Janssen Research & Development

Statistical Analysis Plan

A Randomized, Placebo-Controlled, Double-Blind, Multicenter Study to Assess the Efficacy and Safety of Nipocalimab in Adults with Primary Sjögren's Syndrome (pSS)

Protocol 80202135SJS2001; Phase 2

JNJ-80202135 (nipocalimab)

Status: Approved
Date: 04 August 2023
Prepared by: Janssen Research & Development, LLC
Document No.: EDMS-RIM-608067, 2.0

Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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VERSION HISTORY

Table 1 – SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
.4		Not Applicable	Initial release
1	16JUN23	• Updated exploratory objective listed in the Introduction section to include sicca signs. • Updated estimand description to align with other Nipo standard text. • Added MACE, GC Toxicity, and Suicidal ideation/ behavior to the Adverse Events of Interest section. Updated infusion reaction additional condition and anaphylactic reaction preferred term in the Adverse Events of Interest Section. • Added Suicidal/ideation behavior and GC Toxicity to the Adverse Events section • Added Randomized analysis set. • Updated lab summaries and markedly abnormal values to match PSAP. • Added new secondary endpoint STAR. • Added exploratory endpoints altSTAR. altCRESS, ESSDAI, ESSDAI-3. • Demoted secondary endpoint SSRI-20 to an exploratory endpoint. • Added definition of endpoint for DAL, STAR, SSRI-30-2, SSRI-30-3, altSTAR, altCRESS, ESSDAI-3. • Updated section titles of endpoint definitions to match name of endpoint. • Added change from baseline definition for clinESSDAI. • Replaced “Main Estimand” with “Primary Estimand” throughout. • Updated text in the biomarker section to align with protocol. • Updated analysis methods for continuous secondary and	Amendment

SAP Version	Approval Date	Change	Rationale
		tertiary/exploratory endpoints. • Updated analysis methods for MMRM to include that the Kenward-Roger method will be used to derive denominator degrees of freedom and to specify possible covariance structures when there are convergence issues. • Updated levels of "geographic region" to include "Other." • Added IgG and Disease Specific Antibodies subsection to Biomarkers section. • Added fatigue to Sjögren's Symptoms. • Updated minimum IgG levels for AEs, SAEs, and AESI by IgG. • Updated Clinical Laboratory Tests section and removed appendix containing selected laboratory tests. • Replaced "anti-SSA/SSB" with "autoantibodies" in the PK section. • Added details to the Subgroup Analyses section of the Primary Endpoint(s) Analysis section. • Added details to the Subgroup Analyses section to specify how "median" is defined. • Added text to indicate that IA#2 could be submitted to health authorities. • Updated baseline HCQ text to include "or other anti-malarial drug" throughout. • Added planned EoP2 outputs for IA2. • Added that the IA DPS will be shared with the unblinded team if the IAC recommends a Direct Go.	
2	04AUG23	• Changed subgroup variable "Age at diagnosis" to "Baseline age" in the Definition of Subgroups section.	Amendment to align with study protocol

SAP Version	Approval Date	Change	Rationale
		• Removed the paragraph of Adverse Events by Subgroup.	

1. INTRODUCTION

This Statistical Analysis Plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for all planned analyses of efficacy, safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and immunogenicity of Nipocalimab. This SAP is specific to the Week 30 primary database lock (DBL) for the 80202135SJS2001 study.

1.1. Objectives

Primary Objective

- To evaluate the efficacy of nipocalimab in participants with primary Sjögren's syndrome (pSS) versus placebo

Secondary Objectives

- To evaluate the safety of nipocalimab treatment versus placebo in participants with pSS
- To evaluate the PK and immunogenicity of nipocalimab in participants with pSS
- To evaluate the effect of nipocalimab versus placebo on levels of serum biomarkers related to pSS

Exploratory Objectives

- To further evaluate the efficacy of nipocalimab in participants with pSS versus placebo
- To evaluate the effect of nipocalimab versus placebo on key pSS symptoms, impacts, and health-related quality of life (HRQoL)
- To explore the effects of nipocalimab on cellular, transcriptomic, and soluble biomarkers
- To explore genetic associations to response to nipocalimab in pSS
- To explore the effects of nipocalimab on physical activity and sleep measured by actigraphy
- To explore the effects of nipocalimab on Sicca signs
- To evaluate the effect of nipocalimab versus placebo on steroid use

1.2. Study Design

80202135SJS2001 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 nipocalimab 15 mg/kg groups.

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.

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

1) baseline steroid use (yes, no)
2) anti-malarial use (yes, no)
3) geographic region (North America, Eastern Europe, Western Europe, Other)

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 data base lock (DBL) is planned after all participants have completed Week 30 efficacy assessments (or discontinued) and includes 6 weeks of follow up after final efficacy visit. An Interim Analysis Committee (IAC) 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.

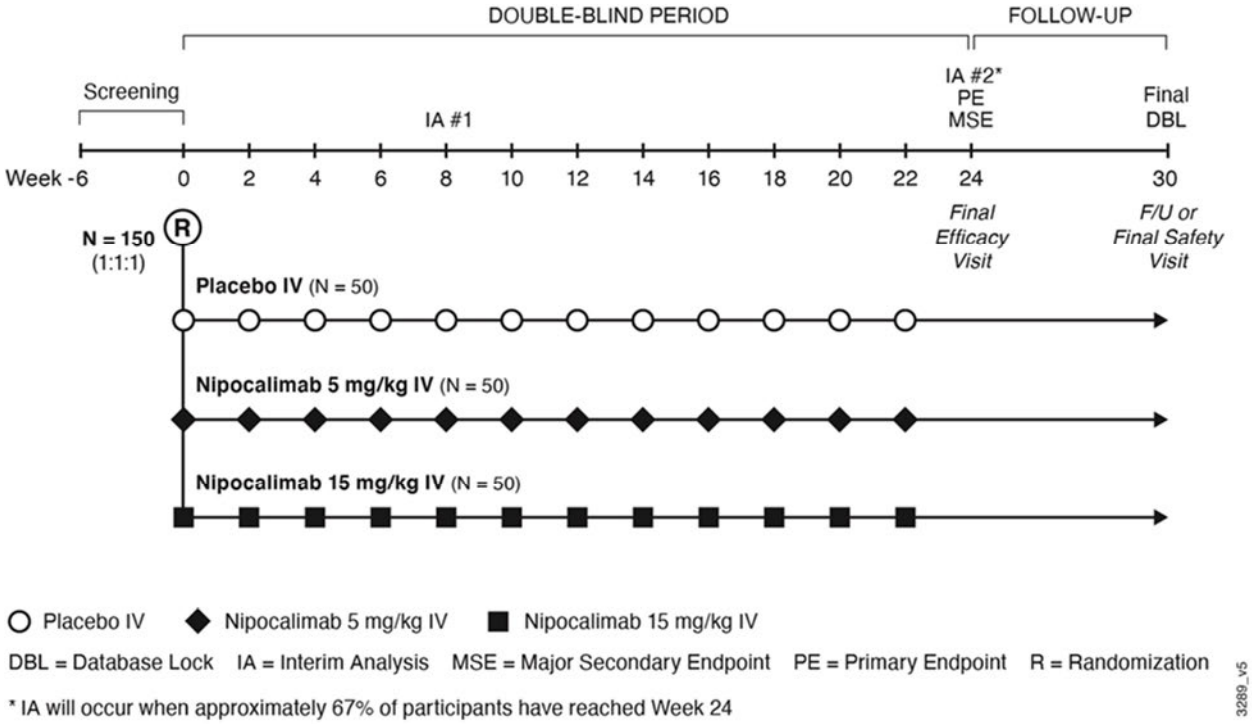
Key safety assessments include adverse events (AEs), serious adverse events (SAEs), AEs of special interest (AESI), AEs temporally associated with infusion, including hypersensitivity reactions, laboratory parameters (hematology and chemistry, including lipid panel, and urinalysis), and vital signs,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

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. Additional DBLs may be added as necessary and will be specified in the SAP prior to the additional DBLs.

A Data Monitoring Committee (DMC) will be commissioned for safety reviews of this study. See DMC Charter for details. A separate IAC, including a limited number of internal members who are not otherwise included in conduct of the study, will be commissioned for interim analysis of unblinded PD and efficacy data, see IAC Charter for details.

The study schema is provided in Figure 1.

Figure 1: Schematic Overview of the Study



2. STATISTICAL HYPOTHESES

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 Clinical European League Against Rheumatism Sjögren's Syndrome Disease Activity Index (clinESSDAI) at Week 24, in adult participants with moderately active pSS.

3. 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 (Baer et al., 2021). 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.

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

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

Analysis Sets	Description
Enrolled	All participants who sign the ICF.
Randomized	The randomized analysis set includes all participants who were randomized in the study.
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.
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.

5. STATISTICAL ANALYSES

5.1. General Considerations

Unless specified otherwise, efficacy data summaries will be provided by intervention group for the FAS. Data primarily will be summarized using descriptive statistics. Simple descriptive summary statistics, such as the number of observations (N), mean, SD, median, interquartile (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, analysis of variance (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 FAS unless otherwise stated. Participants included in the efficacy analyses will be summarized according to their assigned intervention group regardless of whether 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. Biomarker analyses will be based on the Safety Analysis Set and subjects are required to have at least one valid post-dose blood sample drawn for PD analysis.

Unless otherwise stated, baseline is defined as the last observation prior to the start of the first study intervention administration.

5.1.1. Visit Windows

Unless otherwise specified, nominal visits will be used for all by visit analyses. The study visits scheduled after randomization are expected to occur at the time delineated in the SoA.

5.1.2. Pooling Algorithm for Analysis Centers

Unless otherwise specified, data from all investigational centers/sites will be pooled for analyses.

5.1.3. Reference Date, Study day and Relative Day

The Reference Date is the date of the first study intervention administration. If the date of the first study intervention administration is missing or the first study intervention is not done, then the Reference date equals the corresponding visit date (eg, Week 0 visit date). If the corresponding visit date is also missing, then the Reference Date equals the randomization date.

Study Day 1 or Day 1 refers to the reference date (there is no Study Day 0). All efficacy and safety assessments at all visits will be assigned a day relative to this date.

5.1.4. Treatment Failure Criteria

Treatment failure (TF) criteria is applied during the double-blind portion of the study.

Participants who meet 1 or more of the following criteria will be defined as TFs from the time the TF occurs onward through end of double-blind period:

- Exceed the baseline dose of oral glucocorticoids (GCs) between Day 1 and Week 24 visits due to increased pSS disease activity.
- Exceed the baseline dose of, or initiate a new permitted pSS medication (other than oral GCs) between the Week 0 and Week 24 visits. A “new” pSS medication is one that was not present at randomization or is not a replacement for (in the same class as) a medication present at randomization at an equivalent or lower dose (see note below).

- Initiate a new protocol-prohibited medication (eg, disallowed route of systemic GC administration, systemic immunomodulators, cytotoxic agent, biologic agent) at any time between randomization and the Week 24 visit.
- Discontinue study intervention for any reason prior to Week 24.
  - Discontinuation of study intervention due to Coronavirus Disease 2019 (COVID-19) pandemic situation or confirmed COVID-19 infection.

Note:

- Substitution of an agent with a similar mechanism of action at an equivalent or lower dose will not be considered a TF (eg, mycophenolate mofetil [MMF] substitution for MPA or vice versa, AZA substitution for 6-MP or vice versa, GC substitutions for other GCs). In addition, methotrexate [MTX] oral can replace MTX subcutaneous (or IM) or MTX subcutaneous (or IM) can replace MTX oral).
- Where replacement of a medication (i.e. dose equivalent is equal or less than current dose) is permitted, the reason for replacement should not be due to pSS worsening. If the replacement is due to pSS worsening, the subject may be classified as a TF.

Periodic review for subjects meeting the above TF criteria is performed by the blinded sponsor medical monitors. The periodic review process consists of (1) applying programmatic definitions of TF based upon the above criteria to the collected data to generate listings of subjects meeting treatment failure criteria and (2) medical monitor in-depth assessment of clinical data including concomitant medications, medical history, laboratory assessments, and potentially other pertinent information to confirm the treatment failure criteria met and (3) maintaining results of the reviews within a tracking document. All subjects meeting TF criteria will be reviewed in a blinded manner. Within the programmed dataset(s), there will exist variables for the programmed TF criteria met, the confirmed TF criteria met after medical review, as well as a detailed summary reason for any differences between the programmed and clinically reviewed TF criteria. The medically reviewed and confirmed TF variables will serve as the basis for all analyses where TF rules are in effect.

Subjects who met TF criteria, reason for meeting criteria, confirmed TF criteria, and detailed summary of reason for any differences between the programmed and clinically reviewed TF criteria will be listed.

5.2. Participant Dispositions

Screened participants and reason for screen failures will be summarized overall.

The number of participants in the following disposition categories will be summarized throughout the study by intervention group and overall:

- Participants randomized
- Participants who received study intervention
- Participants who completed the study
- Participants who discontinued study intervention and reason for discontinuation

- Participants who terminated study prematurely and reason for termination
- Participants who met TF criteria and which criteria were met

The above categories will include summaries through Week 24.

A listing of participants will be provided for the following categories:

- Participants who discontinued study intervention
  - Reasons for discontinuation of study intervention (including discontinuation due to COVID-19 related reasons)
- Participants who terminated study prematurely
  - Reasons for termination of study (including termination due to COVID-19 related reasons)
- Participants who were unblinded during the study period
- Participants who were randomized yet did not receive study intervention
- Participants who met TF criteria

5.3. Primary Endpoint(s) Analysis

The primary endpoint is change from baseline in clinESSDAI score at Week 24.

5.3.1. Definition of Endpoint(s)

5.3.1.1. clinESSDAI

The clinESSDAI is a validated tool used in clinical studies to measure the systemic disease activity in patients with Sjögren'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 (Seror, 2016).

Change from baseline in clinESSDAI: Measures the change from baseline (post baseline – baseline) in systemic disease activity as measured by clinESSDAI score where a negative change reflects improvement, and a positive change reflects worsening.

5.3.2. Estimand

5.3.2.1. Primary Estimand

Primary Trial Objective: To evaluate the efficacy of nipocalimab vs placebo in participants with pSS.

Estimand Scientific Question of Interest: What is the difference between nipocalimab and placebo in the change from baseline in clinESSDAI score after the pre-specified treatment period (24 weeks), administered in addition to the protocol allowed background standard-of-care medication that the participants received at baseline?

Primary Estimand, based on the primary objective and scientific question of interest above, is defined by the following 5 components:

- **Study Intervention:**
  - 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 up to one immunomodulator with or without low-dose GCs (≤10 mg/day prednisone equivalent).

