STATISTICAL ANALYSIS PLAN

Protocol title:	**A randomized, double-blind, placebo controlled, parallel group study of the safety, tolerability, pharmacokinetics, and therapeutic efficacy of SAR441344 in adult patients with primary Sjögren's syndrome (pSjS)**
Protocol number:	**ACT16618**
Compound number (INN/Trademark):	**SAR441344 (frexalimab)**
Study phase:	**Phase 2**
Short title:	**Safety, tolerability, pharmacokinetics, and therapeutic efficacy of SAR441344 in primary Sjögren's syndrome (pSjS) phaethuSA**
Statistician:	[redacted]
Statistical Project Leader:	[redacted]
Date of issue:	**24-Nov-2023**

Regulatory agency identifier number(s):

IND:	147616
EudraCT:	2020-000511-77
NCT:	NCT04572841
WHO:	U1111-1244-2266
EUDAMED	Not applicable
Other:	Not applicable

Total number of pages: 52

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VERSION HISTORY

This Statistical Analysis Plan (SAP) for Study ACT16618 is based on the Amended Clinical Trial Protocol Version 03 dated 05-Apr-2022. This section summarizes major changes to the statistical analysis features in the SAP.

The first participant was randomized on 22-Feb-2021. Version 1.0 of this SAP was approved before the first code release for an interim analysis was conducted.

Major changes in statistical analysis plan

SAP version	Approval date	Changes	Rationale
1	16-Jan-2023	Change: Treatment emergent adverse event incidence tables will be presented by system organ class, ~~highlevel group term, highlevel term,~~ and preferred term for each intervention group and overall, showing the number (n) and percentage (%) of participants experiencing a TEAE	Only system organ class and preferred term will be shown in the CSR analyses
		Change: On-treatment period changed from "until EOT+7 days" to "until last IMP+16 days"	To follow the standards to use the planned maximal distance between two planned IMP administrations, and disconnect the definition from EOT, which could be missing
		Change: The confidence interval used for all modeling results was changed from 90% to 95%	To provide the more standard confidence interval used in literature
		Change: Change from baseline MFI will be analyzed using an ANCOVA instead of MMRM	Only one post-baseline visit planned for MFI
2	current	Change: Throughout document the wording for imputation of a value by missing was replaced by exclusion of the value from analysis (Section 1.2.1, 3.2.2, 3.4.2 and 5.4)	Clarification
		Changed: data handling rules in case of issues with blood samples at time of ESSDAI (Section 3.2.1). Details of rules were shifted to Section 5.4.	Rules have been adapted: major deviations for ESSDAI will be excluded from primary analysis
		Added: Sensitivity analysis (Section 3.2.3)	Added to investigate potential site effects
		Added: Additional graphs and exploratory analyses were defined for efficacy analyses (Section 3.2-3.4)	Added to provide further insights on efficacy results
		Added: [redacted] was added as additional exploratory efficacy endpoint (Section 3.4)	The new endpoint [redacted] was published after study start as endpoint with potential for Sjögren's Syndrome
		Added: Additional graphs and exploratory analyses were defined for BM analyses (Section 3.7.1.3)	Added to provide further insights on biomarker results

SAP version	Approval date	Changes	Rationale
		Deleted: some analyses and graphs were deleted for biomarkers (Section 3.7.1.3)	Decrease the number of outputs in deleting analyses of low interest based on current knowledge
		Changed: Section 3.7.1.3 on biomarkers was updated to specify in more details which analyses will be performed for which parameters	Provide further clarity on parameters used for the respective analyses, and on analyses in general. For [redacted], analysis is not planned, as data will not be available
		Added: Subgroup analyses based on high and moderate/low total ESSDAI score at baseline (Section 3.7.2)	Unbalanced ESSDAI baseline values between intervention groups were observed at time of interim analysis
		Added: Section 5.5 Questionnaires dedicated to table on ESSDAI weights and added [redacted] and [redacted]	Provide information on weights used for [redacted] and definition used for [redacted]
		Deleted: Intra-class Correlation Coefficient in placebo group (Section 3.7.1.3.1.2)	Will be describe in separate document, if needed
		Added: Gene expression levels (Section 3.7.1.3.2)	Decision to include it in SAP even if not all analyses will be included in CSR

1 INTRODUCTION

This statistical analysis plan (SAP) provides a comprehensive and detailed description of strategy and statistical techniques to be used to analyze data for SAR441344 study protocol ACT16618. The purpose of the SAP is to ensure the credibility of the study findings by prespecifying the statistical approaches to the analysis of study data prior to interim analysis (after approximately 50% of participants).

1.1 STUDY DESIGN

This study is a multicenter, multinational, randomized, double-blind, placebo-controlled, parallel-group, stratified proof of concept Phase 2 study.

Participants included are diagnosed with pSjS according to the American College of Rheumatology/EULAR 2016 criteria with systemic disease (EULAR Sjögren's Syndrome Disease Activity Index [ESSDAI] score ≥5) and significant biological activity.

Participants are centrally randomized via Interactive Response Technology (IRT) at Baseline (Day 1) to SAR441344 or placebo in a 1:1 ratio. They receive a single IV loading dose on Day 1, followed by 5 SC doses administered once every 2 weeks (q2w). The 12 weeks treatment period (including end of treatment visit (EOT)) will be followed by a 12 week follow-up period. Randomization is stratified by Baseline EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) score ≥5 versus <5. Approximately 88 participants will be randomized from approximately 32 sites.

Study primary analysis will be conducted after completion of the 12-week treatment period (EOT).

1.2 OBJECTIVE AND ENDPOINTS

This study will evaluate the therapeutic efficacy of SAR441344 in adult patients with pSjS, as well as safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD).

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the therapeutic efficacy of one dose level of SAR441344 versus placebo over 12 weeks in adult patients with primary Sjögren's syndrome (pSjS), assessed by the change of the European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI).	• Change in ESSDAI from Baseline to Week 12.

Objectives	Endpoints
Secondary	
• To evaluate the therapeutic efficacy of one dose level of SAR441344 versus placebo over 12 weeks in adult patients with pSjS, assessed by the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI).	• Change in ESSPRI from Baseline to Week 12.
• To evaluate the therapeutic efficacy on fatigue of one dose level of SAR441344 versus placebo over 12 weeks in adult patients with pSjS, assessed by the Multidimensional Fatigue Inventory (MFI).	• Change in MFI general fatigue subscale and other subscales from Baseline to Week 12.
• To evaluate the pharmacokinetic (PK) exposure of one dose level of SAR441344 over 12 weeks in adult patients with pSjS.	• Descriptive statistics of SAR441344 concentrations, including mean, median, and standard deviation. • Pharmacokinetic parameters for SAR441344 will be reported (maximum concentration [C_{max}], time to Cmax [t_{max}], area under the curve over the dosing interval [$AUC_{0\text{-}tau}$], and terminal half-life [$t_{1/2z}$]).
• To evaluate the safety and tolerability of one dose level of SAR441344 versus placebo in adult patients with pSjS as determined by adverse events (AEs).	• Incidence of treatment-emergent AEs (TEAEs), serious AEs (SAEs), and AEs of special interest (AESIs) from Baseline to Week 24 (End of Study [EoS]). • Incidence of study investigational medicinal product discontinuation and withdrawals due to TEAEs from Baseline to Week 24 (EoS).
• To evaluate the local tolerability of one dose level of SAR441344 versus placebo over 12 weeks in adult patients with pSjS.	• Change in participant reported local tolerability scale. • Incidence of AEs related to local tolerability findings.
• To evaluate the safety and tolerability of one dose level of SAR441344 versus placebo over 12 weeks in adult patients with pSjS determined by electrocardiogram, vital signs, and laboratory evaluations.	• Participants with medically significant changes in vital signs, electrocardiogram, and/or laboratory evaluations.
• To measure the immunogenicity of one dose level of SAR441344 versus placebo over 12 weeks in adult patients with pSjS.	• Antidrug antibodies at Baseline, Week 4, Week 8, Week 12, and Week 24.
[redacted]	[redacted]

Objectives	Endpoints
[redacted]	[redacted]

1.2.1 Estimands

Primary estimand defined for main endpoints is summarized in Table 2 below. More details are provided in Section 3.

