16.1.9. Documentation of statistical methods

Hardware and software tools

Statistical analysis plan

Statistical analyses were performed using SAS®/PC Software version 9.4.

Coding was performed using Medical Dictionary for Regulatory Activities for the medical events and World Health Drug Dictionary for the treatments.

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Document title	**STATISTICAL ANALYSIS PLAN (SAP)**
Full title	**A phase IIa efficacy and safety trial with intravenous S95011 in primary Sjögren's Syndrome patients.** **An international, multicentre, randomised, double-blind,placebo-controlled study.**
Short title	**Efficacy and safety of S95011 in primary Sjögren's Syndrome patients.**
Acronym	**Not applicable**
Test drug code	**S95011**
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INSTITUT DE RECHERCHES INTERNATIONALES SERVIER
Siège social - 50, rue Carnot - 92284 Suresnes cedex - France - Tél. 01.55.72.60.00 - www.servier.com
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List of abbreviations

Ab	Antibody
ADA	Anti-Drug Antibody
AE	Adverse Event
ANA	Anti-Nuclear Antibodies
Anti-SSA (Ro)	Anti-Sjögren's Syndrome related antigen A Antibodies
ASSE	Selection visit
BMI	Body Mass Index
b.p.m	beats per minute (heart rate unit)
CD127	interleukin-7 receptor-α
CI	Confidence Interval
cm	Centimetre
CPMP	Committee for Proprietary Medicinal Products
CRO	Contract Research Organisation
CSR	Clinical Study Report
D	Day
DAP	Data Analysis Plan
DBP	Diastolic blood pressure
e-CRF	Electronic Case Report Form
ECG	Electrocardiogram
e.g.	Exempli gratia (for example)
ERIN	Event Requiring Immediate Notification
ESSDAI	EULAR Sjögren's Syndrome Disease Activity Index
ESSPRI	EULAR Sjögren's Syndrome Patient Reported Index
ESR	Erythrocyte Sedimentation Rate
EULAR	European League against Rheumatism
FU	Follow-up (period)
GCP	Good Clinical Practice
ICF	Information Consent Form
ICH	International Conference on Harmonisation
i.e.	id est (that is)
IE	Intercurrent Event
IL-7	Interleukin 7
IL-7Rα	Alpha chain of the Interleukin 7 (IL-7) Receptor (=CD127)
IMP	Investigational Medicinal Product (S95011/Placebo)
I.R.I.S.	Institut de Recherches Internationales Servier
IV	Intravenous
IWRS	Interactive Web Response System
kg	kilogram
L	Litre
LLN	Lower Limit of Normal laboratory reference range
LLOD	Lower Limit Of Detection
LLOQ	Lower Limit Of Quantification
LLS	Lower Limit used to define potentially clinically Significant abnormal values
MAR	Missing At Random

MFI	Multidimensional Fatigue Inventory
mg	milligram
min	minute
mL	Millilitre
mm	Millimetre
mmHG	Millimetre of mercury
MNAR	Missing Not At Random
NRS	Numerical Rating Scale
NSAID	Non-steroidal anti-inflammatory drugs
OSS	Ocular Staining Score
PBMCs	Peripheral Blood Mononuclear Cells
PD	Pharmacodynamics
PK	Pharmacokinetics
PGA	Patient's global assessment
PhGA	Physician's global assessment
PSS	Primary Sjögren's Syndrome
QoL	Quality Of Life
RF	Rheumatoid Factor
RNA	RiboNucleic Acid
RO	Receptor Occupancy
RS	Randomised Set
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SF-36	Short Form Health Survey
SSA	Sjögren's syndrome A
STAR	Sjogren's Tool for Assessing Response
TEAE	Treatment Emergent Adverse Event
TLG	Tables Listings and Graphs
TU	Therapeutic Units
ULN	Upper Limit of Normal laboratory reference range
ULS	Upper Limit used to define potentially clinically Significant abnormal values
ULOD	Upper Limit Of Detection
W	Week
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan deals with the main analysis of the study (ASSE-W013 period) and the follow-up period (ASSE-W028) and details the planned analyses to be performed, in accordance with the main characteristics of the amended study protocol version 4.0 dated from 24/03/2022.

The templates for Tables, Listings and Graphs (TLG) are described in a separate document.

The main analysis of the study concerns the ASSE-W013 period and will be performed as soon as all efficacy and safety data of the ASSE-W013 period are available and the mandatory steps required for study unblinding have been performed. The descriptive analysis including data after W013 will be performed subsequently when all data are available.

Of note, this SAP does not cover analyses of data associated to some exploratory objectives and the pharmacokinetics and pharmacodynamics data analyses described in the study protocol.

1.1. Study objectives and endpoints

1.1.1. Objectives

The purpose of this trial is to assess the efficacy and safety of multiple intravenous infusions of 750 mg of S95011 versus placebo as well as tolerability, pharmacokinetics and pharmacodynamics in patients with primary Sjögren's syndrome (pSS). The results of this first study in patients with primary Sjogren's syndrome will be informative for further development in treatment of pSS.

The primary objective of the study is to assess the effect of multiple intravenous infusions of 750 mg of S95011 compared to placebo after 13 weeks of treatment in reducing disease activity using European League against Rheumatism (EULAR) Sjögren Syndrome Disease Activity Index (ESSDAI).

