glomerulonephritis or important interstitial lymphoid infiltrate
	High = 18	Highly active renal involvement, such as glomerular involvement with proteinuria >1.5 g/day or haematuria or renal failure (GFR <60 mL/min), or histological evidence of proliferative glomerulonephritis or cryoglobulinemia related renal involvement

GFR: glomerular filtration rate

Muscular domain

Domain	Activity level	Description
Muscular *Exclusion of weakness due to corticosteroids*	No = 0	Absence of currently active muscular involvement
	Low = 7	Mild active myositis shown by abnormal EMG, MRI* or biopsy with no weakness and creatine kinase (N ≤CK ≤ 2N)
	Moderate = 14	Moderately active myositis proven by abnormal EMG, MRI* or biopsy with weakness (maximal deficit of 4/5), or elevated creatine kinase (2N <CK ≤4N),
	High = 21	Highly active myositis shown by abnormal EMG, MRI* or biopsy with weakness (deficit ≤3/5) or elevated creatine kinase (>4N)

EMG= electromyogram; MRI= magnetic resonance imaging

Peripheral nervous system domain

Domain	Activity level	Description
PNS *Rate as "No activity" stable long-lasting features related to damage or PNS involvement not related to the disease*	No = 0	Absence of currently active PNS involvement
	Low = 5	Mild active PNS involvement, such as pure sensory axonal polyneuropathy shown by NCS or trigeminal (V) neuralgia ** Proven small fibre neuropathy*
	Moderate = 10	Moderately active PNS involvement shown by NCS, such as axonal sensory-motor neuropathy with maximal motor deficit of 4/5, pure sensory neuropathy with presence of cryoglobulinemic vasculitis, ganglionopathy with symptoms restricted to mild/moderate ataxia, inflammatory demyelinating polyneuropathy (CIDP) with mild functional impairment (maximal motor deficit of 4/5 or mild ataxia), Or cranial nerve involvement of peripheral origin (except trigeminal (V) neuralgia)
	High = 15	Highly active PNS involvement shown by NCS, such as axonal sensory-motor neuropathy with motor deficit ≤3/5, peripheral nerve involvement due to vasculitis (mononeuritis multiplex etc.), severe ataxia due to ganglionopathy, inflammatory demyelinating polyneuropathy (CIDP) with severe functional impairment: motor deficit ≤3/5 or severe ataxia

NCS: Nerve conduction study; CIPD: chronic inflammatory demyelinating polyneuropathy

Central nervous system domain

Domain	Activity level	Description
CNS *Rate as "No activity" stable long-lasting features related to damage or CNS involvement not related to the disease*	No = 0	Absence of currently active CNS involvement
	Moderate= 10	Moderately active CNS features, such as cranial nerve involvement of central origin, optic neuritis or multiple sclerosis-like syndrome with symptoms restricted to pure sensory impairment or proven cognitive impairment
	High = 15	Highly active CNS features, such as cerebral vasculitis with cerebrovascular accident or transient ischaemic attack, seizures, transverse myelitis, lymphocytic meningitis, multiple sclerosis-like syndrome with motor deficit.

Haematological domain

Domain	Activity level	Description
Haematological *For anaemia, neutropenia, and thrombopenia, only auto-immune cytopenia must be considered* *Exclusion of vitamin or iron deficiency, drug-induced cytopenia*	No = 0	Absence of autoimmune cytopenia
	Low = 2	Cytopenia of autoimmune origin with neutropenia (1000 < neutrophils < 1500/mm^3), and/or anaemia (10< haemoglobin <12 g/dL), and/or thrombocytopenia (100,000 < platelets <150,000/mm^3) Or lymphopenia (500 <lymphocytes <1000/mm^3)
	Moderate = 4	Cytopenia of autoimmune origin with neutropenia (500 ≤ neutrophils ≤1000/mm^3), and/or anaemia (8≤ haemoglobin ≤10 g/dL), and/or thrombocytopenia (50,000 ≤ platelets ≤100,000/mm^3) Or lymphopenia (≤500/mm^3)
	High = 6	Cytopenia of autoimmune origin with neutropenia (neutrophils <500/mm^3), and/or anaemia (haemoglobin <8 g/dL) and/or thrombocytopenia (platelets <50,000/mm^3)