For all these estimands, the comparison of interest will be the comparison of SAR441344 versus placebo.

Table 2 - Summary of primary estimand for main endpoints

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary objective:				
To evaluate the therapeutic efficacy of one dose level of SAR441344 versus placebo over 12 weeks in patients with primary Sjögren's syndrome (pSjS), assessed by the change of ESSDAI				
Primary endpoint	Change in ESSDAI from Baseline to Week 12	Efficacy	Permanent Study/Treatment discontinuation: Data up to 32 days after last IMP will be included in the analysis for defined analysis windows, unless prohibited medication has been taken (composite variable strategy) Prohibited medications: Measurements post intake will be excluded from the analysis (composite variable strategy) AEs leading to treatment discontinuation: Measurements after start/worsening of infectious/inflammatory AEs will be excluded from the analysis (composite variable strategy)	The difference between intervention groups for change from baseline ESSDAI at Week 12 will be estimated based on a mixed effects model Having missing data: handled in the mixed effects model with repeated measurements by assuming missing at random (MAR), if changes from baseline data (Week 4 or Week 8) are evaluable for the participant.

2 ANALYSIS POPULATIONS

The following populations for analyses are defined:

Table 3 - Populations for analyses

Population	Description
Screened	All participants who signed the informed consent form (ICF).
Randomized	All participants from screened population who have been allocated to a randomized intervention (by IRT) regardless of whether the intervention was received or not. Participants treated with the study intervention without being randomized or before the randomization will not be considered as randomized.
Efficacy	All randomly assigned participants who did actually receive at least 1 complete dose of IMP with at least 1 post-IMP administration measurement, with available Baseline assessment of the ESSDAI. Participants will be analyzed according to the intervention they actually received.
Safety	All randomized participants exposed to the IMP (regardless of the amount of treatment administered) are included in the safety population. Participants will be analyzed according to the intervention they actually received.
Pharmacodynamic (PD)	All randomized and treated participants (safety population) with at least one post-baseline PD data. Participants will be analyzed according to the intervention they actually received. (For optional use.)
Baseline Biomarker	All randomized and treated participants (safety population) who had a sample drawn for biomarker measurement and successfully analyzed at baseline. Participants will be analyzed according to the intervention they actually received.
Pharmacodynamic Biomarker (PD BM)	All randomized and treated participants (safety population) who had a sample drawn for biomarker measurement and successfully analyzed at baseline and at least one post-baseline visit. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic (PK)	All randomized and treated participants (safety population) with adequate PK results. Participants having received only placebo will not be part of the PK population. Participants will be analyzed according to the intervention they received. (For optional use.)
PK/PD	All participants being included in both the PK and the PD populations will be included in the PK/PD population. However, participants being included in the PD population and having received only placebo will be part of the PK/PD population. (For optional use.)
Anti-drug antibody (ADA)	All randomized participants treated with SAR441344 with at least one post-baseline ADA result (positive, negative or inconclusive). Participants will be analyzed according to the intervention they actually received.
Population without trial impact (disruption) due to COVID-19	any participant: - without any critical or major deviation related to COVID-19 - and who didn't permanently discontinue treatment due to COVID-19 - and who didn't permanently discontinue study due to COVID-19.

Note: "Screened" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process.

Participants exposed to study intervention before or without being randomized will not be considered randomized and will not be included in any analysis population. The safety experience of these participants will be reported separately.

Randomized participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety population as randomized.

For any participant randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be reported separately.

For participants receiving more than one study intervention during the study, the intervention group for as-treated analyses will be the as-randomized intervention group if the participant has received at least one administration of the as-randomized intervention.

3 STATISTICAL ANALYSES

3.1 GENERAL CONSIDERATIONS

Study primary analysis will be conducted after all participants have completed their EoT (Week 12) visit, but prior to the formal completion of the study (early analysis data base lock). The final analysis to be included in the clinical study report will be conducted after formal completion of the study and final database lock.

In general, unless otherwise specified, continuous data will be summarized using the number of observations available, mean, Standard Deviation (SD), median, [Q1, Q3,] minimum, and maximum. Categorical and ordinal data will be summarized using the count and percentage of participants, as appropriate.

The baseline value is defined as the last available value before the first dose of Investigational Medicinal Product (IMP). For participants randomized but not treated, the baseline value is defined as the last available value before randomization.

Unless otherwise specified, analyses will be performed by intervention group (and overall, for baseline and demographics characteristics).

Observation period

The observation period will be divided into 3 segments:

- The **pre-treatment period** is defined as the time between informed consent signature and Investigational Medicinal Product (IMP) administration.
- The **Treatment-Emergent (TE) period** is defined as the period from the first IMP administration up to the End-Of-Study (EOS) visit (included). The treatment-emergent period includes the following 2 periods:
  - The on-treatment period is defined as the period from the first IMP administration to the last administration of the IMP +16 days (last day included).
  - The residual treatment period is defined as the period from the end of the on-treatment period to the end of the treatment-emergent period.
- The **post-treatment period** is defined as the period from the end of the treatment-emergent period.

3.2 PRIMARY ENDPOINT(S) ANALYSIS

If not mentioned otherwise, all analyses below are provided using analysis windows for premature EOT visits (see Section 5.4) for any by-visit analyses. The analyses will be based on the efficacy population.

3.2.1 Definition of endpoint(s)

The primary endpoint is the change from baseline to Week 12 in ESSDAI (European League Against Rheumatism Sjögren's Syndrome Disease Activity Index).

The score consists of 12 organ specific domains (constitutional, lymphadenopathy, glandular, articular, cutaneous, pulmonary, renal, muscular, PNS, CNS, hematological, and biological), which are scored based on organ specific items in 3 to 4 different severity grades. This score is summed up over all 12 domains in a weighted way (see Table 10) to summarize into a total score. The ESSDAI score ranges from 0 to 123. A higher score is related with a higher disease activity. In case of a missing domain, the total score will not be calculated.

The ESSDAI score will be calculated as:

1. Domain score=Severity grade * domain weight
2. ESSDAI score=sum of all 12 domain scores

The ESSDAI will be performed on screening, Day 1, W4, W8, W12 and EOS.

If ESSDAI on Day 1 is missing, screening data may be used as baseline. Local lab used for screening has been confirmed to be comparable to central lab used in later visits.

The primary endpoint is based on the total score. Main analysis will be on the change from baseline.

Unplanned laboratory data are allowed to be used for the hematology domain of ESSDAI, if planned lab samples are not possible to be analyzed, eg, due to hemolyzed blood samples. Detailed rules are described in data handling Section 5.4.

Data handling will be described in Section 5.4 in more detail for all efficacy parameters.

3.2.2 Main analytical approach

For the primary analysis, a linear mixed model with repeated measurements (MMRM) will be fitted to estimate the difference in mean change in ESSDAI from Baseline to Week 12 of SAR441344 versus placebo.

All post-baseline data until Week 12 (Week 4, 8 and 12) will be taken into account, including all participants in the efficacy population. The model for change from baseline ESSDAI includes fixed effects for participant specific baseline ESSDAI, visit, intervention group, and visit by intervention group interaction. Repeated measurements for each visit are taken within subject using an unstructured variance-covariance matrix. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom will be estimated using Kenward-Roger adjustment.