- **Population:** Men and women between the ages of 18 to 75 years, inclusive with active, Sjögren's Syndrome related antigen A (SSA) autoantibody-positive pSS.
- **Variable/endpoint:** Change from baseline in clinESSDAI score at Week 24.
- **Summary Measure (Population-level summary):** Difference in the means of the variable (ie, change from baseline in clinESSDAI score at Week 24) between nipocalimab and placebo treatment groups.
- **Intercurrent Events (ICEs) and their corresponding strategies:**

ICEs	Analysis Strategy for Addressing Intercurrent Events
1. Initiation or adjustment of concomitant medication that meets TF criteria	**Hypothetical Strategy:** This ICE is addressed with a hypothetical strategy, as if the ICE would not have occurred. Data from the time an ICE occurred and onward will not be utilized.
2. Discontinuation of study intervention prior to Week 24 for any reason unrelated to COVID-19	
3. Discontinuation of study intervention prior to Week 24 due to COVID-19 or confirmed COVID-19 pandemic situation or confirmed COVID-19 infection	

5.3.2.2. Supplementary Estimands

Supplementary Estimand 1 (Composite Estimand)

Estimand Scientific Question of Interest: What is the difference between nipocalimab and placebo in the change from baseline in clinESSDAI score after the pre-specified treatment period (24 weeks), administered in addition to the protocol allowed background standard-of-care medication that the participants received at baseline, where participants did not experience an intercurrent event?

Composite estimand is defined to support the primary estimand.

- **Study Intervention:** Same attributes as primary estimand.
- **Population:** Same attributes as primary estimand.
- **Variable/endpoint:** Change from baseline in clinESSDAI score at Week 24.
- **Summary Measure (Population-level summary):** Difference in the means of the variable (ie, change from baseline in clinESSDAI score at Week 24) between nipocalimab and placebo treatment groups.
- ICEs and their corresponding strategies:

ICEs	Analysis Strategy for Addressing Intercurrent Events
1. Initiation or adjustment of concomitant medication that meets TF criteria	**Composite Strategy:** Assign 0 as the change from baseline in clinESSDAI at Week 24 for participants with this ICE.
2. Discontinuation of study intervention prior to Week 24 for any reason unrelated to COVID-19	
3. Discontinuation of study intervention prior to Week 24 due to COVID-19 or confirmed COVID-19 pandemic situation or confirmed COVID-19 infection	

Supplementary Estimand 2 (Treatment Policy Estimand)

Estimand Scientific Question of Interest: What is the difference between nipocalimab and placebo in the change from baseline in clinESSDAI score after the pre-specified treatment period (24 weeks), administered in addition to the protocol allowed background standard-of-care medication that the participants received at baseline, regardless of occurrence of any intercurrent events?

Treatment policy estimand is defined to support the primary estimand.

- **Study Intervention:** Same attributes as primary estimand.
- **Population:** Same attributes as primary estimand.
- **Variable/endpoint:** Change from baseline in clinESSDAI score at Week 24.
- **Summary Measure (Population-level summary):** Difference in the means of the variable (ie, change from baseline in clinESSDAI at Week 24) between nipocalimab and placebo treatment groups.

- **ICEs and their corresponding strategies:**

ICEs	Analysis Strategy for Addressing Intercurrent Events
1. Initiation or adjustment of concomitant medication that meets TF criteria	**Treatment Policy Strategy:** Target the treatment effect regardless of whether or not this ICE had occurred.
2. Discontinuation of study intervention prior to Week 24 for any reason unrelated to COVID-19	
3. Discontinuation of study intervention prior to Week 24 due to COVID-19 or confirmed COVID-19 pandemic situation or confirmed COVID-19 infection	

5.3.3. Analysis Methods

The primary efficacy endpoint (change from baseline in clinESSDAI) will be based on the primary estimand (Section 5.3.2.1.) and the data from all participants in the FAS (Section 4.) will be analyzed according to randomized intervention group, regardless of actual intervention received.

In this primary analysis, n, mean, SD, median, IQ range, minimum, and maximum change from baseline will be summarized for each intervention group. Mixed-Effect Model Repeated Measure (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 will be used to address the primary objective. The Kenward-Roger method will be used to derive the denominator degrees of freedom. If the model lacks convergence, other covariance structures such as Autoregressive moving average, Toeplitz, or Ante-dependence may be used. No missing data imputation will be performed explicitly. Given the hypothesis-generating nature of the study, no multiplicity control is planned.

For the analyses described above, the primary endpoint will be analyzed using the primary estimand. For participants with ICEs 1-3, data collected at or after the ICE will not be utilized in the analysis.

Subgroup Analyses

To evaluate the consistency of the primary endpoint (change from baseline in clinESSDAI at Week 24), subgroup analyses may be performed when the number of participants in the subgroup categories permit (at least 5 subjects for each intervention group within each category of a subgroup variable). If one or more of the categories of a subgroup variable have fewer than 5 subjects in any intervention group, pooling of subgroup categories may be performed to carry out

the subgroup analysis.

The change from baseline in clinESSDAI at Week 24 will also be summarized, by treatment group and by baseline clinESSDAI Domain scores, as well as by treatment group and by baseline and ESSPRI Domain scores.

The primary estimand (Section 5.3.2.1.) will be used for these subgroup analyses and the same analysis methods defined in this section used for primary estimand will be applied.

The subgroups for subgroup analysis are defined in Section 5.7.7.

5.3.4. Supplementary Analyses

5.3.4.1. Supplementary Analysis 1 (Composite Estimand)

The primary endpoint will be analyzed the same way as for the primary estimand but targeting the Supplementary Estimand 1 (Composite Estimand) defined in Section 5.3.2.2. Participants with ICEs in categories 1-3 will be assumed to have 0 change from baseline in clinESSDAI at Week 24.

5.3.4.2. Supplementary Analysis 2 (Treatment Policy Estimand)

The primary endpoint will be analyzed the same way as for the primary estimand but targeting the Supplementary Estimand 2 (Treatment Policy Estimand) defined in Section 5.3.2.2. For participants who experience ICEs categories 1-3 through Week 24, the treatment policy strategy will be used, and the analysis will be performed using observed data regardless of ICEs.

5.4. Secondary Endpoint(s) Analysis

5.4.1. Secondary Endpoint(s)

Objective: to characterize additional assessments of efficacy for nipocalimab vs placebo in participants with pSS.

The secondary endpoints for Week 24 analyses to address the objective are the following (acronyms are defined in 5.4.2):

1. Change from baseline in ESSPRI score at Week 24
2. Proportion of subjects who achieve ESSDAI-4 responses at Week 24
3. Proportion of subjects who achieve clinESSDAI-4 responses at Week 24
4. Proportion of subjects who achieve ESSPRI responses at Week 24
5. Proportion of subjects who achieve STAR responses at Week 24
6. Proportion of subjects who achieve DAL responses at Week 24

7. Proportion of subjects who achieve CRESS responses at Week 24

5.4.2. Definition of Endpoint(s)

5.4.2.1. 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 pSS (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).

Change from baseline in ESSPRI score: Measures the change from baseline (post baseline – baseline) in the patient-reported assessment of the severity of dryness, fatigue, and pain associated with pSS, where a negative change reflects improvement, and a positive change reflects worsening.

ESSPRI response: Reduction of ≥ 1 point or a decrease of ≥15% in the ESSPRI score from baseline.

ESSPRI component response: Reduction of ≥ 1 point or a decrease of ≥15% in any ESSPRI subcategory from baseline.

5.4.2.2. ESSDAI-4

The EULAR Sjögren Syndrome Disease Activity Index (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 screening study visit (i.e., Week 0 through the end of study, inclusive).

ESSDAI-4 response: Reduction of the composite ESSDAI score by at least 4 points from baseline.

5.4.2.3. clinESSDAI-4

Details refer to section 5.3.1.1.

clinESSDAI-4 response: Reduction of the composite clinESSDAI score by at least 4 points from baseline.

5.4.2.4. STAR

The Sjögren's Tool for Assessing Response (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. The measurements and associated definition of response for each item is described by Seror, et al. and summarized in Table 2 below.

Other thresholds for defining STAR response will also be analyzed, as appropriate. (Seror 2022).

Table 2: STAR response criteria and instructions

Domain	Point	Definition of response
Systemic activity	3	Decrease of ≥ 3 in clinESSDAI
Patient-reported outcome	3	Decrease of ≥ 1 point or ≥ 15% in ESSPRI.
Lachrymal gland function (assessed by Schirmer's test or ocular staining score)	1	Schirmer's test: If abnormal at baseline: increase ≥ 5 mm from baseline. If normal score at baseline: no change to abnormal. *Or* Ocular staining score: If abnormal score at baseline: decrease of ≥ 2 points from baseline. If normal score at baseline: no change to abnormal.
Salivary gland function (assessed by unstimulated whole salivary flow or ultrasound)	1	Unstimulated whole salivary flow: If score is > 0 at baseline: increase of ≥ 25% from baseline. If score is 0 at baseline: any increase from baseline.

Table 2: STAR response criteria and instructions

Domain	Point	Definition of response
		Or Ultrasound: Decrease of ≥ 25% in total Hocevar score from baseline.
Biological (assessed by serum IgG or RF level)	1	Serum IgG level: decrease of ≥ 10%. *Or* RF level: decrease of ≥ 25%.
Candidate STAR responder		≥5 points

STAR response: A composite score of ≥5 points in the 5 STAR domains (systemic activity, patient-reported outcome, lachrymal gland function, salivary gland function, and biological).

If a subject meets the STAR response criteria, regardless of missing data, then the subject is a responder.

5.4.2.5. DAL

Disease Activity Level (DAL) refers the level of disease activity severity (i.e., no, low, moderate, or severe) in each clinESSDAI or ESSDAI domain (e.g., biological, hematological, cutaneous, constitutional, lymphadenopathy and lymphoma, and glandular).

Details refer to section 5.4.2.2. and 5.3.1.1.

DAL response: Reduction from baseline in disease activity level by at least one level in at least one clinESSDAI or ESSDAI domain (e.g., biological, hematological, cutaneous, constitutional, lymphadenopathy and lymphoma, and glandular).

5.4.2.6. CRESS

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. The measurements and associated definition of response for each item is described by Arends, et al. and summarized in the Table 3 below. A CRESS response is defined as a response in ≥3 of these 5 categories (Arends 2020).

Table 3: Overview of the Composite of Relevant Endpoints in Sjögren's Syndrome (CRESS): definition of response of the 5 complementary items

Item	Measurement	Definition of response
Systemic disease activity	clinESSDAI	Score <5 (low disease activity)
Patient-reported symptoms	ESSPRI	Decrease of ≥ 1 point or ≥ 15% from baseline

Table 3: Overview of the Composite of Relevant Endpoints in Sjögren's Syndrome (CRESS): definition of response of the 5 complementary items

Item	Measurement	Definition of response
Tear gland*	Schirmer/OSS**	If abnormal score at baseline: • Or increase of ≥5 mm in Schirmer • Decrease of ≥ 2 points in OSS Or if both normal at baseline: • No change to abnormal in Schirmer and OSS
Salivary gland*	UWS/SGUS	• Increase of ≥ 25% or if score is 0 at baseline any increase in UWS • Or decrease of ≥ 25% in total Hocevar score
Serological	RF/igG	• Decrease of ≥ 25% in RF • Or decrease of ≥ 10% in IgG
Total CRESS responder		Response on ≥ 3 of 5

*CRESS can also be used without OSS and SGUS if these tests are not available

**Mean of both eyes

Abbreviations: clinESSDAI: Clinical EULAR Sjögren's syndrome disease activity index; ESSPRI: EULAR Sjögren's syndrome patient reported index; OSS: Ocular Staining Score; UWS: unstimulated whole saliva; SGUS: salivary gland ultrasonography; RF: rheumatoid factor; IgG: Immunoglobulin G

clinESSDAI

Details refer to section 5.3.1.1.

ESSPRI

Details refer to section 5.4.2.1.

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. The Schirmer's test should precede the OSS evaluation, if they occur on the same day.

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 (Whitcher 2010). The ocular staining score 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.

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.

CRESS response: An improvement in ≥3 of 5 CRESS categories (systemic disease activity, patient reported symptoms, salivary gland function, tear gland function, and serological activity).

If a subject meets the CRESS response criteria, regardless of missing data, then the subject is a responder.

5.4.3. Estimands for Secondary Endpoints

5.4.3.1. Primary Estimand for the Secondary Endpoint of Change from Baseline in ESSPRI Score at Week 24

The following describes the attributes of the estimand for the secondary endpoint # 1 defined in Section 5.4.1.

- **Study intervention:**
  - 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 up to one immunomodulator 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, Sjögren's Syndrome related antigen A (SSA) autoantibody-positive pSS.
- **Variable/endpoint:** Change from baseline in ESSPRI score at Week 24.
- **Summary Measure (Population-level summary):** Difference in the means of the variable (ie, change from baseline in ESSPRI score at Week 24) between nipocalimab and placebo treatment groups.
- **ICEs and their corresponding strategies:**

ICEs	Analysis Strategy for Addressing Intercurrent Events
1. Initiation or adjustment of concomitant medication that meets TF criteria	**Hypothetical Strategy:** This ICE is addressed with a hypothetical strategy, as if the ICE would not have occurred. Data from the time an ICE occurred and onward will not be utilized.
2. Discontinuation of study intervention prior to Week 24 for any reason unrelated to COVID-19	
3. Discontinuation of study intervention prior to Week 24 due to COVID-19 or confirmed COVID-19 pandemic situation or confirmed COVID-19 infection	

5.4.3.2. Supplementary Estimand for the Secondary Endpoint of Change from Baseline in ESSPRI Score at Week 24

The treatment policy estimand is defined to support the primary estimand. In its definition, the only component that changes from the definition of the primary estimand is the strategy used for addressing ICEs 1-3.

ICEs	Analysis Strategy for Addressing Intercurrent Events
1. Initiation or adjustment of concomitant medication that meets TF criteria	**Treatment Policy Strategy:** Target the treatment effect regardless of whether or not this ICE had occurred.
2. Discontinuation of study intervention prior to Week 24 for any reason unrelated to COVID-19	
3. Discontinuation of study intervention prior to Week 24 due to COVID-19 or confirmed COVID-19 pandemic situation or confirmed COVID-19 infection	

5.4.3.3. Primary Estimands for Secondary Binary Endpoints

The following describes the attributes of the estimands for the secondary binary endpoints (#2, 3, 4, 5, 6,7) defined in Section 5.4.1.