The following domain is specific to the ESSDAI and is omitted from the ClinESSDAI: For Reference Only

Biological domain

Domain	Activity level	Description
Biological	No = 0	Absence of any of the following biological feature
	Low = 1	Clonal component and/or hypocomplementemia (low C4 or C3 or CH50) and/or hypergammaglobulinemia or high IgG level between 16 and 20 g/L
	Moderate = 2	Presence of cryoglobulinemia and/or hypergammaglobulinemia or high IgG level >20 g/L, and/or recent onset hypogammaglobulinemia or recent decrease of IgG level (<5 g/L)

(1) Seror R, Meiners P, Baron G, Bootsma H, Bowman SJ, Vitali C, Gottenberg JE, Theander E, Tzioufas A, De Vita S, Ramos-Casals M, Dörner T, Quartuccio L, Ravaud P, Mariette X; EULAR Sjögren Task Force. Development of the ClinESSDAI: a clinical score without biological domain. A tool for biological studies. Ann Rheum Dis. 2016 Nov;75(11):1945-1950.

(2) ©2016 The Authors. Arthritis & Rheumatology published by Wiley Periodicals, Inc. on behalf of the American College of Rheumatology.

10.7. Appendix 7: Contraceptive and Barrier Guidance

Participants must follow contraceptive measures as outlined in Section 5.1. Pregnancy information will be collected and reported as noted in Section 8.5.5 and Section 10.5.

Definitions

Woman of Childbearing Potential (WOCBP)

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

Woman Not of Childbearing Potential

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

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

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

Contraceptive (birth control) use by men or women should 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 should 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 MALE OR 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[b]
• 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 woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should 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[b] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – 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[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)

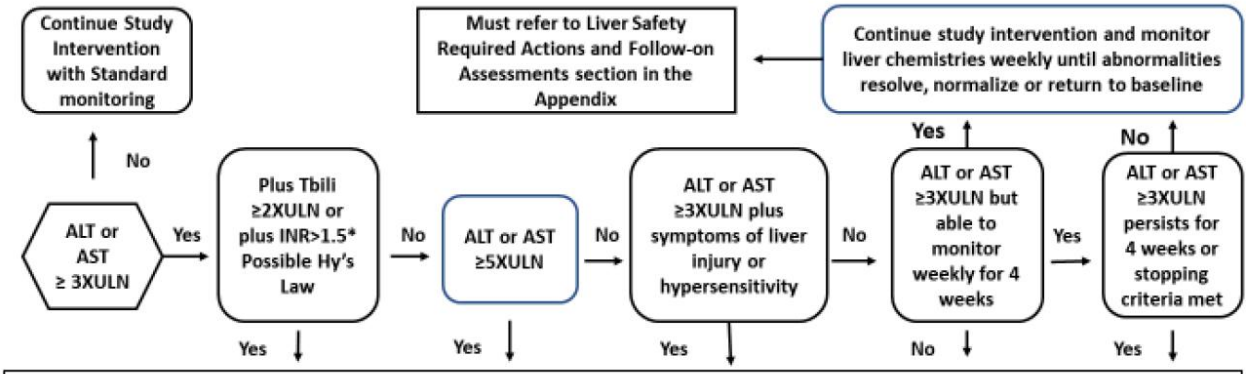
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)
a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies. b) Hormonal contraception may be susceptible to interaction with the study intervention or concomitant medications (eg, MMF/MPA in combination with oral hormonal contraceptives), which may reduce the efficacy of the contraceptive method. In female participants who are of child-bearing potential and are receiving MMF/MPA, a barrier contraceptive method should be used concurrently with oral hormonal contraception methods Inclusion Criteria 13). c) Male condom and female condom should not be used together (due to risk of failure with friction).

10.8. Appendix 8: Liver Safety: Suggested Actions and Follow-up Assessments

10.8.1. Stopping Algorithm

Study intervention will be discontinued for a participant if liver chemistry stopping criteria are met.