In case of convergence issues, simpler variance-covariance matrices may be tested by order of decreasing complexity (heterogeneous Toeplitz (TOEPH), antedependence (ANTE(1)), heterogeneous autoregressive (ARH(1)), Toeplitz (TOEP), autoregressive (AR(1)), compound symmetry (CS) or variance components (VC)).

```
proc mixed data=dataset method=reml;
        class AVISITN USUBJID TRT;
        model CHG=BASE TRT AVISITN TRT*AVISITN/solution ddfm=kr  ;
        repeated AVISITN/type=un subject=USUBJID;
        lsmeans TRT*AVISITN/slice=AVISITN cl;
        estimate "visit W4 trt eff"   TRT -1 1   TRT*AVISITN -1 1 0 0 0 0 /cl;
        estimate "visit W8 trt eff"   TRT -1 1   TRT*AVISITN 0 0 -1 1 0 0 /cl;
        estimate "visit W12 trt eff" TRT -1 1   TRT*AVISITN 0 0 0 0 -1 1 /cl;
run;
```

SAS proc mixed code to be used as bases for programming of mixed model

Point estimate and two-sided 95% confidence interval for the difference of means between the 2 groups (SAR443144 versus placebo) at Week 12 will be derived from the linear model framework.

The treatment difference in primary endpoint will be assessed based on a Quantitative Decision Making methodology for internal decision making. Specific decision criteria to be used will be documented separately before database lock and will not be included in the clinical study report.

It is assumed that the ESSDAI will follow an approximate normal distribution. If this assumption appears to not be met, alternative statistical methods may be applied, eg, data may be transformed for analysis.

The following “intercurrent event” strategy will be followed:

- Permanent Study/Treatment discontinuation: Data for premature EOT up to 32 days after last IMP will be included in the analysis, if they fall into defined analysis windows (Section 5.4).
- Taking prohibited medications (see Table 4): data will be excluded from the analysis after the medication usage.
- Treatment discontinuation due to infectious or inflammatory AEs (for grouping see Section 5.4): data will be excluded from the analysis after the AE.

Table 4 - Prohibited medications that impact efficacy

Medication/Vaccine[a]	Data to be excluded from the main statistical analysis after taking medication
High-dose steroids [redacted]/ change in dose	yes (Identified during blinded review of deviations)
High dose of hydroxychloroquine or chloroquine [redacted]/change in dose	no
High dose of methotrexate [redacted]/change in dose	yes (Identified during blinded review of deviations)
Pharmacological stimulant treatment for lacrimal and salivary gland function with [redacted]	no
Ocular dryness treatment with [redacted].	no
Previous or ongoing treatment with azathioprine or other thiopurines, mycophenolate mofetil, sulfasalazine, or cyclosporine A	yes (Identified during blinded review of deviations)
Previous or ongoing treatment with cyclophosphamide, leflunomide, or belimumab	yes (Identified during blinded review of deviations)
Previous treatment with rituximab.	yes (Identified during blinded review of deviations)
Previous treatment with bone marrow transplantation, total lymphoid irradiation or ablative ultrahigh-dose cyclophosphamide or IV Ig.	yes (Identified during blinded review of deviations)
Previous treatment with any other biologic drug[redacted]	yes (Identified during blinded review of deviations)
Received administration of any[redacted]	no
Products [redacted]	yes (Identified during blinded review of deviations)

a Details for the prohibited doses and time courses are described in the protocol [Section 6.5.1].

Blinded review of prohibited treatment (medication or procedure, protocol Section 6.5.1, Table 4) will be performed before database locks by considering the type of medication or procedure, indication, timing, frequency and the potential impact of the use of the prohibited medications/procedures (see Section 5.4).

Handling of missing data:

Missing data in ESSDAI categories will not be replaced for calculation of total ESSDAI score.

In case of a missing D1 total ESSDAI score the screening total ESSDAI score will be used as baseline. In case of only a part of domains are missing on Day 1, these can be replaced using the same domains from screening visit to calculate a baseline ESSDAI score.

Participants with missing ESSDAI at baseline will not be included in the analysis. Participants with baseline and one or more postdose timepoints (Week 4, 8, and/or 12) will be included. Mixed model for repeated measures (MMRM) is used for the primary analysis assuming missing at random (MAR).

The reason for non-available primary endpoint will be provided in a table (including premature study discontinuation, premature EOT out of EOT window, prohibited medication leading to treatment discontinuation (see Table 4), SARS-CoV-2 infection or any other infectious/inflammatory AEs leading to treatment discontinuation (see Section 5.4), other).

3.2.3 Sensitivity analysis

The primary analysis model used for change from baseline ESSDAI will be used to extract residual and provide a scatterplot of studentized residuals versus Site ID for Week 12. The sites will be ordered by number of evaluable participants and the graph will be provided by study intervention group.

The primary model for change from baseline ESSDAI (Section 3.2.2) will be done including Site ID as random factor.

3.2.4 Supplementary analyses

Modeling

Using the MMRM model fitted for the primary analysis, the differences between Placebo and SAR441344 will be estimated for change from baseline for Weeks 4, 8 and 12. A graph will be provided presenting the LSmean (+/- SE) by each intervention and visit, and for the difference of interventions (with 95% CI).

In addition, the differences between Placebo and SAR441344 may be estimated for change from baseline for Week 4, 8 and 12 of the individual domains of the ESSDAI, using the MMRM as for the primary analysis, if possible. In case of no convergence of a model of one of the domains only descriptive analysis will be provided for this domain (Section 3.2.5). Graphs will be provided presenting the LSmean (+/- SE) by each intervention and visit, and for the difference of interventions (with 95% CI).

As supplementary analysis, the primary analysis model above will be performed, using the data as measured including the data after prohibited treatment and inflammatory AEs and data in hematology domain with major deviations (Section 3.2.1) (treatment policy strategy). Domains entered using unplanned lab after first dosing for screening or Day 1 (baseline) will still be kept as missing, if any (see Section 3.2.1).

In addition, a linear mixed model with repeated measurements including stratum will be fitted to estimate the mean change in ESSDAI over time, including fixed factors for participant specific baseline ESSDAI, visit, stratum, intervention group, visit-by-stratum interaction, visit-by-intervention group interaction, stratum-by-intervention group interaction, and visit-by-stratum-by-intervention group interaction. Repeated measurements for each visit are taken within participant (using an unstructured Covariance matrix). In case of non-convergence of the underlying model the latter will be simplified by reducing the number of interaction terms.
As a second step simpler variance-covariance matrices will be tested.

Least square means will be calculated for change from baseline to Week 12 for both study intervention groups and differences of means for SAR441344 versus placebo with two-sided 95% confidence interval will be derived from the model framework.

In case of many missing data, alternative models may be used for supplemental analysis.

[redacted]

Section 5.4 [redacted]

[redacted]

A table of descriptive statistics will also be provided for ESSDAI using only the 7 domains used for screening.

3.3 SECONDARY ENDPOINT(S) ANALYSIS

The secondary endpoints detailed in this section are change in ESSPRI from baseline to Week 12 and change in MFI general fatigue subscale and other subscales from Baseline to Week 12. Other secondary endpoints analyses are defined in Section 3.6.2 (AE, SAE), Section 3.6.3 (medically significant changes VS, ECGs and laboratory evaluations), Section 3.6.3.2 (Local tolerability), Section 3.7.1.1 (PK) and Section 3.7.1.2 (immunogenicity).