- **Study intervention:**
  - 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 up to one immunomodulator 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, Sjögren's Syndrome related antigen A (SSA) autoantibody-positive pSS.
- **Variable/endpoint and Population-level summary:**

Estimand	Variable (Endpoint)	Population-level summary
Secondary Endpoint #2 Primary Estimand	Response binary variable, where a responder is defined as achieving an improvement of ≥4 points from baseline in ESSDAI score (minimal clinically important improvement) at Week 24	Difference in proportion of responders defined in the variable attribute at Week 24 between each nipocalimab group and placebo
Secondary Endpoint #3 Primary Estimand	Response binary variable, where a responder is defined as achieving an improvement of ≥4 points from baseline in clinESSDAI score (minimal clinically important improvement) at Week 24	Difference in proportion of responders defined in the variable attribute at Week 24 between each nipocalimab group and placebo
Secondary Endpoint #4 Primary Estimand	Response binary variable, where ESSPRI response is defined as a decrease of one point or a decrease of ≥15% from baseline (minimal clinically important improvement) at Week 24	Difference in proportion of responders defined in the variable attribute at Week 24 between each nipocalimab group and placebo
Secondary Endpoint #5 Primary Estimand	Response binary variable, where a responder is defined as achieving a composite score of ≥5 points in the 5 STAR domains at Week 24: systemic activity, patient-reported outcome, lachrymal gland function, salivary gland function, and biological	Difference in proportion of responders defined in the variable attribute at Week 24 between each nipocalimab group and placebo
Secondary Endpoint #6 Primary Estimand	Response binary variable, where a responder is defined as achieving an 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	Difference in proportion of responders defined in the variable attribute at Week 24 between each nipocalimab group and placebo
Secondary Endpoint #7 Primary Estimand	Response binary variable, where a responder is defined as achieving an improvement from baseline in ≥3 of 5 CRESS categories at Week 24: systemic disease activity, patient reported symptoms, salivary gland	Difference in proportion of responders defined in the variable attribute at Week 24 between each nipocalimab group and placebo

Estimand	Variable (Endpoint)	Population-level summary
	function, tear gland function, and serological activity	

- **ICEs and their corresponding strategies:**

ICEs	Analysis Strategy for Addressing Intercurrent Events
1. Initiation or adjustment of concomitant medication that meets TF criteria	**Composite Strategy:** A participant with this ICE is considered as a non-responder after this event, the occurrence of this ICE being captured in the variable definition.
2. Discontinuation of study intervention prior to Week 24 for any reason unrelated to COVID-19	
3. Discontinuation of study intervention prior to Week 24 due to COVID-19 or confirmed COVID-19 pandemic situation or confirmed COVID-19 infection	

5.4.3.4. Supplementary Estimands for Key Secondary Binary Endpoints

The Treatment Policy estimand is defined to support the primary estimand. In its definition, the only component that changes from the definition of the primary estimand is the strategy used for addressing ICEs 1-3.

ICEs	Analysis Strategy for Addressing Intercurrent Events
1. Initiation or adjustment of concomitant medication that meets TF criteria	**Treatment Policy Strategy:** Target the treatment effect regardless of whether or not this ICE had occurred.
2. Discontinuation of study intervention prior to Week 24 for any reason unrelated to COVID-19	

ICEs	Analysis Strategy for Addressing Intercurrent Events
3. Discontinuation of study intervention prior to Week 24 due to COVID-19 or confirmed COVID-19 pandemic situation or confirmed COVID-19 infection	

5.4.4. Analysis Methods

Unless otherwise specified, the analysis population will be the FAS defined in Section 4.The endpoints will be summarized by study intervention groups. For between group comparisons, nominal p-values will be reported. All statistical tests will be performed at α=0.10 (2-sided). However, no multiplicity control is planned.

Simple descriptive 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.

5.4.4.1. Change from Baseline in ESSPRI Score at Week 24

Analyses for change from baseline in ESSPRI score at Week 24 (secondary endpoint #1 in section 5.4.1. above) will be based upon estimands in Section 5.4.3.1. and Section 5.4.3.2.

A Mixed-Effect Model Repeated Measure (MMRM) model with an unstructured variance-covariance structure will be used to test the difference between intervention groups and adjust for missing data. The model will include change from baseline in ESSPRI score at Week 24 as the dependent variable and baseline ESSPRI score, treatment, study visit, treatment by study visit interaction and stratification factors for randomization as independent variables. The Kenward-Roger method will be used to derive the denominator degrees of freedom. If the model lacks convergence, other covariance structures such as Autoregressive moving average, Toeplitz, or Ante-dependence may be used. No missing data imputation will be performed explicitly. Given the hypothesis-generating nature of the study, no multiplicity control is planned. The normality and equal variance assumptions underlying the MMRM model will be assessed graphically. Residuals from the models will be plotted against the predicted values and a QQ plot of the residuals versus the expected quantiles of the standard normal distribution will be presented. If either the equal variance or the normality assumption appears to be grossly violated, other methods including an ANCOVA on ranks model or an appropriate transformation (e.g., log, square root) might be considered.

In general, point estimates and 90% confidence intervals for comparison between treatment groups will be reported.

5.4.4.2. Binary Endpoints

Analyses for binary secondary endpoints (secondary endpoints #2, 3, 4, 5, 6 and 7 in Section 5.4.1. above) will be based upon the estimands in Section 5.4.3.3. and Section 5.4.3.4.

The Cochran-Mantel-Haenszel (CMH) test stratified by 1) baseline steroid use (Y/N), 2) anti-malarial use (Y/N), and 3) geographic region (North America, Eastern Europe, Western Europe, Other) will be used to analyze the binary secondary endpoints. The difference in proportions and associated 90% confidence interval will be provided.

5.5. Tertiary/Exploratory Endpoint(s) Analysis

5.5.1. Tertiary/Exploratory Endpoint(s)

Other Efficacy Endpoints for Week 24 Analyses (acronyms are defined in 5.5.2.):

To further evaluate the efficacy of nipocalimab in participants with pSS versus placebo, the following endpoints will be summarized by intervention group. Differences between each nipocalimab group and placebo group will be summarized. Nominal p-values will be reported.

- Change from baseline in PhGA over time 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 in DAS28 CRP over time through Week 24
- Change from baseline in IDSSTS, Identification test, and Detection test scores over time through Week 24
- Proportion of subjects who achieve SSRI-20 response at Week 24
- Proportion of subjects who achieve SSRI-30-2 response over time through Week 24
- Proportion of subjects who achieve SSRI-30-3 response over time through Week 24
- Change from baseline in ESSDAI score at Week 24
- Proportion of subjects who achieve ESSDAI-3 responses at Week 24
- Proportion of subjects who achieve altSTAR responses at Week 24
- Proportion of subjects who achieve altCRESS responses at Week 24

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 Patient Reported Outcome tools:
  - 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

To evaluate the effect of nipocalimab versus placebo on SICCA Signs:

- 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
- To evaluate the effect of nipocalimab versus placebo on steroid use:
- Change from baseline in steroid use in comparison to mean doses between groups over time through Week 24

5.5.2. Definition of Endpoint(s)

5.5.2.1. PhGA

The Physician's Global Assessment of Disease Activity (PhGA) (Divi 2015) independent of participants' assessment is recorded on a VAS with responses ranging from 0 to 100 mm, with the anchors "No Sjögren's Syndrome Activity" (0) at one end of the scale and "Extremely Active Sjögren'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 patient reported outcome 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).

Change from baseline in PhGA: Measures the change from baseline (post baseline – baseline) in Sjögren's Syndrome Activity, where a negative change reflects improvement, and a positive change reflects worsening.

5.5.2.2. ESSPRI

Details refer to section 5.4.2.1.

Change from baseline in ESSPRI components: Measures the change from baseline (post baseline – baseline) in ESSPRI components (dryness, fatigue, and pain associated with pSS), where a negative change reflects improvement, and a positive change reflects worsening.

5.5.2.3. DAS28 CRP

The Disease Activity Score 28 C-reactive Protein (DAS28 CRP) is a continuous parameter and is defined as follows: DAS28(CRP) = 0.56 × SQRT(TEN28) + 0.28 × SQRT(SW28) + 0.36 × ln (CRP+1) + 0.014 × GH + 0.96; where: TEN28 is 28 joint count for tenderness, SW28 is 28 joint count for swelling, Ln (CRP+1) is natural logarithm of (CRP value [mg/L] + 1), SQRT(TEN28) is square root of TEN28, SQRT(SW28) is square root of SW28 , and GH is Patient's Global Assessment of Disease Activity (arthritis).

Change from baseline in DAS28 CRP: Measures the change from baseline (post baseline – baseline) in disease activity, where a negative change reflects improvement, and a positive change reflects worsening.

5.5.2.4. IDSSTS

The International Digit Symbol Substitution Test – Symbols (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.

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.

Identification (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.

Change from baseline in IDSSTS, Identification test, and Detection test scores: Measures the change from baseline (post baseline – baseline) in cognitive function, psychomotor function, and visual attention where a positive change reflects improvement, and a negative change reflects worsening.

5.5.2.5. SSRI-20, SSRI-30-2, SSRI-30-3

Sjögren's Syndrome Responder Index (SSRI) is a composite index capable of detecting therapeutic responses in patients with pSS. The five outcome measures in the SSRI center on objective and subjective sicca symptoms, including visual analog scale (VAS) fatigue score, VAS oral dryness score, VAS ocular dryness score, unstimulated whole saliva flow, and erythrocyte sedimentation rate (ESR). An SSRI-20 response is defined as a ≥20% improvement in at least two of these five outcome measures. An SSRI-30-2 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). An SSRI-30-3 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).

SSRI-20 response: Reduction of at least 20% from baseline in at least two of the following domains: fatigue, oral dryness, ocular dryness, unstimulated whole salivary flow, erythrocyte sedimentation rate.

If a subject meets the SSRI-20 response criteria, regardless of missing data, then the subject is a responder.

SSRI-30-2 response: Reduction of at least 30% from baseline in at least two of the following domains: fatigue, oral dryness, ocular dryness, unstimulated whole salivary flow, erythrocyte sedimentation rate.

If a subject meets the SSRI-30-2 response criteria, regardless of missing data, then the subject is a responder.

SSRI-30-3 response: Reduction of at least 30% from baseline in at least three of the following domains: fatigue, oral dryness, ocular dryness, unstimulated whole salivary flow, erythrocyte sedimentation rate.

If a subject meets the SSRI-30-3 response criteria, regardless of missing data, then the subject is a responder.

5.5.2.6. ESSDAI, ESSDAI-3

Details refer to section 5.4.2.2.

Change from baseline in ESSDAI: Measures the change from baseline (post baseline – baseline) in systemic disease activity as measured by ESSDAI score where a negative change reflects improvement, and a positive change reflects worsening.

ESSDAI-3 response: Reduction of the composite ESSDAI score by at least 3 points from baseline.

5.5.2.7. altSTAR

altSTAR is an alternative definition of STAR that excludes IgG. Details refer to section 5.4.2.4.

altSTAR response: A composite score of ≥5 points in the following 5 STAR domains: systemic activity, patient-reported outcome, lachrymal gland function, salivary gland function, and biological (rheumatoid factor).

If a subject meets the altSTAR response criteria, regardless of missing data, then the subject is a responder.

5.5.2.8. altCRESS

altCRESS is an alternative definition of CRESS that excludes IgG. Details refer to section 5.4.2.6.

altCRESS response: An improvement in ≥3 of the following 5 CRESS categories: systemic disease activity, patient reported symptoms, salivary gland function, tear gland function, and serological activity (rheumatoid factor).

If a subject meets the altCRESS response criteria, regardless of missing data, then the subject is a responder.

5.5.2.9. Patient Reported Outcome Tools

HADS

The Hospital Anxiety and Depression Scale (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).

Change from baseline in HADS: Measures the change from baseline (post baseline – baseline) in HADS, where a negative change reflects improvement, and a positive change reflects worsening.

WLQ

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).

Change from baseline in WLQ: Measures the change from baseline (post baseline – baseline) in WLQ, where a negative change reflects improvement, and a positive change reflects worsening.

Sjögren's Symptoms

For assessment of Sjögren's symptoms, participants will be asked to report the worst severity of their fatigue, 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.

Change from baseline in Sjögren's Symptoms: Measures the change from baseline in Sjögren's Symptoms, where a negative change reflects improvement, and a positive change reflects worsening.

FACIT-Fatigue

The Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) questionnaire 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).

Change from baseline in FACIT-Fatigue: Measures the change from baseline (post baseline – baseline) in FACIT-Fatigue, where a positive change reflects improvement, and a negative change reflects worsening.

PGIS

The Patient Global Impression of Severity (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 patient reported outcomes.

Change from baseline in PGIS: Measures the change from baseline (post baseline – baseline) in PGIS, where a negative change reflects improvement, and a positive change reflects worsening.

PGIC

The Patient Global Impression of Change (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 patient reported outcome measures included in the study.

Change from baseline in PGIC: Measures the change from baseline (post baseline – baseline) in PGIC, where a negative change reflects improvement, and a positive change reflects worsening.

SF-36 v2

The Short Form Health Survey 36 Standard version 2 (SF-36 v2) is a participant self-administered, 36-item questionnaire measuring HRQoL. The recall period for all items is the past 4 weeks. The SF-36 v2 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 v2 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.

Change from baseline in SF-36 v2: Measures the change from baseline (post baseline – baseline) in SF-36 v2, where a positive change reflects improvement, and a negative change reflects worsening.

PtGA

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 VAS, with responses ranging from 0 (Very well) to 100 (Very poor). The PtGA will be used to calculate the DAS28 composite index.

Change from baseline in PtGA: Measures the change from baseline (post baseline – baseline) in PtGA, where a negative change reflects improvement, and a positive change reflects worsening.

5.5.2.10. Unstimulated Salivary Flow Rate

Details refer to "Unstimulated Salivary Flow Test" in section 5.4.2.6.

Change from baseline in unstimulated salivary flow rate: Measures the change from baseline (post baseline – baseline) in unstimulated salivary flow rate, where a positive change reflects improvement, and a negative change reflects worsening.

Improvement from baseline in salivary unstimulated flow rate: An increase from baseline in salivary unstimulated flow rate.

5.5.2.11. Tear Secretion Amount

Details refer to "Schirmer's Test" in section 5.4.2.6.

Change from baseline in tear secretion amount: Measures the change from baseline (post baseline – baseline) in tear secretion amount using the Schirmer's Test, where a positive change reflects improvement, and a negative change reflects worsening.