Phase 2 Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm (no preexisting liver disease)



- **Must refer to Liver Safety Required Actions and Follow-up Assessments section in the Appendix**
- **Report possible Hy's Law case to Sponsor in an expedited manner :** ALT or AST ≥3XULN and total bilirubin ≥2XULN (or at least a doubling of direct bilirubin for known Gilbert's syndrome) or INR>1.5* (if measured), when no other reason can be found to explain the combination of increases (eg, ALP >2XULN indicating cholestasis). Cases that meet Hy's law criteria should be reported as SAEs.
- *INR value not applicable to participants on anticoagulants

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal; Tbili = total bilirubin

10.8.2. Follow-up Assessments

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 not able to 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** international normalized ratio (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 an 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 <2xULN, 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, AST, alkaline phosphatase, total and direct bilirubin and INR) and perform liver event follow-up assessments within **24 hours**	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for pharmacokinetic (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

• Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline • 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, ALP, 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.**	acetaminophen, herbal remedies, recreational drugs and other over-the-counter medications) • Record alcohol use on the CRF as per CRF completion guidelines **If ALT or AST ≥3xULN AND total bilirubin ≥2xULN or INR >1.5 (if measured)** obtain the following in addition to the assessments listed above**:** • Anti-nuclear 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: – In participants when serology raises the possibility of autoimmune hepatitis (AIH) – In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention – 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, stop 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 <2xULN, ALT or AST ≥3 ULN **and** total bilirubin ≥2xULN (or at least a doubling of direct bilirubin in known Gilbert's syndrome) or ALP <2xULN , ALT or AST ≥3xULN **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; HBsAg 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 Laboratory Manual.

Phase 2 Liver Chemistry Increased Monitoring Criteria with Continued Study Intervention

Liver Chemistry Increased Monitoring Criterion and Actions with Continued Study Intervention	
Criterion	**Actions**
ALT or AST ≥3xULN and <5xULN **and** total bilirubin <2xULN (and INR<1.5 if measured)**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the sponsor within **24 hours** of learning of the abnormality to discuss participant safety • Participant must return weekly for repeat liver chemistry tests (ALT, AST, ALP, total bilirubin) until the abnormalities resolve, stabilize or return to baseline • If at any time, the participant meets liver chemistry stopping criteria, proceed as described in Section 7.1.1. • If, after 4 weeks of monitoring, ALT or AST <3xULN and total bilirubin <2xULN, monitor participants twice monthly until liver chemistry tests resolve, stabilize, or return to baseline

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10.9. Appendix 9: Hepatitis B Virus (HBV) Screening with HBV DNA

Participants must undergo screening for hepatitis B virus (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 hepatitis B virus deoxyribonucleic acid (HBV DNA) test. 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 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.

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.

10.10. Appendix 10: Example of Equivalent Doses of Prednisone

Glucocorticoid	Replacement/Equivalence
Cortisone acetate	25 mg
Hydrocortisone	20 mg
Prednisone	5 mg
Prednisolone	5 mg
Triamcinolone	4 mg
Methylprednisolone	4 mg
Dexamethasone	0.75 mg
Betamethasone	0.6-0.75 mg
Deflazacort	7.5 mg

10.11. Appendix 11: Guidance on Study Conduct during the COVID-19 Pandemic (or Other Major Disruption)

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

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

Scheduled visits that cannot be conducted in-person at the study site 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 between the participant and investigator, and with the agreement of the sponsor (see below).

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

If a participant has tested positive for COVID-19, the investigator should contact the sponsor's medical officer or designee to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic (or other major disruption) should be summarized in the clinical study report.

ADDITIONAL ELEMENTS, WHERE APPLICABLE:

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

- procurement of study drug by patients (or designee) or shipment of study drug from the study site directly to patients for at home administration
- laboratory assessments using a suitably accredited local laboratory; for selected measures (eg, urine pregnancy), home testing may be employed
- other procedures may be conducted at an appropriate facility

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

10.12. Appendix 12: 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 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

Key: PEF=Peak expiratory flow; BP=blood pressure.

*Low systolic blood pressure 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.