3.3.1 Definition of endpoints

ESSPRI

European League Against Rheumatism Sjögren's Syndrome Patient Reported Index (ESSPRI) is designed to assess the severity of patient's symptoms.

Participants rate the key disease manifestations fatigue, dryness, and pain. Each of the items is based on a numeric scale ranging from 0 to 10, where 0 is defined as no symptoms and 10 as maximum imaginable complaints.

The ESSPRI will be performed on Day 1 (baseline) W4, W8, W12 and EOS.

The analysis is based on the score, which is the mean of the 3 scales.

MFI

Multidimensional Fatigue Inventory (MFI) is a 20 item self-report instrument with 5 subscales (2): general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. Each scale ranges from 1 ("yes, this is true") to 5 ("no, this is not true"). Each of the 5 scales is to be considered independently and a total score is calculated. Positively worded items are reversed scored. Scores can range from the minimum of 4 to the maximum of 20. A total score ranged from 20 to 100 will also be derived. A higher score is related with a higher degree of fatigue.

The MFI is done on Day 1 (baseline), W12 and EOS.

3.3.2 Analyses

If not mentioned otherwise, all analyses below are provided using analysis windows for premature EOT visits (see Section 5.4) for any by-visit analyses.

The baseline is the assessment done on Day 1 prior dosing. The analyses will be provided based on the efficacy population.

Data after prohibited medication (see Table 4) or premature discontinuation due to infectious or inflammatory AEs (for grouping see Section 5.4) will be set to missing for the analyses described below, if not mentioned otherwise.

ESSPRI

Change from baseline ESSPRI score will be analyzed using MMRM with the same factors as the primary analysis, using ESSPRI baseline score as Covariate. Data for all visits until Week 12 will be included in this analysis.

Least square means will be calculated for change from baseline to Week 12 for both intervention groups and differences of means for SAR441344 versus placebo with two-sided 95% confidence interval will be derived from the model frameworks.

Change from baseline to Week 4 and Week 8 results will be derived in the same model.

The same analysis will be provided for each ESSPRI scale separately.

MFI

Change from baseline total MFI score will be analyzed using an ANCOVA including total MFI score baseline and intervention (TRT) as fixed effects. The same analysis will be done for each of the MFI subscales. Visits until Week 12 will be included in this analysis.

Least square means will be calculated for change from baseline to Week 12 for both intervention groups and differences of means for SAR441344 versus placebo with two-sided 95% confidence interval will be derived from the model frameworks.

As additional analysis, the ESSPRI stratum will be added to the ANCOVA model.

ESSPRI and MFI

A graphical presentation of model predicted values will be provided presenting the LSmean (+/- SE) by each intervention and visit, and for the difference of interventions (with 95% CI).

Missing data handling:

Participants with missing data at baseline will not be included in the analyses. Participants with one or more postdose timepoints will be included. For ESSPRI post dose missing values will not be imputed, A MMRM will be used assuming missing at random. For MFI there is only one post dose timepoint, and missing data will not be imputed. For MFI with only some but not all questions missing, all subscales without missing data will be calculated.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] (see Section 3.4.1.1) [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

The tertiary endpoints detailed in this section are efficacy assessments (abbreviations of the questionnaires explained below: [redacted]). Other tertiary endpoints analyses, including PD biomarkers [redacted]), are defined in Section 3.7.1.3 (biomarker).

3.4.1 Definition of endpoints

If not mentioned otherwise, the baseline is the assessment done on Day 1 prior to dosing. The analyses will be provided based on the efficacy population.

3.4.1.1 Assessments with measurements planned at baseline and Week 12

[redacted]

[redacted]

[redacted] See Table 11 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.4.2 Analyses

If not mentioned otherwise, all analyses below are provided using analysis windows (see Section 5.4) for premature EOT visit in by-visit analyses.

Data after prohibited medication (see Table 4) or premature discontinuation due to infectious or inflammatory AEs (see Section 5.4) will be excluded from the analyses described below, if not mentioned otherwise.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] (see Table 12), [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.5 MULTIPLICITY ISSUES

No multiplicity adjustment will be made for efficacy. For multiplicity adjustment in biomarker and PD analysis see Section 3.7.1.3.1.2.

3.6 SAFETY ANALYSES

All safety analyses will be performed on the safety population as defined in Section 2, unless otherwise specified, using the following common rules:

- The analysis of the safety variables will be descriptive, and no testing is planned.
- Safety data in participants who do not belong to the safety population (eg, exposed but not randomized) will be provided separately.

3.6.1 Extent of exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure and summarized within the safety population. Dosings are planned on Day 1, W2, W4, W6, W8 and W10.

The following listings will be provided:

- Participants receiving IMP from specified batch.
- Randomization scheme (Strata, Block number, Order within the block, Randomization number, Study intervention group, Randomization date and time, Participant identifier, and Comments (if needed)).

Duration of IMP exposure

Duration of IMP exposure is defined as last IMP administration date – first IMP administration date +14 days, regardless of intermittent discontinuations.

Duration of IMP exposure will be summarized quantitatively and categorically by intervention group and overall: 14 to 20, 21 to 34, 35 to 48, 49 to 62, 63 to 76, 77 to 90, >=91.

Treatment compliance

A given administration will be considered noncompliant if the participant did not receive the number of administrations as required by the protocol.

Percentage of treatment compliance for a participant will be defined as the number of administrations that the participant was compliant divided by the total number of administrations that the participant was planned to take from the first administration of IMP up to the actual last administration of IMP, multiplied by 100.

Treatment compliance will be summarized quantitatively and categorically by intervention group and overall: <80%, ≥80% and =100%

Of note, according to the protocol, cases of overdose are reported in the e-CRF as Adverse Events and will be described as part of the AE analyses.

If applicable, summaries for exposure and compliance will be provided for the population with trial impact (disruption) due to COVID-19.

3.6.2 Adverse events

General common rules for adverse events

All adverse events (AEs) will be coded to a Lower-Level Term (LLT), Preferred Term (PT), High-Level Term (HLT), High-Level Group Term (HLGT), and associated primary System Organ Class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version currently in effect at Sanofi at the time of database locks.

The AEs will be analyzed in the following 3 categories:

1. Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.
2. Treatment-Emergent Adverse Events (TEAE)s: AEs that occurred, worsened or became serious during the treatment-emergent period.
3. Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period.

Similarly, any AEs leading to deaths will be analyzed in the pre-treatment, treatment-emergent and post-treatment periods.

The primary focus of AE reporting will be on TEAEs. Pre-treatment and post-treatment AEs will be described separately.

An AE with incomplete or missing date/time of onset (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment or a post-treatment AE.

If the assessment of the relationship to IMP is missing for an AE, this AE will be assumed as related to IMP. If the severity is missing for an AE, the severity will be left as missing.

The AE tables will be sorted as indicated in Table 5.

Table 5 - Sorting of AE tables

AE presentation	Sorting rules
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs[a, b]
PT	By decreasing frequency of PTs[a]

a Sorting will be based on the SAR441344 intervention group.
b The table of all TEAEs presented by SOC and PT will define the presentation order for all other tables (eg, treatment-emergent SAE) presented by primary SOC and PT, unless otherwise specified.

Analysis of all adverse events

The overview of TEAE with the details below will be generated:

- Any TEAE
- Any severe TEAE
- Any treatment emergent SAE
- TEAE leading to death, if any
- Any TEAE leading to permanent intervention discontinuation
- Any TEAE leading to permanent study discontinuation
- Any treatment emergent AESI

The AE summaries of Table 6 will be generated with number (%) of participants experiencing at least one event and sorted by the internationally agreed SOC order and decreasing frequency of PTs. Sorting will be based on experimental study drug intervention group (see Table 5).