5.5.2.12. Artificial Tears and/or Saliva

Change from baseline in frequency of use and the amount of artificial tears and/or saliva: Measures the change from baseline (post baseline – baseline) in frequency of use and the amount of artificial tears and/or saliva to treat dryness, where a negative change reflects improvement, and a positive change reflects worsening.

5.5.2.13. Ocular Surface Staining

Details refer to "Ocular Staining Score" in 5.4.2.6.

Change from baseline in Ocular Surface Staining: Measures the change from baseline (post baseline – baseline) in OSS, where a negative change reflects improvement, and a positive change reflects worsening.

5.5.2.14. Steroid Use

Change from baseline in Steroid Use: Measures the average change from baseline (post baseline – baseline) in Steroid Use, where a negative change reflects improvement, and a positive change reflects worsening.

5.5.3. Analysis Methods

This section outlines the analyses of exploratory endpoints. Unless otherwise specified, the analysis population will be the FAS defined in Section 4. The endpoints will be summarized by study intervention groups. For between group comparisons, p-values will be reported. However, no multiplicity control is planned.

Simple descriptive 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.

Continuous Endpoints

The hypothetical and treatment policy estimand approaches specified for the primary endpoint in Section 5.3.2. will be applied to all continuous tertiary/exploratory endpoints as the primary estimand and supplementary estimand.

For continuous endpoints, a Mixed-Effect Model Repeated Measure (MMRM) model with an unstructured variance-covariance structure will be used to test the difference between intervention groups and adjust for missing data. The models will include the baseline of the continuous endpoint, treatment, study visit, treatment by study visit interaction and stratification factors for randomization as independent variables. The Kenward-Roger method will be used to derive the denominator degrees of freedom. If the model lacks convergence, other covariance structures such as Autoregressive moving average, Toeplitz, or Ante-dependence may be used. No missing data imputation will be performed explicitly. Given the hypothesis-generating nature of the study, no multiplicity control is planned. The normality and equal variance assumptions underlying the MMRM model will be assessed graphically. Residuals from the models will be plotted against the predicted values and a QQ plot of the residuals versus the expected quantiles of the standard normal distribution will be presented. If either the equal variance or the normality assumption appears to be grossly violated, other methods including an ANCOVA on ranks model or an appropriate transformation (e.g., log, square root) might be considered.

In general, point estimates and 90% confidence intervals for comparison between treatment groups will be reported.

Binary Endpoints

The composite and treatment policy estimand approaches and the corresponding analysis methods specified for the secondary endpoint in Sections 5.4.3.3., 5.4.3.4., and 5.4.4.2., will be applied to all binary tertiary/exploratory endpoints as the primary estimand and supplementary estimand, respectively.

5.5.3.1. Sensitivity Analysis (SSRI endpoints)

To evaluate the robustness of key tertiary endpoints SSRI-20, SSRI-30-2, and SSRI-30-3 defined in Section 5.5.2.5. the following sensitivity analysis will be performed:

The composite and treatment policy estimand approaches and the corresponding analysis methods specified for the secondary endpoint in Sections 5.4.3.3., 5.4.3.4., and 5.4.4.2., will be applied to the SSRI-20, SSRI-30-2, and SSRI-30-3 binary endpoints as the primary estimand and supplementary estimand, respectively, for subjects using the old kit only, new kit only, and a combination of the new and old kits.

5.5.3.2. Sensitivity Analysis (ESR data)

To evaluate the robustness of the ESR data from subjects using the old kit only, new kit only, and a combination of the new and old kits, the following sensitivity analysis will be performed:

The hypothetical and treatment policy estimand approaches and corresponding analysis methods specified for tertiary/exploratory continuous endpoints in Section 5.5.3. will be applied to the ESR data from subjects using the old kit only, new kit only, and a combination of the new and old kits as the primary estimand and supplementary estimand, respectively.

5.6. Safety Analyses

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

For all continuous safety variables, descriptive statistics by intervention group will include the N, mean, standard deviation (SD), median, and range (minimum, maximum). Categorical variables will be summarized by intervention group using frequency counts and percentages.

5.6.1. Extent of Exposure

The number and percentage of participants who receive study intervention (placebo q2w, nipocalimab 5 mg/kg IV q2w, nipocalimab 15mg/kg IV q2w) will be summarized.

The number and percentage of participants will also be summarized by visit.

Descriptive statistics for duration of a study intervention and duration of follow-up (N, mean, SD, median, and range (minimum, maximum)) will be summarized. Participant-years of study intervention duration are calculated as days of intervention/365.25. Participant-years will be presented by intervention group.

Study intervention duration is defined as (date of last dose of study intervention – date of first dose of study intervention) +1.

Follow-up duration is defined as [date of last study visit or last study contact (whichever is later)-date of first dose of study intervention] +1.

Descriptive statistics will be presented by intervention group for the following parameters:

- Number of administrations
- Cumulative total dose: Cumulative total dose is the total dose in mg a participant received over all infusions in the study. The dose in mg for a given infusion is the dose level administered in mg/kg multiplied by the participant's weight.

A listing of participants with an infusion interruption or change in infusion flow rate will be provided.

Study intervention compliance will be summarized descriptively. See Appendix 7 for further details.

5.6.2. 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.

Summary tables will be provided for treatment-emergent (TE) adverse events for:

- All AEs
- Serious AEs (SAEs)
- AEs leading to discontinuation of study intervention/termination of study participation
- AEs by severity
- AEs by relationship to study intervention
- AEs of special interest (AESI)
  - Infections that are severe or require IV anti-infective or operative/invasive intervention
  - New onset Hypoalbuminaemia with albumin < 20 g/L
- AEs of clinical interest
  - Infusion reactions
  - Infusion site reaction
  - Opportunistic infections
  - Hypersensitivity reactions
  - Anaphylactic reactions or serum sickness reactions
  - Suicidal ideation/behavior
  - Potentially associated with glucocorticoid toxicity

In addition to the summary tables, listings will be provided for participants who had:

- SAEs
- AEs leading to discontinuation of study intervention/termination of study participation
- Deaths
- AEs of special interest or clinical interest
- Major adverse cardiovascular events (MACE) identified through independent adjudication committee

See Appendix 9 for the definitions of adverse events in each special or clinical interest category.

Since safety should be assessed relative to exposure and follow-up, most AE summary tables will include average number of study agent administrations and average weeks of follow-up for each intervention group.

AEs, SAEs and AESI by IgG
Treatment-emergent AEs, SAEs and AESIs will be summarized by minimum IgG levels (<=2.0, >2.0-4.0, >4.0 g/L). Events that will be included in these summaries are those that occurred since previous dosing prior to the date of minimum IgG level until the end of the phase. Additionally, IgG values over time will be plotted for those subjects who experience an AESI.

5.6.3. Additional Safety Assessments

5.6.3.1. Clinical Laboratory Tests

Clinical laboratory tests will be displayed for the participants included in the safety analysis set.

Hematology: hemoglobin, hematocrit, mean corpuscular hemoglobin (MCH)%, mean corpuscular volume (MCV), platelet count, red blood cell (RBC) count, reticulocytes, white blood cell (WBC) count with differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils, absolute neutrophil count, absolute lymphocyte count), activated partial thromboplastin time, erythrocyte sedimentation rate (ESR), prothrombin international normalized ratio, prothrombin time.

Clinical Chemistry: alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT), albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, creatine phosphokinase (CPK), gamma-glutamyltransferase (GGT), glucose, lactic acid dehydrogenase (LDH), magnesium, phosphate, potassium, sodium, total bilirubin, total protein, uric acid, lipid panel, D-dimer, total Immunoglobulin G (IgG), Immunoglobulin G1 (IgG1), Immunoglobulin G2 (IgG2), Immunoglobulin G3 (IgG3), Immunoglobulin G4 (IgG4), Immunoglobulin A (IgA), Immunoglobulin M (IgM), Immunoglobulin E (IgE), anti-double stranded DNA (anti-dsDNA), antinuclear antibody (ANA), C1Q binding immune complex, complement C3, complement C4, total complement activity (CH50), C3D circulating immune comp, kappa light chain free, lambda light chain free, ratio of kappa light chain free and lambda light chain free, rheumatoid factor (RF), anti-Sjögren's Syndrome A (anti-SSA)/Ro52 IgG antibody, anti-SSA/Ro60 IgG antibody, anti-Sjögren's Syndrome B (anti-SSB) IgG antibody, anti-Smith antibody, thyroid antithyroglobulin antibodies, monoclonal M-spike, c-reactive protein (CRP), cryoglobulins, thyroid stimulating hormone (TSH), free thyroxine (T4), free triiodothyronine (T3), anti-negative antinuclear ribonucleoprotein (anti-nRNP) IgG, anti-cardiolipin (IgG & IgM), and beta-2 glycoprotein 1 IgG antibody, and beta-2 glycoprotein 1 IgM antibody.

Lipid Panel: high density lipoprotein [HDL], low density lipoprotein [LDL], very low density lipoprotein (VLDL), total cholesterol, triglycerides, and ratio of HDL to total cholesterol. Only fasting lipid samples will be included in summaries.

Urinalysis: dipstick (bilirubin, blood, glucose, ketones, leukocyte esterase, nitrite, pH, specific gravity, and urobilinogen), sediment (bacteria, casts, crystals, epithelial cells, RBCs, WBCs).

Urine chemistry: Urine protein/creatinine ratio

Descriptive statistics will be presented for chemistry, hematology and urinalysis (pH and specific gravity) laboratory tests at scheduled time points. Change from baseline to Week 24 will be summarized for chemistry, hematology and urinalysis (pH and specific gravity) tests and displayed by intervention group. Descriptive statistics will be provided for percent change from baseline to each scheduled time point for albumin and total cholesterol by intervention group. Boxplots and plots of mean (±SE) value, change, and percent change from baseline to each scheduled time point will be provided for albumin and total cholesterol. Plots of mean (±SE) value and change to each scheduled time point will be provided for ALT, AST, and total bilirubin.

Shift tables will be provided summarizing the shift in select laboratory values from baseline to the maximum post-baseline value and to the minimum post-baseline value with respect to the normal range criteria (e.g., low, normal, high).

Markedly abnormal criteria will be applied to baseline and postbaseline values and are provided in Appendix 11. The number and percentage of participants with treatment-emergent markedly abnormal values will be presented by intervention group over time. A listing of markedly abnormal laboratory values will be provided. Additionally, abnormal laboratory findings to be reported for albumin and liver enzyme tests are described below. For criteria that do not include an increase or decrease from baseline, post baseline abnormalities will be compared with their corresponding baseline result. Specifically, if the postbaseline value is above the upper limit and the baseline value is below the upper limit (e.g., Normal or Low), then the postbaseline abnormality will be considered TE. The same applies to the postbaseline value being below the lower limit with the baseline value being above the lower limit (e.g., Normal or High). If the baseline value is missing, a postbaseline abnormality will always be considered as TE.

- Albumin <20g/L
- ALT, AST: >1xULN; ≥ 3xULN; ≥ 5xULN; ≥ 10xULN; ≥ 20xULN
- ALP: >1xULN; ≥ 3xULN; ≥ 5xULN; ≥ 10xULN; ≥ 20xULN
- Bilirubin: ≥ 2xULN

A listing of patients meeting biochemical Hy's law criteria will be provided:

- ALT or AST ≥3xULN and
- ALP <2xULN and
- Total bilirubin ≥2xULN or INR >1.5 (if measured)

5.6.3.2. Vital Signs

Continuous vital sign parameters including temperature, weight, pulse, blood pressure (systolic and diastolic), and respiratory rate will be summarized at each assessment time point. Change from

baseline will be summarized through Week 24. Descriptive statistics (mean, SD, median, and range) will be presented.

Abnormality criteria (based on criteria in Table 4) will be applied to baseline and postbaseline values. For baseline values, increase or decrease criteria are not applied.

Postbaseline values will be considered TE if they meet both value and change criteria in Table 4.

For criteria that do not include an increase or decrease from baseline:

- TE will be concluded if the postbaseline value is above the upper limit and the baseline value is below the upper limit (e.g., Normal or Low). The same applies to the postbaseline value being below the lower limit with the baseline value being above the lower limit (e.g., Normal or High).
- If the baseline value is missing, a post baseline abnormality will always be considered as TE.

Incidence of TE markedly abnormal vital signs during intervention will be summarized. A listing of participants with markedly abnormal vital signs will be presented. Markedly abnormal criteria are defined in Table 4 below.

Table 4: Markedly Abnormal Vital Signs

Vital Sign	Criteria
Pulse	≥120 bpm and with ≥15 bpm increase from baseline
	≤50 bpm and with ≥15 bpm decrease from baseline
Systolic blood pressure	≥160 mmHg and with ≥20 mmHg increase from baseline
	≤ 90 mmHg and with ≥20 mmHg decrease from baseline
Diastolic blood pressure	≥100 mmHg and with ≥15 mmHg increase from baseline
	≤50 mmHg and with ≥15 mmHg decrease from baseline
Temperature	> 38°C
	< 36°C

5.7. Other Analyses

5.7.1. Pharmacokinetics

Pharmacokinetics (PK) samples for measuring serum nipocalimab concentrations will be collected from all subjects at the specified visits as shown in the Schedule of Activities. All PK evaluations will be performed on the PK analysis set for the main study, defined as participants who have received at least 1 administration of nipocalimab and have at least one post-dose sample collection.

Descriptive statistics (N, mean, SD, median, range, CV (%) and IQ range) will be used to summarize nipocalimab serum concentrations at each sampling time point. PK data may be displayed graphically, such as median +/- IQ range PK concentrations over time by intervention group. The following analyses will be performed as appropriate:

- Summary of serum nipocalimab concentrations at each visit
- Summary of serum nipocalimab concentrations at each visit by baseline body weight quartiles
- Summary of serum nipocalimab concentrations at each visit by baseline age categories (≤ 65 years, > 65 years)
- Summary of nipocalimab concentrations by presence of serologic activity (single positive anti-Ro60, single positive anti-Ro52, double positive anti-Ro60/52, or RF positive) at screening (yes, no)
- Summary of nipocalimab concentrations by presence of serologic activity (autoantibody titers, total IgG, ESR, CRP, RF) at screening (≤ median, > median)
- Summary of nipocalimab concentrations at each visit by baseline hydroxychloroquine (or other anti-malarial drug) use (yes, no)
- Summary of nipocalimab concentrations at each visit by baseline corticosteroid use (yes, no)
- Summary of nipocalimab concentrations at each visit by prior non-biologic immunosuppressant other than hydroxychloroquine (or other anti-malarial drug) use (yes/no)
- Summary of nipocalimab concentrations at each visit by baseline immunomodulator use, other than anti-malarial drugs, (yes/no)
- Proportion of subjects without detectable serum nipocalimab concentrations (below the lower limit of quantification x minimum required dilution (LLOQxMRD) at each visit
- Plot of median +/- IQ range serum nipocalimab concentrations over time
- In addition, the relationship between serum nipocalimab concentrations and antibodies to nipocalimab status, safety, and efficacy may be explored using graphical displays. Median serum nipocalimab concentrations will be plotted. Box plots of serum nipocalimab concentrations will be plotted by clinESSDAI at Week 24.