10.13. Appendix 13: Protocol Amendment History

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

Amendment 2 (04 February 2022)

Overall Rationale for the Amendment: Data from screening visits in this study so far indicate that the current eligibility criteria exclude many Sjogren's Syndrome patients from the patient population that the protocol was intended to study; eligibility criteria are amended to include a broader population of Sjogren's Syndrome patients. Additional typo corrections and minor clarifying changes to enhance the safety and scientific rigor of the study are also included in this amendment.

Section Number and Name	Description of Change	Brief Rationale
Synopsis; Section 4.1, Overall Study Design	Additional specificity for the database lock timing.	Align and clarify timing of DBL
Section 1.3, Schedule of Activities	Several biomarker sample collections were removed from the Schedule of Activities	Reduce participant burden
Section 1.3, Schedule of Activities	Included one additional instance of a blood test (free light chains) to the screening visit.	Enhance safety as screening for light chain multiple myeloma.
Section 1.3, Schedule of Activities	Modified description of CRP.	Clarify information on the CRP test.
Section 1.3, Schedule of Activities	Added a note regarding local SSA testing.	Clarify testing requirement.
Section 2.3.1, Risks for Study Participation; Section 5.2, Exclusion Criteria; Section 5.3, Lifestyle Considerations	Explicitly included the Bacille Calmette-Guerin (BCG) vaccine as a live vaccine with specific associated time constraints for study eligibility.	Enhances participant safety.
Synopsis; Section 3, Objectives and Endpoints	Explicitly included TEAE leading to treatment discontinuation to the safety endpoints.	Enhance analytical rigor of safety data.
Section 4.2, Scientific Rationale for Study Design	Clarify laboratory result masking plan.	Enhance participant safety and strengthen the study blinding.
Section 4.3, Justification for Dose (Safety Considerations)	Removed mention of a "loading dose" from the description of the dose regimen.	Correct the description of the dosing regimen.
Section 5.1, Inclusion Criteria	Modified inclusion criterion (IC) #1	Expand patient population, facilitate recruitment.
Section 5.1, Inclusion Criteria	Modified IC #4	Clarify SSA criterion
Section 5.1, Inclusion Criteria	Modified IC #2	Expand participant population, facilitate recruitment.
Section 5.1, Inclusion Criteria	Combined IC # 6 and #8 by deleting #6 and Modified IC #8	Expand participant population, facilitate recruitment.
Section 5.1, Inclusion Criteria	Modified IC #7	Expand participant population, facilitate recruitment.
Section 5.1, Inclusion Criteria	Modified IC #9	Expand participant population, facilitate recruitment.

Section Number and Name	Description of Change	Brief Rationale
Section 5.2, Exclusion Criteria	Modified exclusion criterion (EC) #1	Enhance participant safety.
Section 5.2, Exclusion Criteria	Modified EC #7	Expand participant population, facilitate recruitment.
Section 5.2, Exclusion Criteria	Modified EC #9	Clarify criterion.
Section 5.2, Exclusion Criteria	Modified EC #18	Expand participant population, facilitate recruitment.
Section 5.2, Exclusion Criteria	Modified EC #24	Clarify concomitant medication guidance.
Section 5.2, Exclusion Criteria	Modified EC #33	Clarify concomitant medication guidance.
Section 5.2, Exclusion Criteria	Modified EC #42	Clarify concomitant medication guidance.
Section 5.2, Exclusion Criteria	Modified EC #42	Enhance participant safety.
Section 5.2, Exclusion Criteria	Modified EC #54	Clarify criterion.
Section 5.2, Exclusion Criteria	Added an EC for granulomatous infections.	Enhance participant safety.
Section 5.3, Lifestyle Considerations	Modified #2	Enhance participant safety.
Section 5.3, Lifestyle Considerations	Modified #7	Enhance participant safety.
Section 5.3, Lifestyle Considerations	Added criteria #10	Clarify concomitant medication/substance guidance
Section 6.1, Study Intervention(s) Administered	Clarify the classification and sourcing of placebo product.	Enhance participant safety.
Section 6.3, Measures to Minimize Bias: Randomization and Blinding	Modified description of laboratory masking plan and criteria for unmasking results for safety.	Enhance participant safety and strengthen blinding.
Section 6.8, Concomitant Therapy	Added marijuana to list of products to avoid prior to assessments in Table 4.	Enhance data quality.
Section 6.8 Concomitant Therapy	Modified medication history eligibility in Table 4.	Expand participant population, facilitate recruitment.
Section 6.8.7, Prohibited Therapies	Added defined washout periods for prohibited medications; re-ordered the list of prohibited medications.	Clarify the guidance on prohibited medications to enhance participant safety and data integrity.
Section 8, Study Assessments and Procedures	Updated list of manuals.	Enhance participant safety and provide additional instruction to investigators.
Section 8, Study Assessments and Procedures	Updated description of the study visit.	Simplify and clarify the operational aspects of clinician assessments.
Section 8, Study Assessments and Procedures	Modified Table 5 to clarify timing of laboratory test.	Increase rigor of laboratory data.
Section 8.2, Exit Interviews	Added a new section describing the exit interview.	Enhance protocol clarity.
Section 8.4.5, Pregnancy Testing	Updated description of pregnancy test options	Enhance participant safety.