Table 6 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC and PT
Common TEAE (≥5% across all groups)	Primary SOC, and PT
TEAE related to IMP as per Investigator's judgment	Primary SOC, and PT
TEAE by maximal intensity	Primary SOC and PT
Treatment emergent SAE *[optional]*	Primary SOC, and PT
Treatment emergent SAE related to IMP as per Investigator's judgment *[optional]*	Primary SOC, and PT
TEAE leading to permanent intervention discontinuation *[optional]*	Primary SOC, and PT
TEAE leading to death (death as an outcome of the AE as reported by the Investigator in the AE page) *[optional]*	Primary SOC and PT
Pre-treatment AE *[optional]*	Overview[a]

a Will include the following AE categories: any AEs, any serious AEs, any AEs leading to death, any AEs leading to permanent [full] intervention discontinuation

In addition, the all TEAE summary by Primary SOC and PT will be performed by trial impact (disruption) due to COVID-19. The number (%) of participants experiencing at least one treatment emergent COVID19 related adverse event by primary SOC and PT will be provided, if applicable.

Optional tables mentioned in Table 6 are to be done in case of sufficient number of events. Otherwise only listings will be provided.

Deaths, serious, and other significant adverse events

Deaths and serious adverse event will be listed.

Adverse events leading to intervention/study discontinuation

AE leading to intervention or study discontinuation will be listed.

Adverse events of special interest

Adverse events of special interest (AESIs) and other AEs of interest will be selected for analyses as indicated in Table 7. AESI will be listed.

Optional, to be done in case of sufficient events: Number (%) of participants experiencing at least one event will be provided for each event of interest. Tables will be sorted as indicated in Table 5.

Table 7 - Selections for AESIs and other AEs of interest

AESIs and other AEs of interest	Selection
Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP	e-CRF specific tick box on the AE page
Symptomatic overdose (serious or non-serious) with IMP	e-CRF specific tick box on the AE page
Increase in ALT >3 × ULN	e-CRF specific tick box on the AE page
Thromboembolic events	Combined AESIs eCRF tick-box
Lymphoma	Combined AESIs eCRF tick-box
Anaphylaxis	Combined AESIs eCRF tick-box
Severe infusion related reactions.	Combined AESIs eCRF tick-box
Severe IMP injection or infusion site reaction	Combined AESIs eCRF tick-box
Severe infections including opportunistic infections	Combined AESIs eCRF tick-box
Tuberculosis or initiation of medications for suspected tuberculosis	Combined AESIs eCRF tick-box
Diagnosed and biologically proven SARS-CoV-2 infection	Combined AESIs eCRF tick-box
Inflammatory/infectious AEs	CMQ10176 [GLB_INFECTIONS], CMQsn00214 [Hypersensitivity Narrow], CMQ10122 [GLB_AUTOIMMUNE_DISORDERS][a]

a [The list of terms may be adjusted according to MedDRA version changes]

A listing of all AEs will be provided for participants treated but not considered as randomized, if any.

3.6.3 Additional safety assessments

3.6.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)

The following variables will be analyzed. They will be converted into standard international units and conventional unit, if applicable.

1. Laboratory variables (see Section 10.2 of the protocol): hematology, clinical chemistry, coagulation and urinalysis variables.

2. Vital signs (see Section 8.2.2 of the protocol): pulse, systolic and diastolic blood pressure (in sitting position), temperature, body weight, BMI
3. ECG variables (see Section 8.2.3 of the protocol): heart rate, PR, QRS, QT, and corrected QTc

Data below the Lower Limit Of Quantitation/detection limit (LLOQ) will be replaced by half of the LLOQ, data above the Upper Limit Of Quantification (ULOQ) will be replaced by ULOQ value.

For laboratory parameters, out-of-normal range definitions will be listed.

Quantitative analyses

For all laboratory variables, vital signs and ECG variables above, descriptive statistics for results and changes from baseline as appropriate will be provided for each planned visit. Descriptive statistics of changes from Baseline to last on-treatment value and from Baseline to worst on-treatment value will be presented for ECG and VS parameters and for selected laboratory parameters (leukocytes, neutrophiles, lymphocytes, thrombocytes and ALT) by intervention group. (It may also be done for other parameters, especially those with having a substantial number of PCSA values). These analyses will be performed using central measurements only (when available) for laboratory variables. For ECG, only data measured before or on the day of the last IMP administration will be included in the latter analysis.

For leukocytes, neutrophiles, lymphocytes, thrombocytes and ALT mean changes from baseline with the corresponding standard deviation will be plotted over time. For lymphocytes box-whisker plots over time will be provided in addition for raw data and change from baseline. Box-whisker plot could be performed for other parameters, especially for those having a substantial number of PCSA values. For ECG and vital signs parameters mean (+/-SD) will be plotted over time for raw data and change from baseline (percent change for PR and QRS).

Analyses according to PCSA

Potentially Clinically Significant Abnormality (PCSA) analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock. For laboratory parameters for which no PCSA criteria are defined, similar analyses will be done using out-of-normal ranges, if applicable. For lymphocytes a study specific criterion will be added: <0.5*10^9/L. For parameters defined as efficacy/PD endpoints, PCSA summaries will not be provided.

Analyses according to PCSA will be performed based on the worst value during the treatment-emergent period, using all measurements (either local or central, either scheduled, nonscheduled or repeated).

For laboratory variables, vital signs and ECG, the incidence of participants with at least one PCSA during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing

- Abnormal according to PCSA criterion or criteria

Listings of participants with PCSAs will be provided for laboratory variables, vital signs and ECG.

Additional analyses for potential drug-induced liver injury

If any, an intext listing of liver function tests data for participants with potential drug-induced liver injury ("ALT >3 ULN and Total bilirubin >2ULN" or "Direct bilirubin>35% of Total bilirubin and Total bilirubin >1.5 ULN") will be provided.

A graph of the distribution of peak values of ALT versus peak values of total bilirubin during the treatment-emergent period will be provided.

Additionally, listing of ALT increase documentation (including specific medical history, alcohol habits, associated signs and symptoms, trigger factors…) will also be provided for participants with one or more ALT increases greater than or equal to 2 ULN.

Listing of participants with QTc >480 msec and/or change from baseline QTc >60 msec

If any, a listing of participants with QTc >480 msec and/or change from baseline QTc >60 msec will be provided.

[redacted]

3.7 OTHER ANALYSES

3.7.1 Other variables and/or parameters

3.7.1.1 PK analyses

SAR441344 concentrations at selected time points will be reported using descriptive statistics and plotted. A listing of PK concentration will be provided, using "<LLOQ" for values below LLOQ.

PK parameters such as C_{max}, t_{max}, $t_{1/2z}$, and $AUC_{0\text{-}tau}$ will be estimated using a population PK approach. These parameters will be presented in a separate standalone report provided by Sanofi TMED M&S Department.

3.7.1.2 Immunogenicity analyses

Antidrug antibodies were assessed at baseline (before the first IMP administration), at Week 4, Week 8, Week 12, or premature EOT and at EOS (Week 24 or 12 weeks after premature EOT).

SAR441344 related ADAs positive samples will be classified as pre-existing ADA, treatment-induced ADA (ADA developed during the TE period, or positive sample during the post-treatment period preceded by less than 16 weeks by a treatment-induced ADA during the TE period) or treatment-boosted ADA (pre-existing ADA boosted to a significant higher titer than the baseline during the TE period, or boosted positive sample during the post-treatment period preceded by less than 16 weeks by a treatment-boosted ADA during the TE period).

Summary of ADA at baseline, listing of participants with treatment-emergent ADA and summary table of incidence will be provided for each SAR441344 related ADA variables on the ADA population. A summary of ADA at baseline and at each visit during the treatment-emergent period (including follow-up) might be provided depending on ADA incidence.