If sufficient data are available, then population PK analysis using serum nipocalimab concentration time data will be performed using nonlinear mixed-effects modeling to estimate total systemic clearance and volume of distribution. Details will be given in a population PK analysis plan and the results of the analysis will be presented in a separate report.

5.7.1.1. Data Handling Guidelines

Unless otherwise specified, the following data handling guidelines will apply to PK analyses:

- All serum concentration summaries for a particular timepoint will include data obtained from treated participants at the timepoint of interest without imputing any missing data
- A concentration not quantifiable (below LLOQ) will be treated as 0 in the summary statistics and shown as the lower limit of quantification (<LLOQ) in the data listings
- The data from a subject who meets one of the following dosing deviation criteria will be excluded from the by-visit data analyses and from that point onwards:
  - Discontinue nipocalimab administrations

- Skipped a nipocalimab administration
- Received incomplete/incorrect dose
- Received incorrect study agent
- Received additional dose

Of note, serum nipocalimab concentrations prior to the first of such events will be included in the summaries. In addition, if a subject has an administration outside of dosing window, the concentration data collected at and after that will be excluded from the by-visit data analyses. Additional exclusions for PK data to be implemented based on TV-GDL-00362. All participants and samples excluded from analysis will be documented in the Clinical Study Report.

5.7.2. Immunogenicity

Blood samples will be collected to examine the formation of antibodies to nipocalimab at the specified visits as shown in the Schedule of Activities of the protocol.

"Sample ADA status" and sample titer as well as the cumulative "subject ADA status" and peak titer through the visit will be coded and provided by the bioanalytical group.

5.7.2.1. Participant ADA Classifications

Participants evaluable for immunogenicity are defined as having at least one post-dose ADA time point collected for antibodies to nipocalimab detection.

1. Participants with treatment-emergent antibodies to nipocalimab include participants with treatment-induced antibodies to nipocalimab and treatment-boosted antibodies to nipocalimab.

2. Participants with treatment-induced antibodies to nipocalimab have an antibody to nipocalimab negative sample prior to nipocalimab administration and at least one antibodies to nipocalimab positive sample after nipocalimab.

3. Participants with treatment-boosted anti-nipocalimab antibodies have both a sample that is positive for an antibody to nipocalimab prior to nipocalimab administration and at least one sample that is positive for antibodies to nipocalimab after nipocalimab administration, with a 2-fold increase in titer over baseline (the fold difference, referred to as the baseline multiplier, could be greater than 2 for some assays).

If titer remains the same after intervention or if ADA titer reduces or ADA disappears, the participant is classified as "treatment-emergent ADA negative." Participants that are unavailable for treatment-emergent ADA following intervention will be classified as "participants with baseline samples only", i.e., no appropriate sample is available after intervention.

5.7.2.2. Immunogenicity Analyses

The summary and evaluation of antibodies to nipocalimab will be based on the observed data; therefore, no imputation of missing data will be performed. Note: participant status is through each

visit, thus, participant status and peak titers may change as the study progresses over time. Therefore, the 'subject ADA status' at a visit represents the cumulative ADA status through that visit. For example, if a study has a lock at Week 24, datasets through Week 24 will have participant level status (e.g., negative) but at Week 30, they may have developed ADA and the participant status becomes "treatment-emergent ADA positive" from the interim to the final DBL. Peak titers can also change (increase) if a higher titer occurs after an initial DBL.

The summary of participants with baseline positive samples is taken from the sample status at baseline. There is no participant level status at baseline.

The data analysis of antibodies to nipocalimab includes the following:

- Incidence of antibody (evaluable, treatment-emergent ADA positive, treatment-emergent ADA negative) status and neutralizing antibodies (NAb) to nipocalimab will be summarized.
- Descriptive statistics (N, mean, SD, median, range, and IQ range) and incidence (N, %) of the relationship between treatment-emergent antibodies to nipocalimab status (positive or negative) and PK concentration will be assessed.
- Participants in response (N, %) for treatment-emergent antibodies to nipocalimab status (positive or negative) and efficacy endpoints will be assessed:
  - Participants evaluable for immunogenicity
  - Efficacy endpoints repeated for different levels of response (eg, clinESSDAI, ESSDAI, ESSPRI)
    - Number of participants (N)
    - Participants in response (N, %)
- Incidence (N, %) between treatment-emergent antibodies to nipocalimab status (positive or negative) and infusion-related reactions will be assessed:
  - Participants evaluable for immunogenicity
  - Participants with infusion-related reaction
  - Participants with severe infusion-related reaction
  - Participants with serious infusion-related reaction
  - Participants with infusion-related reaction leading to discontinuation
  - Nipocalimab infusions with infusion-related reactions (out of total number of nipocalimab infusions)
  - Placebo infusions with infusion-related reactions (out of total number of placebo infusions)

- In addition, listings of participants with baseline positive ADA samples, participants who are classified as positive for treatment-emergent antibodies to nipocalimab and participants who discontinue the study by antibodies to nipocalimab status as well as graphical representation of median matrix concentration by antibody status may be presented.

- Additional immunogenicity analyses by peak titer groups may be performed if the number of subjects who are positive of antibodies to nipocalimab are sufficient to permit subgroup analyses (eg > 30 to 40 subjects).

5.7.3. Pharmacokinetic/Pharmacodynamic Relationships

Exploratory PK-PD analyses, including graphical exploration of PK-PD data, may be performed such as PK/IgG or PK/pathogenic antibodies, PK/albumin, PK/lipids.

For efficacy, percent responders within each quartile of PK concentration may be presented, if data permits.

If deemed feasible and necessary, exposure-response analyses may be performed. The analysis methods may be summarized in a separate analysis plan. Results of such analyses may be presented in a separate technical report.

5.7.4. 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. 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. Analyses results may be summarized in a separate technical report.

5.7.5. Biomarkers

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 analyses may include but are not limited to serum biomarkers including immunoglobulins, autoantibodies, inflammatory markers, whole blood ribonucleic acid (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 (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.

5.7.5.1. IgG and Disease Specific Antibodies

This section describes the additional planned analyses under the estimand framework for percent reduction in IgG and disease-specific antibodies in the presence of intercurrent events (ICEs) such as discontinuation and/or any missed doses of the study treatment.

5.7.5.1.1. Estimands

5.7.5.1.1.1. Primary Estimand (Hypothetical Estimand)

The main scientific question of interest is the following:

Main Scientific Question of Interest:

What is the expected treatment effect on percent reduction in IgG at Week 24 of nipocalimab 5 mg/kg or nipocalimab 15 mg/kg versus placebo, administered in addition to the protocol allowed background standard-of-care medication that the participants received at baseline, **if taken as directed by Week 24 (i.e as if patients would not have discontinued treatment and would not have missed any dose)**, in men and women between the ages of 18 to 75 years, inclusive with active, Sjögren's Syndrome related antigen A (SSA) autoantibody-positive pSS?

Note: Same question is considered for disease-specific antibodies instead of IgG.

The main Hypothetical Estimand, aligned with the scientific question of interest above, is defined by the following five attributes:

- Study Intervention:
  - 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 up to one immunomodulator with or without low-dose GCs (≤10 mg/day prednisone equivalent).

- **Population:** Men and women between the ages of 18 to 75 years, inclusive with active, Sjögren's Syndrome related antigen A (SSA) autoantibody-positive pSS.
- **Variable/endpoint:** Percent IgG reduction at Week 24.
- **Summary Measure (Population-level summary):** Difference in the means of the variable (i.e., Percent IgG reduction score at Week 24) between nipocalimab and placebo treatment groups.
- **ICEs and their corresponding strategies:**

ICE	Strategy of Addressing ICEs
Discontinuation of study treatment	**Hypothetical Strategy**: A hypothetical scenario is considered in which patients would take treatment as directed (rather than discontinuing treatment and/or missing at least a dose)
Missed dosing of study treatment	

5.7.5.1.1.2. Supplementary Estimand 1 (Treatment Policy Estimand)

Scientific Question of Interest:
What is the expected treatment effect on percent reduction in IgG at Week 24 of nipocalimab 5 mg/kg or nipocalimab 15 mg/kg versus placebo, administered in addition to the protocol allowed background standard-of-care medication that the participants received at baseline, **regardless of treatment discontinuation and/or missing at least a dose**, in men and women between the ages of 18 to 75 years, inclusive with active, Sjögren's Syndrome related antigen A (SSA) autoantibody-positive pSS?

Note: Same question is considered for disease-specific antibodies instead of IgG.

Supplementary Estimand 1, aligned with the scientific question of interest above, will supplement the main Hypothetical Estimand. It will have the same attributes, except the strategy of addressing the intercurrent events:

- **ICEs and their corresponding strategies:**

ICE	Strategy of Addressing ICEs
Discontinuation of study treatment	**Treatment Policy Strategy:** Targets the effect of treatment assignment, regardless of discontinuation and/or missing at least a dose
Missed dosing of study treatment	

5.7.5.1.1.3. Supplementary Estimand 2 (Principal Stratum Estimand)

Scientific Question of Interest:

What is the expected treatment effect on percent reduction in IgG at Week 24 of nipocalimab 5 mg/kg or nipocalimab 15 mg/kg versus placebo, administered in addition to the protocol allowed background standard-of-care medication that the participants received at baseline, in men and women between the ages of 18 to 75 years, inclusive with active, Sjögren's Syndrome related antigen A (SSA) autoantibody-positive pSS, **who, if assigned to nipocalimab, would fully adhere to treatment until Week 24** (i.e., without discontinuing treatment or missing a dose)?

Note: Same question is considered for disease-specific antibodies instead of IgG.

Supplementary Estimand 2, aligned with the scientific question of interest above, will supplement the main Hypothetical Estimand. It will have the same attributes, except for the Population and the strategy of addressing the intercurrent events:

- **Population:** Men and women between the ages of 18 to 75 years, inclusive with active, Sjögren's Syndrome related antigen A (SSA) autoantibody-positive pSS, **who, if assigned to nipocalimab, would fully adhere to treatment until Week 24** (i.e., without discontinuing treatment or missing a dose)
- **ICEs and their corresponding strategies:**

ICE	Strategy of Addressing ICEs
Discontinuation of study treatment	**Principal Stratum Strategy,** as reflected in the Population attribute
Missed dosing of study treatment	

5.7.5.1.2. Analysis Methods (Main Estimators)

Unless otherwise specified, the analysis dataset will be the Safety Analysis set defined in Section 4 (subjects are required to have at least one valid post-dose blood sample drawn for PD analysis), analyzed according to randomized intervention group, regardless of actual intervention received.

For the Primary Estimand (Hypothetical Estimand) and Supplementary Estimand 2 (Principal Stratum Estimand), any observations collected after treatment discontinuation or after the first missed dose will not be used in analysis. For Supplementary Estimand 1, all available observations will be used, including those collected after ICEs.

The main analysis aligned with the main Hypothetical Estimand, and both Supplementary Estimands (Treatment policy Estimand 1 and Principal Stratum Estimand 2) will be based on a Mixed-Effect Model for Repeated Measures (MMRM). The model will include baseline IgG or disease-specific antibody score as a covariate and intervention group, baseline stratification factor (if applicable), visit, and an interaction of treatment and visit as fixed effects. An unstructured covariance matrix for repeated measures within a subject will be used. The F-test will use Kenward-Roger's approximation for degree of freedom. In case of lack of convergence, other structured covariance matrix will be used in the following order until convergence is reached: 1) first order Autoregressive Moving Average 2) Toeplitz. The treatment difference between the groups will be estimated by the difference in the least squares means (LSmeans). The 90% confidence interval (CI) for the treatment difference and corresponding p-values will also be calculated based on the MMRM model, as appropriate.

5.7.6. Digital Health-Actigraphy Measurements

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.

5.7.7. Definition of Subgroups

The subgroups for subgroup analysis may include, but are not limited to, the following:

- Demographic subgroups

Subgroup	Variant	Definition
Baseline age	1	• ≤ 65 • > 65
Race	1	• White • Black • Other
Gender	1	• Male • Female
Region	1	• North America • Eastern Europe • Western Europe • Other
Weight	1	• ≤ median • > median
The median score (≤ median, > median) refers to the median value at baseline across subjects, regardless of treatment group.		

- Disease Characteristics subgroups

Subgroup	Variant	Definition
Disease duration at baseline	1	• ≤ median • > median
Baseline clinESSDAI total score	1	• ≤ median • > median
Baseline clinESSDAI domain scores	1	• ≤ median • > median
Baseline ESSPRI total score	1	• ≤ median • > median
Baseline ESSPRI domain scores	1	• ≤ median • > median

Subgroup	Variant	Definition
Baseline glandular function	1	• ≤ median • > median
Baseline IgG	1	• ≤ median • > median
Baseline anti-Ro60	1	• ≤ median • > median
Baseline anti-Ro52	1	• ≤ median • > median
Baseline anti-SSB/La	1	• ≤ median • > median
Baseline RF	1	• ≤ median • > median
Baseline CRP levels	1	• ≤ median • > median
Baseline ESR levels	1	• ≤ median • > median
The median score (≤ median, > median) refers to the median value at baseline across subjects, regardless of treatment group.		

- Prior Medication subgroups

Subgroup	Variant	Definition
Baseline hydroxychloroquine (or other anti-malarial drug) use		Yes or No
Baseline oral corticosteroid use		Yes or No
Baseline immunomodulator use		Yes or No

5.8. Interim Analyses

5.8.1. 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 hydroxychloroquine use.

An independent IAC (see section 5.8.3.), 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. Further details, including recommendations based upon the interim analysis results will be specified in the IAC SAP/Charter.

5.8.2. 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 5.8.3, 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, i.e., total IgG, autoantibody and albumin levels may also be evaluated, if available. Additional data available at the time of the interim analysis (e.g., 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.