Section Number and Name	Description of Change	Brief Rationale
Section 8.5.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	Added new language to clarify SAE classification procedure.	Enhance participant safety and the rigor of study safety data.
Section 9.4.2, Primary Endpoint	Updated statistical analysis description.	Clarify the statistical plan.
Section 9.4.3.3, Safety Analyses	Expanded the list of AEs to be included in data analysis to include major cardiac or vascular events.	Enhance participant safety and the rigor of study safety data.
Section 10.2, Appendix 2: Clinical Laboratory Tests and throughout	Several changes to clarify clinical laboratory test masking.	Reduce risk of unblinding study staff to treatment.
Section 10.2, Appendix 2: Clinical Laboratory Tests	Several changes to clarify clinical laboratory tests.	Clarify laboratory testing plan.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted

Amendment 1 (26 May 2021)

Overall Rationale for the Amendment: To include additional safety criteria related to hypogammaglobulinemia, hyperlipidemia, and anaphylaxis, to update the use of oral contraceptives (using oral contraceptives with concomitant mycophenolate mofetil (MMF), and to clarify the use of nonsteroidal anti-inflammatory drugs (NSAIDs) prior to study visits involving joint counts or pain assessments. Additionally, minor updates of a clarifying nature were made throughout the protocol.

Section Number and Name	Description of Change	Brief Rationale
Section 2.3.1 Risks for Study Participation Section 5.2 Exclusion Criteria (#23) Section 7.1 Discontinuation of Study Intervention	Added an exclusion criterion and text for stopping criteria related to hypogammaglobulinemia.	To address a safety concern regarding low levels of IgG potentially leading to increased risk of infection.
Section 2.3.1 Risks for Study Participation Section 8.3.11 Increased Lipids	Added text describing hyperlipidemia monitoring and treatment plans.	To address a safety concern that neonatal fragment crystallizable receptor (FcRn) inhibitors may cause hyperlipidemia.
Section 5.1 Inclusion Criteria (#13), Appendix 7 Contraceptive and Barrier Guidance and Collection of Pregnancy Information	Added to text to indicate that women of child-bearing potential will use a method of birth control other than oral contraceptives or will use dual methods of contraception (eg, an oral contraceptive with a barrier method).	To minimize the risk of pregnancy since MMF affects the metabolism of oral contraceptives.