The impact of positive immune response on efficacy, PK and safety variables may be further explored, depending on ADA incidence.

3.7.1.3 Biomarkers analyses

Additional biomarker analyses other than described below, might be described, and reported separately.

Biomarker analyses will be performed on the biomarker populations.

3.7.1.3.1 Protein concentrations and flow cytometry data

3.7.1.3.1.1 Description of biomarkers

[redacted]

3.7.1.3.1.2 Analyses

[redacted]

[redacted]

Pharmacodynamics model

[redacted]

(SAR441344 [redacted]

[redacted]

[redacted]

Association between clinical efficacy endpoints and biomarkers

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

[redacted]

Results may be presented in a separate report.

3.7.1.4 PK/PD analyses

The analysis of PK/PD relationship will be described and reported separately.

3.7.2 Subgroup analyses

The primary analysis model using the MMRM for ESSDAI will be repeated by disease activity at baseline (high [ESSDAI ≥14] and moderate or low [ESSDAI ≤13]). Depending on the number of subjects per category and intervention group, a simpler model may be required, or no model may be presented for a category that is too small.

[redacted]

3.8 INTERIM ANALYSES

Internal decision making

An interim analysis for internal decision making may be implemented once approximately 50% of the planned participants have completed the study up to EoT (Week 12). The outcome may lead to study early termination, continuation without any changes, or continuation with changes.
A protocol amendment/amended protocol will be submitted for approval before any substantial changes to the study conduct are implemented. For this interim analysis, a Statistician, Programmer, and Clinical Study Director will work independently to the study team to ensure maintenance of blinding. A separate interim analysis plan for this interim analysis was written describing the list of analyses (further described in this SAP) to be performed at interim, and documenting the information of personnel to be unblinded.

Beside those described interim analyses, additional analyses for internal decision making might be conducted. For those analyses, if decided to do so, a Statistician, Programmer, and Clinical Study Director will work independently to the study team to ensure maintenance of blinding.

Analyses methods and conventions described in the other sections of this SAP will be applied for all analyses as applicable. The following additional rules will apply for analyses performed at interim analyses using a data cut-off date:

- Participants without end of treatment visit performed at the time of the cut-off date will be considered as ongoing and exposed up to the cut-off date. Therefore:
  - Participants who did not complete treatment period nor prematurely discontinued the study intervention at cut-off date will be analyzed as “ongoing” in the disposition summary.
  - Their TE period, treatment period and concomitant medication period will end at the cut-off date.
  - Their treatment duration will be derived by considering date of cut-off as last IMP date.
  - Analyses of duration of IMP administration will be performed up to the last IMP administration reported in the e-CRF up to the cut-off date.
- AEs occurring, worsening or becoming serious after the cut-off date will not be included in the analyses. However, any available outcome before database lock, regardless of timing in relation to the cut-off date, of an AE starting prior to the cut-off date will be taken into account. Medications, intervention discontinuations/completions and deaths occurring after the cut-off date will not be included in the analyses.

Early Analysis

The study analysis will be conducted in two steps. The first step analysis (early analysis) will be conducted once all randomized participants have completed their 12-weeks treatment phase ie, after the primary endpoint can been evaluated, to support sponsor decision making. Selected sponsor personnel including study statistician and study programmer will be unblinded to generate initial reports (early analysis) based on the final SAP.

The final analysis will be conducted after the end of the study.

3.9 CHANGES TO PROTOCOL-PLANNED ANALYSES

This section summarizes major statistical changes in the protocol amendment(s).

Major statistical changes in protocol amendment(s)

Amendment number	Approval date	Changes	Rationale
1	27-Aug-2020	9.2 Sample size determination: Assuming a variability of [redacted] and an effect size of [redacted], **as derived based on (38)**, a sample size of 80 evaluable participants results in an overall probability [redacted].	Reference is added for clarification.
2	28-Jul-2021	9.3 Populations for analyses: Table 5 - Populations for analyses: ~~Enrolled: All participants who sign the ICF.~~ **Screened: All participants who sign the ICF.** Randomized: ~~All enrolled participants who are randomly assigned to the IMP~~. **All participants from screened population who have been allocated to a randomized intervention (by IRT) regardless of whether the intervention was received or not. Participants treated with the study intervention without being randomized or before the randomization will not be considered as randomized.** **ADA: All randomized participants treated with SAR441344 with at least one post-baseline ADA result (positive, negative or inconclusive).**	Adaptation to follow current standards in population definition and adding a missing population (ADA) needed for analysis.
		9.5. Interim Analyses: ~~In all scenarios mentioned above~~ **For this interim analysis**, a Statistician, Programmer, and Clinical Study Director will work independently to the study team to ensure maintenance of blinding. ~~The~~ **A separate SAP for this interim analysis, if performed**, will describe the **corresponding** analyses to be performed at interim in greater detail, ~~if it is to be performed~~.	For clarification.

Amendment number	Approval date	Changes	Rationale
		9.5 Interim Analyses: **Once all participants have completed their EoT (Week 12) visit, selected sponsor personnel including study statistician and study programmer may be unblinded to generate initial reports (early analysis) based on the final SAP for internal decision making. Details of the personnel to be unblinded will be documented separately.**	Adaption to allow for internal decision making while keeping the blind once all subjects have completed their EoT visit.
3	05-Apr-2022	9.2 Sample size determination: **Approximately** ~~Up to~~ 88 participants are expected to be randomly assigned to the IMP, expecting a total of 80 evaluable participants with approximately 40 evaluable participants per group.	Adaption given the current drop-out rate is above the initial estimated 10%.
		9.3 Populations for analyses: In Table 5, row pharmacokinetic: All **randomized and treated participants (safety population) with adequate PK results** ~~without any important deviation related to IMP administration, for whom the PK data are considered interpretable~~. Participants having received only placebo will not be part of the PK population. **Participants will be analyzed according to the intervention they received.** In Table 5, row pharmacodynamic: All **randomized and treated** participants **(safety population) with at least one post-baseline PD data.** ~~no important deviations impacting PD measurements, for whom the PD data are considered sufficient and interpretable.~~ **Participants will be analyzed according to the intervention they received.**	Clarification.
		9.5. Interim analysis**:** **Beside those described interim analyses, additional analyses for internal decision making might be conducted. For those analyses, if decided to do so, a Statistician, Programmer, and Clinical Study Director will work independently to the study team to ensure maintenance of blinding.**	Adding the option of an additional analysis if needed for internal decision making throughout the study.

4 SAMPLE SIZE DETERMINATION

The sample size was derived with respect to the primary endpoint (mean change from Baseline to Week 12 in the ESSDAI score) for applying the Quantitative Decision Making approach as described by Quan et al (5).

Assuming a variability of [redacted] and an effect size of [redacted], as derived based on (38), a sample size of 80 evaluable participants results in an overall probability [redacted].