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

5.8.2.1. Week 24 Interim Analysis Submission

There exists the possibility that, given meeting the Direct Go criteria as defined in the IA SAP, the Week 24 IA data may be utilized for an End of Phase 2 (EoP2) submission to the health authorities prior to the planned Week 30 DBL. The following operational aspects will be performed to support such a submission:

- An unblinding plan identifying the individuals to be unblinded to support the submission will be developed (Week 24 IA Submission Team). The plan will indicate when these individuals will be unblinded and what data they will be able to access. This team will include representatives from clinical, statistics, programming, medical writing, safety, clinical pharmacology, and others necessary to provide expertise for the submission.
- The Week 24 IA Submission Team will support the development of outputs and documents needed to support a submission. Output will include, but not be limited to, the primary and major secondary endpoints, safety data, and necessary supportive analyses (e.g., additional efficacy endpoints, PK and PD data, and labs). The Briefing Book Data Presentation Specifications (BB DPS) will be the final authoritative source indicating which output will be used for such a possible submission. The IA DPS will be shared with the unblinded team if the IAC recommends a Direct Go. See Appendix 13 for a list of possible EoP2 outputs to be included.

5.8.3. Data Monitoring Committee (DMC) or Other Review Board

Data Monitoring Committee

A Data Monitoring Committee (DMC) will be established to monitor data on an ongoing basis. This committee will consist of at least 2 medical experts in the relevant therapeutic area and at least 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 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 above).

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

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

ADA	anti-drug antibody
AE	adverse event
AESI	adverse events of special interest
ALT/SGPT	alanine aminotransferase
ANOVA	analysis of variance
AST/SGOT	aspartate aminotransferase
BUN	blood urea nitrogen
clinESSDAI	Clinical European League Against Rheumatism Sjögren's Syndrome Disease Activity Index
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease 2019
CRESS	Composite of Relevant Endpoints for Sjögren's Syndrome
CRF	case report form
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DAL	Disease Activity Level
DAS28	Disease Activity Score 28
DBL	database lock
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DPS	Data Presentation Specifications
eCRF	electronic case report form
EoP2	End of Phase 2
ESR	erythrocyte sedimentation rate
ESSDAI	EULAR Sjögren Syndrome Disease Activity Index
ESSPRI	EULAR Sjögren's syndrome patient reported index
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	full analysis set
GC	glucocorticoids
GGT	gamma-glutamyltransferase
HADS	Hospital Anxiety and Depression Scale
HRQoL	health-related quality of life
IAC	Interim Analysis Committee
iARBM	Integrated Analytic Risk-Based Monitoring
ICE	Intercurrent Events
ICF	Informed Consent Form
IDSSTS	International Digit Symbol Substitution Test – Symbols
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IQ	Interquartile
KCS	keratoconjunctivitis sicca
LDH	lactic acid dehydrogenase
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MCH	mean corpuscular hemoglobin
MCS	mental component score
MCV	mean corpuscular volume
MMRM	Mixed-Effect Model Repeated Measure
MRD	minimum required dilution
N	number of observations
Nab	neutralizing antibodies
NCI	National Cancer Institute
NRS	numeric rating scale

OSS	Ocular Surface Staining
PCS	physical component score
PD	pharmacodynamic(s)
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PhGA	Physician's Global Assessment of Disease Activity
PK	pharmacokinetic(s)
pSS	Primary Sjögren's Syndrome
PT	Preferred term
PtGA	Patient's Global Assessment of Disease Activity
q2w	every 2 weeks
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SoA	Schedule of Activities
SOC	System Organ Class
SSRI	Sjögren's Syndrome Responder Index
TE	Treatment-emergent
TEAE	treatment-emergent adverse event
TF	Treatment failure
VAS	visual analog scale
WBC	white blood cell
WLQ	Work Limitations Questionnaire

6.2. Appendix 2 Changes to Protocol-Planned Analyses

N/A

6.3. Appendix 3 Demographics and Baseline Characteristics

The number of participants in each analysis set will be summarized and listed by intervention group, and overall. In addition, the distribution of participants by region, country, and site ID will be presented unless otherwise noted.

Table 5 presents a list of the demographic variables that will be summarized by intervention group, and overall for the full analysis set.

Table 5: Demographic Variables and Disease Characteristics at Baseline

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum]
Weight (kg)	
Height (cm)	
clinESSDAI score	
ESSPRI score	
IgG	
anti-Ro60	
anti-Ro52	
anti-SSB/La	
CRP levels	
RF	
ESR levels	
pSS Duration (years)	
Schirmer's test	
Salivary flow	
C3	
C4	
CH50	
Categorical Variables	**Summary Type**
Age (≤ 65 years, >65 years)	Frequency distribution with the number and percentage of subjects in each category.
Gender (male, female)	
Race (White, Black, Other)	
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)	

6.4. Appendix 4 Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical study. Participants with major protocol deviations will be identified prior to database lock and the participants with major protocol deviations will be summarized by category through Week 24.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other
- Missed visit/assessment due to COVID-19

6.5. Appendix 5 Prior and Concomitant Medications

Prior and Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study intervention. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study intervention, including those that were started before and continue to be used after the first dose of study intervention.

Summaries of concomitant medications will be presented by anatomic and therapeutic class (ATC) term, and intervention group. The proportion of participants who receive each concomitant medication will be summarized as well as the proportion of participants who receive at least 1 concomitant medication. In addition, concomitant medications of special interest will be presented. See Appendix 10 for list of medications in each category.

Prior medications will be summarized by intervention group and ATC term.

Background medication use for active pSS will be summarized by intervention group and schedule visits through Week 24, including the below categories within each medication:

- No change
- Dose increase
- Dose decrease
- New medication
- Medication stopped

6.6. Appendix 6 Medical History

Medical history will be listed by intervention groups and participants

6.7. Appendix 7 Intervention Compliance

Compliance will be summarized descriptively for each study intervention. Compliance to randomized intervention versus actual intervention will be presented in a summary table.

6.8. Appendix 8 Quality Tolerance Limits (QTLs)

Quality Tolerance Limit (QTL) parameters and thresholds are defined and will be monitored in this study. QTL parameters will be summarized. More details are described in the Integrated Analytic Risk-Based Monitoring (iARBM) Plan.

6.9. Appendix 9 Adverse Events of Interest

Adverse events of special interest are indicated on the eCRF via a checkbox and are reconciled with the definition below:

AE Special Interest Category	**SOC**	**Additional condition**
Infections	Infection and Infestations	Checkbox for AESI that indicates it was severe or required IV anti-infective or operative/invasive intervention

AE Special Interest Category	**Preferred term**	**Additional condition**
Hypoalbuminaemia	Hypoalbuminaemia	Checkbox for AESI that indicates 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.

Other adverse events of clinical interest are defined as follows:

AE of Clinical Interest Category	**Preferred term**	**Additional condition**
Infusion reaction	Any	Indicated as infusion reaction by investigator on eCRF and relationship to study intervention='Related'. Exclude infusion site reactions.
Infusion site reaction	HLT of Infusion site reaction	
Serum sickness reaction	Serum sickness	Requires clinical review
	Serum sickness-like reaction	Requires clinical review
Anaphylactic reaction	Anaphylactic reaction, Anaphylactic shock, Anaphylactoid reaction, Anaphylactoid shock, Type I hypersensitivity, Kounis syndrome.	Determined through SMQ algorithmic approach/Sampson's criteria
Potentially Associated with Glucocorticoid Toxicity	**Cardiovascular:** Acute myocardial infarction*, angina pectoris, arteriosclerosis, blood cholesterol increased, blood pressure increased; cardiac failure, cardiovascular insufficiency, congestive cardiomyopathy, dyslipidaemia, fluid retention, hypercholesterolaemia, hyperlipidaemia, hypertension, hypertensive emergency, hypertriglyceridaemia, hypervolaemia, low density lipoprotein increased, myocardial infarction*, myocardial ischaemia, oedema, oedema peripheral, peripheral swelling	*Also a MACE preferred term
	Infections: all serious infections	
	Gastrointestinal: Duodenal ulcer, gastritis, gastritis erosive, gastrointestinal disorder, pancreatitis, pancreatitis acute	
	Psychological: affective disorder, agitation, anxiety,	

AE of Clinical Interest Category	Preferred term	Additional condition
	confusional state, depressed mood, depression, insomnia, irritability, libido decreased, major depression, mania, mental status changes, mood altered, nervousness, poor quality sleep	
	Endocrine/metabolic: adrenal insufficiency, blood glucose increased, blood potassium decreased, central obesity, Cushingoid, Cushing's syndrome, diabetes mellitus, diabetes mellitus inadequate control, glucose tolerance impaired, gynaecomastia, hyperglycaemia, hypokalaemia, influenza like illness, polymenorrhagia, menometrorrhagia, systemic inflammatory response syndrome, type 2 diabetes mellitus, waist circumference increased, weight increased	
	Dermatological: Acne; dermatitis acneiform; ecchymosis; hirsutism; increased tendency to bruise; skin atrophy; skin striae.	
	Musculoskeletal: Hip fracture; humerus fracture; lower limb fracture; lumbar vertebral fracture; muscle atrophy; muscular weakness, myopathy, osteonecrosis; osteopenia; osteoporosis, spinal compression fracture, tendon rupture, wrist fracture	
	Ophthalmological: Cataract, cataract nuclear, glaucoma, intraocular pressure increased, open angle glaucoma, retinopathy hypertensive	

AE of Clinical Interest Category	**SMQ**	**Additional condition**
Opportunistic infections	Opportunistic infections	Narrow scope
Hypersensitivity reaction	Hypersensitivity reaction	Narrow scope
Suicidal ideation/behavior	Suicide/self-injury	Narrow and broad scope
MACE	Conditions associated with central nervous system haemorrhages and cerebrovascular accidents	All potential cases of MACE to be independently adjudicated Narrow and broad scope
	Haemorrhagic central nervous system vascular conditions	Narrow scope
	Ischaemic central nervous system vascular conditions	Narrow scope
	Myocardial infarction	Narrow and broad scope
	Preferred terms of Troponin abnormal, Troponin I abnormal	Preferred terms
	All deaths	

6.10. Appendix 10 Medications of Special Interest

Concomitant medications of special interest are defined as follows:

Concomitant Medication Special Interest Category	**Standard ATC Name**	**Standard Medication Name**	**Route**
Antimalarials	Aminoquinolines	Hydroxychloroquine Chloroquine	Oral
Glucocorticosteroids	Glucocorticoids	Prednisolone Methylprednisolone Prednisone Hydrocortisone Cortisone Deflazacort Triamcinolone Dexamethasone Betamethasone	Oral IV Subcutaneous Intrabursa Intra-articular

6.11. Appendix 11 Markedly Abnormal Laboratory Values

Category	Lab test	Sex	Unit	Markedly Abnormal Lows	Markedly Abnormal High
CHEMISTRY	Albumin	BOTH	g/L	Decrease >10 and value <20	Increase >10 and value > 60
CHEMISTRY	Alkaline phosphatase	BOTH	U/L	N/A	Increase >100 And value >250
CHEMISTRY	Alanine transaminase (ALT)(SGPT)	BOTH	U/L	N/A	≥3xULN
CHEMISTRY	Aspartate transaminase (AST) (SGOT)	BOTH	U/L	N/A	≥3xULN
CHEMISTRY	Bicarbonate	BOTH	mmol/L	Decrease >20% and value <15.1	Increase >20% and value >34.9
CHEMISTRY	Blood urea nitrogen	BOTH	mmol/L	N/A	Increase >20% and value >17.9
CHEMISTRY	Calcium	BOTH	mmol/L	Decrease >20% and value <1.5	Increase >20% and value >3
CHEMISTRY	Chloride	BOTH	mmol/L	Decrease >5 and value <85	Increase >5 and value >120
CHEMISTRY	Creatinine	BOTH	umol/L	N/A	Increase >20% and value >250
CHEMISTRY	Gamma glutamyl transferase	BOTH	U/L	N/A	Increase >100 and value >300
CHEMISTRY	Glucose	BOTH	mmol/L	Decrease >20% and value <2.2	Increase >30% and value >16.7
CHEMISTRY	Phosphate	BOTH	mmol/L	Decrease >10% and value <0.6	Increase >10% and value >2.6

Category	**Lab test**	**Sex**	**Unit**	**Markedly Abnormal Lows**	**Markedly Abnormal High**
CHEMISTRY	Potassium	BOTH	mmol/L	Decrease >10% and value <3	Increase >20% and value >6.0
CHEMISTRY	Sodium	BOTH	mmol/L	Decrease >10% and value <125	Increase >10% and value >155
CHEMISTRY	Total bilirubin	BOTH	umol/L	N/A	Increase >20% and value >45
CHEMISTRY	Total protein	BOTH	g/L	Decrease >20% and value <50	N/A
CHEMISTRY	Creatine Kinase	BOTH	U/L	N/A	Increase >20% and value >960
CHEMISTRY	Total Cholesterol	BOTH	mmol/L	N/A	≥6.2
CHEMISTRY	HDL	BOTH	mmol/L	<1.0	≥2.1
CHEMISTRY	LDL	BOTH	mmol/L	N/A	≥4.1
CHEMISTRY	Triglycerides	BOTH	mmol/L	N/A	>5.6
HEMATOLOGY	Hematocrit female	F	fraction	Decrease >15% and value <0.28	Increase >15% and value >0.50
HEMATOLOGY	Hematocrit male	M	fraction	Decrease >15% and value <0.28	Increase >15% and value >0.55
HEMATOLOGY	Hemoglobin	BOTH	g/L	Decrease >10% and value <80	Increase >10% and value >190

Category	**Lab test**	**Sex**	**Unit**	**Markedly Abnormal Lows**	**Markedly Abnormal High**
HEMATOLOGY	Neutrophils/Leukocytes	BOTH	fraction	Decrease> 30% and value <.0.30	Increase >30% and value >0.90
HEMATOLOGY	Monocytes/Leukocytes	BOTH	fraction	N/A	Increase >20% and value >0.20
HEMATOLOGY	Eosinophils/Leukocytes	BOTH	fraction	N/A	Increase >20% and value >0.10
HEMATOLOGY	Basophils/Leukocytes	BOTH	fraction	N/A	Increase >20% and value >0.06
HEMATOLOGY	Lymphocytes/Leukocytes	BOTH	fraction	Decrease > 20% and value <0.08	Increase >20% and value >0.60
HEMATOLOGY	Platelet count	BOTH	x10E9/L	Decrease >20% and value <100	Increase >20% and value >600
HEMATOLOGY	Red blood cell count Female	F	x10E12/L	Decrease >20% and value <3	Increase >20% and value >6.1
HEMATOLOGY	Red blood cell count Male	M	x10E12/L	Decrease >20% and value <3	Increase >20% and value >6.4
HEMATOLOGY	White blood cell count	BOTH	x10E9/L	Decrease >10% and value <2.5	Increase >20% and value >15
URINALYSIS	Urine pH	BOTH		N/A	>8

*Increases and decreases are calculated from baseline values.