Section Number and Name	Description of Change	Brief Rationale
Section 6.8.3 Nonsteroidal Anti-inflammatory Drugs and Other Analgesics	Added statement that participants should not use as needed NSAIDs within 12 to 24 hours before a study visit involving joint counts and pain assessments	To prevent confounding of assessments (eg, joint counts and pain assessments).
Section 7.1 Discontinuation of Study Intervention Section 8.3.9 Hypersensitivity Reactions Section 10.12 Appendix 12: Criteria for Assessing Potential Cases of Anaphylaxis Section 11 References	Added a discontinuation criterion and assessment criteria regarding potential cases of anaphylaxis.	To better define the criteria being used to assess potential cases of anaphylaxis.
Section 1.3 Schedule of Activities and 10.2. Appendix 2: Clinical Laboratory Tests	Added CH50 (total complement) test to the SOA with the same frequency as the C3, C4 tests	The CH50 can be utilized for assessment of the Biological Domain Activity for the ESSDAI
Section 1.3 Schedule of Activities Section 4.2 Scientific Rationale for Study Design Section 10.2 Appendix 2: Clinical Laboratory Tests	Replace UPEP with Free light chains (FreeLite)	Free light chain testing is more sensitive and reliable than UPEP
Section 1.3 Schedule of Activities	Added Schirmer's test and Unstimulated Salivary Flow Test at Week 30	Schirmer's test and salivary flow testing at Week 30 will be performed for the purpose of saliva and tear biomarker collection
Section 1.3 Schedule of Activities Section 4.2. Scientific Rationale for Study Design, Salivary Gland Biopsy Substudy	Added note to the Minor Salivary Gland biopsy: 'the time between the biopsy and Week 0 should be ≥11 days' The biopsy procedure should be performed after all screening results are available and ≥11 days ~~less than 7 days~~ leading up to the Week 0 study visit…'	The increase in minimum time between the biopsy and Week 0 assessments will allow sufficient time and opportunity to heal and finish a 7 to 10-day chlorhexidine post-biopsy treatment
Section 1.3 Schedule of Activities	Added the following PerfOs at the Screening Visit: International Digit Symbol Substitution Test - Symbols (IDSSTS) Detection Test Identification Test Added 'Familiarization with PerfO tests will occur during Screening visit' to the note	Clarification to allow participants to get familiar with the PerfO tests prior to study start
Section 1.3 Schedule of Activities	Delete Cryoglobulins at Weeks 2, 16, 20 Add footnote on Lipid panel and	Clarifying sample collection requirements

Section Number and Name	Description of Change	Brief Rationale
	cryoglobulins at Weeks 0, 4, 8, 12 tests at every other timepoint except Screening - Participants should be in a fasting condition unless medically contraindicated (ie, no food or beverages [except water]) for at least 6 hours before blood is drawn for laboratory testing Add to Cryoglobulins notes: Fasting should be for at least 6 hours unless medically contraindicated.	
Section 4.2 Scientific Rationale for Study Design	Added 'and permitted immunosuppressive drugs (see Table 4)' after glucocorticoids	Some consider HCQ to be an immunosuppressant. As such, it would be helpful to clarify that HCQ is not considered to be an immunosuppressant agent for the purpose of this study. This statement refers to the table specifying permitted background SOC medications.
4.1 Overall Study Design 6.3. Measures to Minimize Bias: Randomization and Blinding	The stratification 'HCQ use (Y/N)' should be changed to 'Anti-malarial use (Y/N)'	The use of more generalized language for treatment stratification will help prevent exclusion of participants that might be on medications other than HCQ.
Section 8.1 Efficacy Assessments	Inserted the following sentence in the first paragraph: The Ocular Assessor for the OSS should be a qualified ophthalmologist or optometrist, and the OSS should be performed by the same Ocular Assessor at specified visits for a given participant. A similarly qualified backup Ocular Assessor should be identified in case the designated assessor is unavailable.	Clarify OSS information in Table 5.
Table 4, oral glucocorticoid	Added 'If currently in use, must have been treated for ≥6 weeks with stable dosing ≥4 weeks.'	Clarify that glucocorticoids are not required at baseline
Section 1.3 Schedule of Activities	Cryoglobulins: Insert ", where feasible" after (local)	Provides some flexibility to sites on details of the cryoglobulin arrangements.
Section 10.2 Appendix 10.2 Clinical Laboratory Tests	Cryoglobulins: Replace "performed" with "arranged"	Provides some flexibility to sites on details of the cryoglobulin arrangements.
Table 5	Insert "(where feasible)" in row 4, and after 'cryoglobulins' in *footnote	Provides some flexibility to sites on details of the cryoglobulin arrangements
Section 6.8.7 Prohibited Therapy	Add IVIg and plasmapheresis or plasma exchange	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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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

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	20-Jul-2022 20:29:32 (GMT)	Document Approval