Up to 88 participants are expected to be randomly assigned to the IMP (randomization ratio [1:1]), expecting a total of 80 evaluable participants with approximately 40 evaluable participants per group.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

ACR: American College of Rheumatology
ADA: Anti-drug antibody
AE: Adverse event
AESIs: adverse events of special interest
[redacted]
BM: Biomarker
EOS: End of Study
EOT: End of Treatment
ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index
ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index
EULAR: European Alliance of Associations for Rheumatology
HLT: High level term
ICF: Informed consent form
[redacted]
IgG: Immunoglobulin G
[redacted]
IMP: Investigational medicinal product
IRT: Interactive Response Technology
IV: Intravenous injection
LLOQ: Lower limit of quantitation
LLT: Lower-level term
MedDRA: Medical dictionary for regulatory activities
MFI: Multidimensional Fatigue Inventory
[redacted]
PBMC: Peripheral Blood Mononuclear Cell
PCSA: Potentially clinically significant abnormality
PD: Pharmacodynamic
[redacted]
PK: Pharmacokinetic
PT: Preferred term
q2w: Once every two weeks
RF: Rheumatoid Factor
SAP: Statistical Analysis Plan
SC: Subcutaneous
SD: Standard deviation
SjS: Sjögren's Syndrome
SOC: System organ class

[redacted]

TE:	Treatment-emergent
TEAE:	Treatment-emergent adverse event
TMED M&S:	Translational Medicine & Early Development Modeling & Simulation
ULOQ:	Upper limit of quantitation
WHO-DD:	World Health Organization-drug dictionary

5.2 APPENDIX 2 PARTICIPANT DISPOSITION

The number (%) of participants included in each of the analysis populations listed in Table 3 will be provided.

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomized. The number (%) of screen failures and reasons for screen failures will be provided in the screened population.

The number (%) of participants in the following categories will be provided:

- Randomized participants
- Randomized but not exposed participants
- Randomized and exposed participants (ie, having a randomization number assigned and who received at least one administration of investigational medicinal product (IMP))
- Participants who completed the study treatment period as per protocol
- Participants who did not complete the study treatment period as per protocol and main reason for permanent intervention discontinuation
- Reason for study intervention withdrawal by subject
- Participants who completed the study period as per protocol
- Participants who did not complete the study period as per protocol and main reason for study discontinuation

Reasons for permanent study intervention and study discontinuation “adverse event” and “other reasons” will be split as related versus not related to COVID-19.

The number (%) of exposed and not randomized participants will also be summarized, if applicable.

In addition, the number (%) of participants screened, screened-failed, randomized, randomized and exposed, with permanent intervention discontinuation and with early study discontinuation will be provided by country and site.

Listings of participants with permanent study intervention discontinuation or with premature end of study (ie, who did not complete the study period as per protocol) will be provided for the safety population along with the main reason of discontinuations and related to covid or not, respectively.

A summary of visits impacted by COVID-19 pandemic will be provided along with the description of the impact (visit not done, visit partially done on site/by phone, visit done but delayed), if applicable. In addition, the number (%) for reasons for exclusion from COVID19 non-impacted population will be provided, if applicable. A listing of participants excluded from this population will be provided.

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be listed in the randomized population. They will be displayed separately as related versus not related to COVID-19. The list of predefined protocol deviations can be found in the eTMF (Trial management Section).

In case of more than 30 cases (or more than 5 deviations of one kind), critical and major protocol deviations (automatic or manual) will be summarized in the randomized population. In addition, the summary will be displayed separately as related versus not related to COVID-19, if applicable.

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

Demographics, baseline characteristics, medical surgical history

The following demographics and baseline characteristics, medical and surgical history and disease characteristics at baseline will be summarized using descriptive statistics. They will also be provided by ESSPRI stratum.

Demographic and baseline characteristics

Provided for safety population, and other analyses populations if deemed necessary,

- age in years as quantitative variable and in categories (18 to 45, 45 to 60, ≥60, as well as 18 to 64, 64 to 84)
- gender (Male, Female)
- race (American Indian or Alaska Native, Asian (plus origin reported by subject), Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple [if several races are selected for a participant])
- ethnicity [(Hispanic or Latino, not Hispanic or Latino)]
- weight
- BMI

Disease characteristics at baseline

Provided for efficacy population

- time since SjS first diagnosis in years
  - Where time since first diagnosis (years) = [date of ICF - date of diagnosis + 1] /365.25
- ACR (American College of Rheumatology)/EULAR score at screening
- ESSDAI score at screening and Day 1 (total ESSDAI score and ESSDAI score only based on 7 domains used for screening (Inclusion criteria I 04))

- ESSDAI activity levels by domain at screening and Day 1 (done for the 7 domains used for screening (Inclusion criteria I 04))
- Stratum (ESSPRI score ≥5 versus <5 at baseline)

Baseline safety and efficacy/PD parameters (apart from those listed above) will be presented along with the safety and efficacy/PD summaries.

Imputation of Date for first diagnosis in years

- If date partial, the imputation rules will be followed: If only the day is missing, the day will be imputed by the last day of month. If the day and the month are missing, the day and month will be imputed by 31DEC.

Medical and surgical history

Additionally, all medical and surgical history will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the MedDRA version currently in effect at Sanofi at the time of database lock. All medical history will be summarized by primary SOC and PT using a frequency table (number and % of participants) by study intervention group.

Prior or concomitant medications

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the participant used prior to first IMP intake. Prior medications can be discontinued before first administration or can be ongoing during study intervention period.
- Concomitant medications are any medications received by the participant concomitantly to the IMPs during the time period from the first administration of IMP to EOS.
- Post-treatment medications are those the participant took in the period running from the end of the concomitant medications period up to the end of the study.

A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

The prior and concomitant medications will be summarized for the safety population, by anatomic and therapeutic level. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. The summary of concomitant medication will be done in addition for medications for Sjögren's Syndrome by anatomic class and standardized medication name.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

Analysis windows for time points

For planned visits provided in the clinical database (Visit 1 to Visit 14), and for unscheduled assessments, visits will not be re-allocated. The only exception is visit 7 (Week 12/EOT) in case of early treatment termination.

- For safety parameters there will be no re-allocation of premature EOT visits. They will be summarized with completers of the treatment period in EOT visit.
- For efficacy, PD and biomarkers, premature EOT visits (EOT visit in case of early treatment termination) will be re-allocated to visits using analysis windows defined in Table 8. These re-allocated visits will be used in all by-visit analyses.

Visit re-allocation using analysis windows:

The analysis windows in Table 8 determine the re-allocation visit for the premature EOT visits, to allow comparable conditions based on number of dosings and time from first dosing for these premature EOT visits in the analyses.

After applying these time windows, if multiple assessments are associated to the same time point, the closest from the targeted study day will be used. If the difference is a tie, the value after the targeted study day will be used. If multiple valid values exist within a same day, then the first value of the day will be selected when time is available, otherwise the scheduled exam will be used.

If there is no measurement for a given parameter in an analysis window, data will be considered missing for the corresponding visit. (For handling of missing data, see the corresponding sections of the parameters.)

Table 8 - Analyses window definition for efficacy, biomarkers & PD parameters for premature EOT

Study period	Scheduled visit post baseline	Targeted study days	Analysis window in study days for assessments on Week 4, 8, 12 only	Analysis window in study days for assessments on Week 4, 12 only	Analysis window in study days for assessments on Week 12 only
Treatment Period	Week 4 (Visit 3)	29 (27 to 31)	15 to 40	15 to 40	
	Week 8 (Visit 5)	57 (55 to 59)	41 to 68		
	Week 12 (Visit 7)	85 (83 to 87)	69 to 113	41 to 113	41 to 113
Follow-up Period	Week 24 (Visit 14)	169 (+/-4)	114 to 182	114 to 182	114 to 182

Study days are calculated considering Day 1 as the day of first administration of intervention (or the day of randomization for participant not exposed).
Data more than 32 days after last IMP are excluded from efficacy, PD and biomarker analyses up to EOT/Week 12 visit
For efficacy, PD and biomarkers with early treatment discontinuation, the premature EOT will be re-allocated to the next planned visit after drop-out according to analysis windows presented above.

Intercurrent Events

[redacted] (see Table 4), [redacted]

[redacted]

[redacted]

General data handling conventions

Unscheduled visit measurements of efficacy, laboratory data, electrocardiogram, vital signs, biomarkers and ADA will be used, in particular for computation of baseline, the last on-treatment value, analysis according to PCSAs, and the shift summaries for safety.