6.12. Appendix 12 COVID-19 Related Summaries

Participant disposition as related to COVID-19 will be summarized by intervention group. This includes the following COVID-19 related disposition events:

- Termination of study due to COVID-19 and reason
- Discontinuation of study agent due to COVID-19 and reason
- Death related to COVID-19

Participants discontinuing treatment or terminating study participation due to COVID-19 and reason(s) will be listed.

Assessment of study compliance as related to COVID-19 will be summarized, including number of missed visits, and number of remote visits conducted. Participants whose visit compliance was impacted by COVID-19 will be listed.

Concomitant medications used for COVID-19 will be summarized. Participants receiving concomitant medications related to COVID-19 will be listed.

Protocol deviations (major and minor) as related to COVID-19 will be summarized and listed.

Study agent modifications due to COVID-19 will be summarized and listed.

Adverse events related to COVID-19 will be identified and coded using the MedDRA coding guidance for COVID-19, and summary tables will be provided for COVID-19 related TEAEs. The following will be listed by participant:

- TEAEs related to COVID-19
- Serious TEAEs related to COVID-19
- Deaths related to COVID-19

6.13. Appendix 13 Planned EoP2 Outputs for Interim Analysis #2

The following list contains planned EoP2 outputs for Interim Analysis #2 (see Section 5.8.2.). It is up to the discretion of the Sponsor to determine if all, a subset, or additional outputs will be delivered to the Week 24 IA Submission Team and/or utilized in any health interactions. The Briefing Book DPS will act as authoritative list of final outputs delivered.

Planned EOP2 outputs will use the first 100 treated subjects. **In addition to this,** SAEs, AESI, and AEs of Clinical Interest will **also** be summarized on all available patient data.

SAFETY

Demographics and Baseline Characteristics

- Summary of Baseline Disease Characteristics at Week 0, Full Analysis Set

- Summary of Baseline Disease Characteristics at Week 0 (Japan Subpopulation), Full Analysis Set
- Summary of Demographics and Baseline Characteristics at Week 0, Full Analysis Set
- Summary of Demographics and Baseline Characteristics at Week 0 (Japan Subpopulation), Full Analysis Set
- Summary of pSS Medication History (Japan Subpopulation), Safety Analysis Set

Disposition

- Study Disposition, Randomized Analysis Set
- Study Disposition Through Week 24 (Japan Subpopulation), Full Analysis Set
- Treatment Disposition Through Week 22, Full Analysis Set
- Treatment Disposition Through Week 22 (Japan Subpopulation), Full Analysis Set
- Summary of Study Agent Compliance Through Week 22, Safety Analysis Set
- Number of Subjects Who Experienced Intercurrent Events Prior to Week 24, Full Analysis Set

Study Drug Exposure

- Summary of Treatment With Study Agent Through Week 22, Safety Analysis Set
- Summary of Treatment With Study Agent Through Week 22 (Japan Subpopulation), Safety Analysis Set
- Number of Subjects Who Received Scheduled Study Agent by Time Point Through Week 22, Safety Analysis Set

Adverse Events

- Overall Summary of Treatment-emergent Adverse Events, Safety Analysis Set
- Overall Summary of Treatment-emergent Adverse Events (Japan Subpopulation), Safety Analysis Set
- Overall Summary of Treatment-emergent Adverse Events (First 100 Randomized Subjects), Safety Analysis Set
- Number of Subjects With Treatment-emergent Adverse Events by System Organ Class and Preferred Term, Safety Analysis Set
- Number of Subjects With Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Japan Subpopulation), Safety Analysis Set
- Number of Subjects With Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Agent, Safety Analysis Set
- Number of Subjects With Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term, Safety Analysis Set
- Number of Subjects With Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term (First 100 Randomized Subjects), Safety Analysis Set

- Number of Subjects With Treatment-emergent Adverse Events Leading to Discontinuation of Study Treatment by System Organ Class and Preferred Term, Safety Analysis Set
- Number of Subjects With Treatment-emergent Infections That are Severe or Require IV Anti-Infective Operative/Invasive Intervention Through the End of Study by System Organ Class and Preferred Term, Safety Analysis Set
- Number of Subjects With Treatment-emergent Infections That are Severe or Require IV Anti-Infective Operative/Invasive Intervention Through the End of Study by System Organ Class and Preferred Term (First 100 Randomized Subjects), Safety Analysis Set
- Number of Subjects With Treatment-emergent Hypoalbuminemia with Albumin < 20 g/L Through the End of Study by System Organ Class and Preferred Term, Safety Analysis Set
- Number of Subjects With Treatment-emergent Hypoalbuminemia with Albumin < 20 g/L Through the End of Study by System Organ Class and Preferred Term (First 100 Randomized Subjects), Safety Analysis Set
- Number of Subjects With Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and pSS Disease Duration at Baseline, Safety Analysis Set
- Number of Subjects With Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Baseline clinESSDAI Total Score, Safety Analysis Set
- Number of Subjects With Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Baseline Immunoglobulin Gamma (IgG) Value, Safety Analysis Set
- Number of Subjects With Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Baseline C-Reactive Protein (CRP) Level, Safety Analysis Set
- Number of Subjects With Treatment-emergent Serious Adverse Events by System Organ Class, Preferred Term, and Minimum Post-Baseline IgG Level, Safety Analysis Set
- Number of Subjects With Treatment-emergent Infusion Reaction Through the End of Study by System Organ Class and Preferred Term, Safety Analysis Set
- Number of Subjects With Treatment-emergent Infusion Reaction Through the End of Study by System Organ Class and Preferred Term (First 100 Randomized Subjects), Safety Analysis Set
- Number of Subjects With Treatment-emergent Infusion-site Reaction Through the End of Study by System Organ Class and Preferred Term, Safety Analysis Set
- Number of Subjects With Treatment-emergent Infusion-site Reaction Through the End of Study by System Organ Class and Preferred Term (First 100 Randomized Subjects), Safety Analysis Set
- Number of Subjects With 1 or More Treatment-emergent Opportunistic Infections Through the End of Study by System Organ Class and Preferred Term, Safety Analysis Set
- Number of Subjects With 1 or More Treatment-emergent Opportunistic Infections Through the End of Study by System Organ Class and Preferred Term (First 100 Randomized Subjects), Safety Analysis Set
- Number of Subjects With 1 or More Treatment-emergent Hypersensitivity Reactions Through the End of Study by System Organ Class and Preferred Term, Safety Analysis Set

- Number of Subjects With 1 or More Treatment-emergent Hypersensitivity Reactions Through the End of Study by System Organ Class and Preferred Term (First 100 Randomized Subjects), Safety Analysis Set
- Number of Subjects With 1 or More Treatment-emergent Anaphylactic or Serum Sickness Reactions Through the End of Study by System Organ Class and Preferred Term, Safety Analysis Set
- Number of Subjects With 1 or More Treatment-emergent Anaphylactic or Serum Sickness Reactions Through the End of Study by System Organ Class and Preferred Term (First 100 Randomized Subjects), Safety Analysis Set
- Number of Subjects With Treatment-emergent Glucocorticoid toxicity Events by System Organ Class and Preferred Term, Safety Analysis Set
- Number of Subjects With Treatment-emergent Glucocorticoid toxicity Events by System Organ Class and Preferred Term (First 100 Randomized Subjects), Safety Analysis Set
- Number of Subjects With Treatment-emergent Suicidal Ideation/Behavior Events by System Organ Class and Preferred Term, Safety Analysis Set
- Number of Subjects With Treatment-emergent Suicidal Ideation/Behavior Events by System Organ Class and Preferred Term (First 100 Randomized Subjects), Safety Analysis Set
- Listing of Treatment-emergent Adverse Events (Japan Subpopulation), Safety Analysis Set
- Listing of Serious Treatment-emergent Adverse Events, Safety Analysis Set
- Listing of Treatment-emergent Adverse Events Leading to Discontinuation of Study Treatment, Safety Analysis Set
- Listing of Treatment-emergent Adverse Events through Week 24 in Participants with IgG Level <1 g/L
- Listing of Treatment-emergent Adverse Events through Week 24 in Participants with IgG Level >=1 g/L
- Listing of Treatment-emergent Infusion Reactions, Safety Analysis Set
- Listing of Treatment-emergent Opportunistic Infections, Safety Analysis Set
- Listing of Treatment-emergent Major Cardiovascular Events (MACE), Safety Analysis Set
- Listing of Treatment-emergent Anaphylactic or Serum Sickness-like Reactions, Safety Analysis Set
- Listing of Deaths During Treatment, Safety Analysis Set

Laboratory

- Summary of Fasting Lipid Laboratory Values and Change From Baseline Over Time, Safety Analysis Set
- Summary of Liver Enzyme Laboratory Values and Change From Baseline Over Time, Safety Analysis Set

- Summary of Albumin Laboratory Values and Change From Baseline Over Time, Safety Analysis Set
- Box Plot of Percent Change From Baseline in Albumin (g/L) Over Time, Safety Analysis Set
- Box Plot of Percent Change From Baseline in Total Cholesterol (mmol/L) Over Time, Safety Analysis Set
- Shift in Liver Enzyme Laboratory Values From Baseline to Maximum Value Through Week 24, Safety Analysis Set
- Shift in Albumin Laboratory Values From Baseline to Maximum Value Through Week 24, Safety Analysis Set
- Number and Percentage of Subjects With Treatment-emergent Markedly Abnormal Laboratory Values Over Time, Safety Analysis Set
- Number and Percentage of Subjects With Treatment-emergent Markedly Abnormal Albumin Laboratory Values, Safety Analysis Set
- Number and Percentage of Subjects With Treatment-emergent Markedly Abnormal Liver Enzyme Laboratory Values, Safety Analysis Set
- Listing of Subjects With Treatment-emergent Markedly Abnormal Laboratory Values, Safety Analysis Set

Vital Signs

- Number and Percentage of Subjects With Treatment-emergent Markedly Abnormal Vital Signs, Safety Analysis Set

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Primary Endpoint Analysis

- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 Based on a Mixed Effects Repeated Measures Model (MMRM), Full Analysis Set
- Primary Endpoint Analysis (Supplementary Estimand 1, Composite Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 Based on a Mixed Effects Repeated Measures Model (MMRM), Full Analysis Set
- Primary Endpoint Analysis (Supplementary Estimand 2, Treatment Policy Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 Based on a Mixed Effects Repeated Measures Model (MMRM), Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Age, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Race, Full Analysis Set

- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Gender, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Region, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Weight, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Disease Duration at Baseline, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline clinESSDAI Total Score, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline clinESSDAI Constitutional Domain Score, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline clinESSDAI Lymphadenopathy and Lymphoma Domain Score, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline clinESSDAI Glandular Domain Score, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline clinESSDAI Articular Domain Score, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline clinESSDAI Cutaneous Domain Score, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline clinESSDAI Pulmonary Domain Score, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline clinESSDAI Renal Domain Score, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline clinESSDAI Muscular Domain Score, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline clinESSDAI Peripheral Nervous System Domain Score, Full Analysis Set

- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline clinESSDAI Central Nervous System Domain Score, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline clinESSDAI Haematological Domain Score, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline ESSPRI Total Score, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline ESSPRI Dryness Severity Domain Score, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline ESSPRI Fatigue Severity Domain Score, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline ESSPRI Pain Severity Domain Score, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline Glandular Function Schirmer's Test, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline Glandular Function Unstimulated Whole Salivary Flow Test, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline IgG, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline Autoantibody Anti-Ro52/SSA Levels, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline Autoantibody Anti-Ro60/SSA Levels, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline Autoantibody Anti-La/SSB Levels, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline Autoantibody Rheumatoid Factor Levels, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline CRP Levels, Full Analysis Set

- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline ESR Levels, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline Hydroxychloroquine (or Other Anti-Malarial Drug) Use, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline Oral Corticosteroid Drug Use, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score at Week 24 by Baseline Immunomodulator Use, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score Over Time Through Week 24, Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in clinESSDAI Score Over Time Through Week 24 (Japan Subpopulation), Full Analysis Set
- Primary Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Mean (+/- SE) Change From Baseline Values for clinESSDAI Score Over Time Through Week 24, Full Analysis Set

Key Secondary Endpoints Analyses

- Secondary Endpoint Analysis 1 (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in ESSPRI Score at Week 24 Based on a Mixed Effects Repeated Measures Model (MMRM), Full Analysis Set
- Secondary Endpoint Analysis 1 (Supplementary Estimand, Treatment Policy Strategy): Summary of Change from Baseline in ESSPRI Score at Week 24 Based on a Mixed Effects Repeated Measures Model (MMRM), Full Analysis Set
- Secondary Endpoint Analysis 2 (Primary Estimand, Composite Strategy): Number of Subjects who Achieved ESSDAI-4 Response at Week 24 Based on a CMH Test, Full Analysis Set
- Secondary Endpoint Analysis 2 (Primary Estimand, Composite Strategy): Number of Subjects who Achieved ESSDAI-4 Response at Week 24 (Japan Subpopulation), Full Analysis Set
- Secondary Endpoint Analysis 2 (Supplementary Estimand, Treatment Policy Strategy): Number of Subjects who Achieved ESSDAI-4 Response at Week 24 Based on a CMH Test, Full Analysis Set
- Secondary Endpoint Analysis 3 (Primary Estimand, Composite Strategy): Number of Subjects who Achieved clinESSDAI-4 Response at Week 24 Based on a CMH Test, Full Analysis Set
- Secondary Endpoint Analysis 3 (Supplementary Estimand, Treatment Policy Strategy): Number of Subjects who Achieved clinESSDAI-4 Response at Week 24 Based on a CMH Test, Full Analysis Set
- Secondary Endpoint Analysis 3 (Primary Estimand, Composite Strategy): Number of Subjects who Achieved clinESSDAI-4 Response Over Time Through Week 24, Full Analysis Set

- Secondary Endpoint Analysis 3 (Primary Estimand, Composite Strategy): Number of Subjects who Achieved clinESSDAI-4 Response Over Time Through Week 24 (Japan Subpopulation), Full Analysis Set
- Secondary Endpoint Analysis 4 (Primary Estimand, Composite Strategy): Number of Subjects who Achieved ESSPRI Response at Week 24 Based on a CMH Test, Full Analysis Set
- Secondary Endpoint Analysis 4 (Supplementary Estimand, Treatment Policy Strategy): Number of Subjects who Achieved ESSPRI Response at Week 24 Based on a CMH Test, Full Analysis Set
- Secondary Endpoint Analysis 4 (Primary Estimand, Composite Strategy): Number of Subjects who Achieved ESSPRI Response Over Time at Week 24, Full Analysis Set
- Secondary Endpoint Analysis 4 (Primary Estimand, Composite Strategy): Number of Subjects who Achieved ESSPRI Response Over Time at Week 24 (Japan Subpopulation), Full Analysis Set
- Secondary Endpoint Analysis 5 (Primary Estimand, Composite Strategy): Number of Subjects who Achieved STAR Response at Week 24 Based on a CMH Test, Full Analysis Set
- Secondary Endpoint Analysis 5 (Supplementary Estimand, Treatment Policy Strategy): Number of Subjects who Achieved STAR Response at Week 24 Based on a CMH Test, Full Analysis Set
- Secondary Endpoint Analysis 5 (Primary Estimand, Composite Strategy): Number of Subjects who Achieved STAR Response Over Time Through Week 24, Full Analysis Set
- Secondary Endpoint Analysis 5 (Primary Estimand, Composite Strategy): Number of Subjects who Achieved STAR Response Over Time Through Week 24 (Japan Subpopulation), Full Analysis Set
- Secondary Endpoint Analysis 6 (Primary Estimand, Composite Strategy): Number of Subjects who Achieved DAL Response at Week 24 Based on a CMH Test, Full Analysis Set
- Secondary Endpoint Analysis 6 (Primary Estimand, Composite Strategy): Number of Subjects who Achieved DAL Response at Week 24 (Japan Subpopulation), Full Analysis Set
- Secondary Endpoint Analysis 6 (Supplementary Estimand, Treatment Policy Strategy): Number of Subjects who Achieved DAL Response at Week 24 Based on a CMH Test, Full Analysis Set
- Secondary Endpoint Analysis 7 (Primary Estimand, Composite Strategy): Number of Subjects who Achieved CRESS Response at Week 24 Based on a CMH Test, Full Analysis Set
- Secondary Endpoint Analysis 7 (Supplementary Estimand, Treatment Policy Strategy): Number of Subjects who Achieved CRESS Response at Week 24 Based on a CMH Test, Full Analysis Set
- Secondary Endpoint Analysis 7 (Primary Estimand, Composite Strategy): Number of Subjects who Achieved CRESS Response Over Time Through Week 24, Full Analysis Set
- Secondary Endpoint Analysis 7 (Primary Estimand, Composite Strategy): Number of Subjects who Achieved CRESS Response Over Time Through Week 24 (Japan Subpopulation), Full Analysis Set

Tertiary/Exploratory Endpoint Analysis

- Tertiary/Exploratory Endpoint Analysis (Primary Estimand, Composite Strategy): Number of Subjects who Achieved ESSDAI-3 Response at Week 24 Based on a CMH Test, Full Analysis Set
- Tertiary/Exploratory Endpoint Analysis (Primary Estimand, Composite Strategy): Number of Subjects who Achieved ESSDAI-3 Response at Week 24 (Japan Subpopulation), Full Analysis Set
- Tertiary/Exploratory Endpoint Analysis (Supplementary Estimand, Treatment Policy Strategy): Number of Subjects who Achieved ESSDAI-3 Response at Week 24 Based on a CMH Test, Full Analysis Set
- Tertiary/Exploratory Endpoint Analysis (Primary Estimand, Composite Strategy): Number of Subjects who Achieved ESSDAI-3 Response Over Time Through Week 24
- Tertiary/Exploratory Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in PhGA Over Time Through Week 24 Based on a Mixed Effects Repeated Measures Model (MMRM), Full Analysis Set
- Tertiary/Exploratory Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in ESSPRI Score Over Time Through Week 24 (Japan Subpopulation), Full Analysis Set
- Tertiary/Exploratory Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in Sjögren's Symptoms Over Time Through Week 24 Based on a Mixed Effects Repeated Measures Model (MMRM), Full Analysis Set
- Tertiary/Exploratory Endpoint Analysis (Supplementary Estimand, Treatment Policy Strategy): Summary of Change from Baseline in Sjögren's Symptoms Over Time Through Week 24 Based on a Mixed Effects Repeated Measures Model (MMRM), Full Analysis Set
- Tertiary/Exploratory Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in FACIT-Fatigue Score Over Time Through Week 24 Based on a Mixed Effects Repeated Measures Model (MMRM), Full Analysis Set
- Tertiary/Exploratory Endpoint Analysis (Supplementary Estimand, Treatment Policy Strategy): Summary of Change from Baseline in FACIT-Fatigue Score Over Time Through Week 24 Based on a Mixed Effects Repeated Measures Model (MMRM), Full Analysis Set
- Tertiary/Exploratory Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in PtGA Score Over Time Through Week 24 Based on a Mixed Effects Repeated Measures Model (MMRM)
- Tertiary/Exploratory Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Summary of Change from Baseline in ESSDAI Score Over Time Through Week 24, Full Analysis Set
- Tertiary/Exploratory Endpoint Analysis (Primary Estimand, Hypothetical Strategy): Mean (+/- SE) Change From Baseline Values for ESSDAI Score Over Time Through Week 24, Full Analysis Set

Supplement Efficacy

- Number of Subjects who Achieved Composite clinESSDAI-4 and ESSPRI Component Response or a CRESS Response Over Time Through Week 24, Full Analysis Set
- Number of Subjects With clinESSDAI Score Less Than 5 Over Time Through Week 24, Full Analysis Set
- Number of Subjects With a Reduction of clinESSDAI Score by at Least 3 Points From Baseline Over Time Through Week 24, Full Analysis Set
- Number of Subjects With a Reduction of at Least 25% in Rheumatoid Factor From Baseline or a Reduction of at Least 10% in IgG From Baseline Over Time Through Week 24, Full Analysis Set
- Summary of Schirmer's Test and Ocular Staining Score Over Time Through Week 24, Full Analysis Set
- Number of Subjects With an Unstimulated Whole Salivary Flow Response Over Time Through Week 24, Full Analysis Set
- Number of Subjects who Achieved Composite clinESSDAI-4 and ESSPRI Component Response Over Time Through Week 24, Full Analysis Set
- Summary of ESSPRI Dryness Severity Level and Percent Change From Baseline Over Time Through Week 24, Full Analysis Set
- Summary of ESSPRI Fatigue Severity Level and Percent Change From Baseline Over Time Through Week 24, Full Analysis Set
- Summary of ESSPRI Pain Severity Level and Percent Change From Baseline Over Time Through Week 24, Full Analysis Set
- Shift in clinESSDAI Constitutional Domain Activity Level From Baseline to Week 24 Over Time, Full Analysis Set
- Shift in clinESSDAI Lymphadenopathy and Lymphoma Domain Activity Level From Baseline to Week 24 Over Time, Full Analysis Set
- Shift in clinESSDAI Glandular Domain Activity Level From Baseline to Week 24 Over Time, Full Analysis Set
- Shift in clinESSDAI Articular Domain Activity Level From Baseline to Week 24 Over Time, Full Analysis Set
- Shift in clinESSDAI Cutaneous Domain Activity Level From Baseline to Week 24 Over Time, Full Analysis Set
- Shift in clinESSDAI Pulmonary Domain Activity Level From Baseline to Week 24 Over Time, Full Analysis Set
- Shift in clinESSDAI Renal Domain Activity Level From Baseline to Week 24 Over Time, Full Analysis Set
- Shift in clinESSDAI Muscular Domain Activity Level From Baseline to Week 24 Over Time, Full Anaysis Set

- Shift in clinESSDAI Peripheral Nervous System Domain Activity Level From Baseline to Week 24 Over Time, Full Analysis Set
- Shift in clinESSDAI Central Nervous System Domain Activity Level From Baseline to Week 24 Over Time, Full Analysis Set
- Shift in clinESSDAI Haematological Domain Activity Level From Baseline to Week 24 Over Time, Full Analysis Set

PK, PD, and Immunogenicity

- Summary of Serum Nipocalimab Concentrations (µg/mL) Over Time, PK Analysis Set
- Summary of Serum Nipocalimab Concentrations (µg/mL) Over Time (Japan Subpopulation), PK Analysis Set
- Summary of Serum Nipocalimab Concentrations (µg/mL) Over Time by Baseline Body Weight Quartiles, PK Analysis Set
- Summary of Serum Nipocalimab Concentrations (µg/mL) Over Time by Baseline Hydroxychloroquine (or Other Anti-Malarial Drug) Use, PK Analysis Set
- Box Plot of Median +/- IQ Range Serum Nipocalimab Concentrations (µg/mL) Over Time, PK Analysis Set
- Box Plot of Median +/- IQ Range Serum Nipocalimab Concentrations (µg/mL) Over Time by Baseline Hydroxychloroquine (or Other Anti-Malarial Drug) Use, PK Analysis Set
- Listing of Individual Serum Concentrations of Nipocalimab (µg/mL) (Japan Subpopulation), PK Analysis Set
- Summary of Treatment-emergent Antibodies to Nipocalimab Status, Immunogenicity Analysis Set
- Summary of Treatment-emergent Antibodies to Nipocalimab Status (Japan Subpopulation), Immunogenicity Analysis Set
- Summary of Treatment-emergent Neutralizing Antibodies to Nipocalimab Status (Japan Subpopulation), Immunogenicity Analysis Set
- Listing of Subjects with Samples Positive for Antibodies to Nipocalimab (Japan Subpopulation), Immunogenicity Analysis Set
- Listing of Subjects Positive for Treatment-emergent Antibodies to Nipocalimab at Baseline (Japan Subpopulation), Immunogenicity Analysis Set
- Summary of IgG Laboratory Values and Change From Baseline Over Time (Japan Subpopulation), Safety Analysis Set
- Summary of IgG Laboratory Values and Percent Change From Baseline Over Time (Japan Subpopulation), Safety Analysis Set
- Summary of IgG Laboratory Values and Percent Change From Baseline Over Time, Safety Analysis Set
- Summary of IgA Laboratory Values and Percent Change From Baseline Over Time, Safety Analysis Set

- Summary of IgM Laboratory Values and Percent Change From Baseline Over Time, Safety Analysis Set
- Summary of C-Reactive Protein (CRP) Laboratory Values and Percent Change From Baseline Over Time, Safety Analysis Set
- Shift in C-Reactive Protein (CRP) Laboratory Values From Baseline Over Time, Safety Analysis Set
- Number of Subjects With a Reduction of at Least 30% in C-Reactive Protein (CRP) From Baseline Over Time, Safety Analysis Set
- Summary of Erythrocyte Sedimentation Rate (ESR) Laboratory Values and Percent Change From Baseline Over Time, Safety Analysis Set
- Shift in Erythrocyte Sedimentation Rate (ESR) Laboratory Values From Baseline Over Time, Safety Analysis Set
- Number of Subjects With a Reduction of at Least 30% in Erythrocyte Sedimentation Rate (ESR) From Baseline Over Time, Safety Analysis Set
- Number of Subjects With a Reduction of at Least 30% in IgG From Baseline Over Time, Safety Analysis Set
- Summary of Rheumatoid Factor Laboratory Values and Percent Change From Baseline Over Time, Safety Analysis Set
- Shift in Rheumatoid Factor Laboratory Values From Baseline Over Time, Safety Analysis Set
- Number of Subjects With a Reduction of at Least 30% in Rheumatoid Factor From Baseline Over Time, Safety Analysis Set
- Summary of Anti-Ro52/SSA Values and Percent Change From Baseline Over Time in Subjects With a Positive Anti-Ro52/SSA at Baseline, Safety Analysis Set
- Summary of Anti-Ro60/SSA Values and Percent Change From Baseline Over Time in Subjects With a Positive Anti-Ro60/SSA at Baseline, Safety Analysis Set
- Number of Subjects With a Reduction of at Least 30% in Anti-Ro52/SSA (CU) From Baseline Over Time in Subjects With a Positive Anti-Ro52/SSA at Baseline, Safety Analysis Set
- Number of Subjects With a Reduction of at Least 30% in Anti-Ro60/SSA (CU) From Baseline Over Time in Subjects With a Positive Anti-Ro60/SSA at Baseline, Safety Analysis Set
- Mean (+/- SE) Change From Baseline Values for IgG (g/L) Over Time, Safety Analysis Set
- Mean (+/- SE) Percent Change From Baseline Values for IgG (g/L) Over Time, Safety Analysis Set
- Mean (+/- SE) Change From Baseline Values for IgA (g/L) Over Time, Safety Analysis Set
- Mean (+/- SE) Percent Change From Baseline Values for IgA (g/L) Over Time, Safety Analysis Set
- Mean (+/- SE) Change From Baseline Values for IgM (g/L) Over Time, Safety Analysis Set
- Mean (+/- SE) Percent Change From Baseline Values for IgM (g/L) Over Time, Safety Analysis Set

- Mean (+/- SE) Change From Baseline Values for Rheumatoid Factor (IU/m/L) Over Time, Safety Analysis Set
- Mean (+/- SE) Percent Change From Baseline Values for Rheumatoid Factor (IU/m/L) Over Time, Safety Analysis Set
- Mean (+/- SE) Percent Change From Baseline Values for Rheumatoid Factor (IU/m/L) Over Time in Subjects With Elevated Rheumatoid Factor at Baseline, Safety Analysis Set
- Mean (+/- SE) Percent Change From Baseline Values for Erythrocyte Sedimentation Rate (mm/h) Over Time, Safety Analysis Set
- Mean (+/- SE) Percent Change From Baseline Values for Erythrocyte Sedimentation Rate (mm/h) Over Time in Subjects With Elevated Erythrocyte Sedimentation Rate at Baseline, Safety Analysis Set
- Mean (+/- SE) Percent Change From Baseline Values for C-Reactive Protein (mg/L) Over Time, Safety Analysis Set
- Mean (+/- SE) Percent Change From Baseline Values for C-Reactive Protein (mg/L) Over Time in Subjects With Elevated C-Reactive Protein at Baseline, Safety Analysis Set
- Mean (+/- SE) Percent Change From Baseline Values for Anti-Ro52/SSA (CU) Over Time in Subjects With a Positive Anti-Ro52/SSA at Baseline, Safety Analysis Set
- Mean (+/- SE) Percent Change From Baseline Values for Anti-Ro60/SSA (CU) Over Time in Subjects With a Positive Anti-Ro60/SSA at Baseline, Safety Analysis Set
- Listing of Nipocalimab-treated Subjects With a Positive Percent Change From Baseline in IgG at Any Time Through Week 24, Safety Analysis Set
- Listing of Nipocalimab-treated Subjects With a Positive Percent Change From Baseline in IgG at Any Time Through Week 24 (Japan Subpopulation), Safety Analysis Set

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