For parameters with evaluations before administration of IMP and in cases of rechecked value(s) for one participant, only the last observation will be used as baseline in descriptive statistics and derivations of other parameter values. After baseline, only observations planned in the protocol will be used in descriptive statistics by visit.

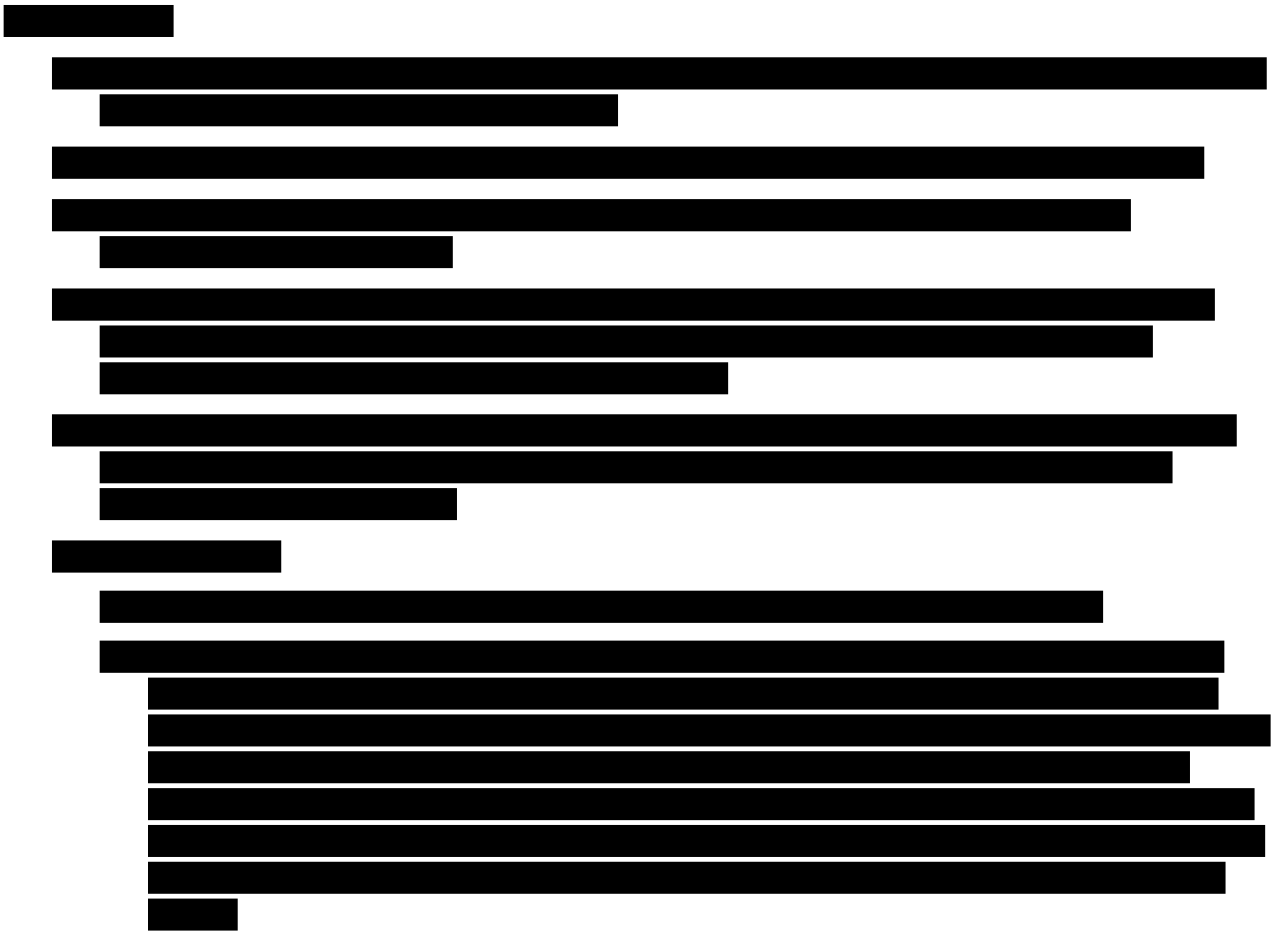
For clinical laboratory parameters (including PD biomarkers) with nonnumeric values, the imputed values used for the descriptive statistics and/or the flags will be determined by considering the following rules:

1. If database value is ‘ <X’, the value used will be X/2
2. If database value is ‘ >X’, the value used will be X
3. If database value is a range (eg, ‘X – Y’), the values used will be (Y + X)/2

Efficacy

- The baseline is the last evaluable non-missing value prior to the first dose of IMP unless otherwise specified. Note: Single domains/(sub)scales of efficacy parameters may have baseline on a different visit than the overall score.
- Until EOT visit, only results until 32 days after last IMP will be used in the analyses.
- EOS visits will only be included (if available) in descriptive statistics and not in efficacy models.

- Missing data:
  - No imputation will be done for descriptive statistics
  - No imputation will be done prior to modeling, unless noted otherwise. MMRM will be used to take care of missing values in modeling (assuming MAR), where applicable.
- Total scores/indices will only be calculated if none of the domains/criteria used for the total score/index is missing.
- Hematology domain values entered in the eCRF based on planned or unscheduled (central or local) lab values will be used in the primary analysis, if they are done within 16 days of the planned visit (and prior to the next dosing). During blinded data review, major deviations will be entered in case the lab samples used for hematology domain were taken more than 16 days from planned visit (or after another IMP dosing), or in case of missing value. For screening, D1 and EOS sampling 32 days after planned visit are allowed without resulting in a major deviation, provided they were done in the same dosing condition (pre-dose for screening and D1).



Pharmacokinetic analysis

Plasma concentrations will be summarized by time point using descriptive statistics such as the number of observations arithmetic mean, geometric mean, SD, SEM, CV (%), minimum, median and maximum.

For ease of presentation, mean values will be arithmetic mean unless specified. Plasma concentration values below the plasma assay limit will be treated as zero in calculating mean values. Mean values below the lower limit of quantification (LLOQ) will be reported as "<LLOQ" in the tables and not plotted in the figures if after C_{max}.

Plasma concentrations and pharmacokinetic parameters of SA441344 will be summarized by arithmetic mean, geometric mean, SD, SEM, CV (%), minimum, median, maximum, and number of observations.

5.5 APPENDIX 5 QUESTIONNAIRES

5.5.1 ESSDAI

Table 10 - ESSDAI domains and weights

Domain	Weight	Activity level				Maximum score/domain
Constitutional [a]	3	No=0	Low=1	Moderate=2		6
Lymphadenopathy [a]	4	No=0	Low=1	Moderate=2	High=3	12
Glandular [a]	2	No=0	Low=1	Moderate=2		4
Articular [a]	2	No=0	Low=1	Moderate=2	High=3	6
Cutaneous	3	No=0	Low=1	Moderate=2	High=3	9
Pulmonary	5	No=0	Low=1	Moderate=2	High=3	15
Renal	5	No=0	Low=1	Moderate=2	High=3	15
Muscular [a]	6	No=0	Low=1	Moderate=2	High=3	18
PNS	5	No=0	Low=1	Moderate=2	High=3	15
CNS	5	No=0		Moderate=2	High=3	15
Hematological [a]	2	No=0	Low=1	Moderate=2	High=3	6
Biological [a]	1	No=0	Low=1	Moderate=2		2

a Domains rated for inclusion reaching an ESSDAI score ≥5 according to Inclusion criterion I04
ESSDAI definitions published in 2010 (6)

[redacted]

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