The secondary objectives are:

- To evaluate efficacy of multiple intravenous (IV) infusions of 750 mg of S95011 compared to placebo after 13 weeks of treatment on:
  - Patient's symptoms using EULAR Sjögren Syndrome patient reported Index (ESSPRI).
  - Disease activity using Sjogren's Tool for Assessing Response (STAR).
  - Disease activity using Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS).
  - Fatigue using the Multidimensional Fatigue Inventory (MFI).
  - Quality of life (QoL) using Short Form Health Survey (SF-36).
  - Physician's global assessment (PhGA) of the disease activity using a 0 to 10 numerical rating scale (NRS).
  - Patient's global assessment (PGA) of the disease activity using a 0 to 10 numerical rating scale (NRS).
  - Tear gland function using the Schirmer test.
  - Tear gland function using Ocular Staining Score (OSS).
  - Salivary gland function measured by sialometry under unstimulated and stimulated conditions.
- To assess the safety and tolerability of multiple intravenous infusions of S95011.
- To assess the pharmacokinetics (PK) of S95011 in serum.
- To assess pharmacodynamics [receptor occupancy (RO)] of S95011 in blood.
- To determine the incidence of anti-drug antibodies (ADA) formation.

The exploratory objectives of the study are:

- To explore the potential effect of S95011 on lymphocytes subsets in particular T cell subsets.
- To explore the potential effect of S95011 on some proteins involved in pSS physiopathology like Interleukin 7 (IL-7), cytokines and specific proteins in blood.
- To explore the potential effect of S95011 on immune panel, β2 microglobulin, and on the auto-antibody panel: Anti-Sjögren's Syndrome related antigen A (anti-SSA (Ro)) antibodies, anti-nuclear antibodies (ANA) and rheumatoid factor (RF).
- To explore drug exposure and perform exploratory histology and exploratory biomarkers assessments on minor salivary glands tissue by performing lip biopsies (optional).
- To set a biocollection to explore further the potential impact of S95011 on Peripheral Blood Mononuclear Cells (PBMC), extracted RiboNucleic Acid (RNA) and blood according to the advancement of the knowledge on the drug and the disease (optional sampling) (not covered by the SAP).

1.1.2. Endpoints

The primary efficacy endpoint is the change from baseline in ESSDAI total score to W013.

The secondary efficacy endpoints are:

- ESSDAI score by domain and total score at each visit (value & change).
- ESSPRI score by symptom and total score at each visit (value & change).
- Proportion of patients with ≥ 3 points, ≥ 5 points, ≥ 7 points of improvement from baseline in ESSDAI at each visit.
- Proportion of patients with ≥ 1 point, ≥ 2 points, ≥ 3 points of improvement from baseline in ESSPRI at each visit.
- Proportion of patients with ≥ 3 points of improvement in ESSDAI and with ≥ 1 point of improvement in ESSPRI from baseline at each visit.
- Proportion of patients with a STAR total score ≥5 at each visit (value).
- Proportion of patients with a CRESS total score ≥3 at each visit (value).
- Fatigue (MFI) by domain, quality of life (SF-36) for mental and physical domains, physician and patient's global assessment of the disease activity (NRS) at each visit (value and change).
- Tear gland function: Schirmer's test and in OSS on the most affected eye and for the mean of both eyes at each visit (value and change).
- Salivary gland function: unstimulated and stimulated salivary flow rate at each visit (value and change).

The other secondary endpoints are:

- **Safety:** The safety and tolerability assessed by incidence of adverse events (AEs), change over time in safety parameters (vital signs, biological laboratory) and incidence of abnormal safety parameters throughout the study.
- **Pharmacokinetics:** Pharmacokinetics of S95011 in serum samples:
  - Pre-dose (before the start of the IMP infusion) at W000, W002, W004, W007, and W010.
  - Right after the end of the IMP infusion and in the [1-3h] interval after the end of the IMP infusion at W000 and W010.
  - Between W011 and W012, and at W013, W016, W019 and W028.

- **Pharmacodynamics:** Receptor Occupancy (RO) of S95011 in blood samples:
  - Pre-dose (before the start of the infusion) at W000, W002, W004, W007 and W010.
  - Right after the end of the infusion of the IMP at W000 and W010.
  - At W013, W019, W028.
- **Incidence of ADA** in serum samples:
  - Pre-dose (before the start of the infusion) at W000, W002, W004, W007 and W010.
  - At W013, W019, W028.

The exploratory endpoints are:

- **In blood:**
  - Lymphocytes subsets (PBMC) assessed at W000, W004, W007, W013.
  - IL-7 and some cytokines measured at W000, W002, W004, W007, W010, W013, W019, W028.
  - Other specific proteins involved in the pSS physiopathology will be measured at W000, W004, W013.
  - Cytokine release panel at W000 and W002.
  - Immune panel at ASSE (Selection visit), W000, W004, W013.
  - Auto antibody-panel at ASSE, W013.
  - β2 microglobulin at W000, W004, W013.
- **In salivary glands:**
  - Lip biopsy for salivary gland collection (S95011 concentration, exploratory histology and exploratory biomarkers assessments) (optional biopsy at W013).

1.1.3. Study design

The study CL2-95011-001 is a phase IIa, international, multicentre, randomised (2:1), double-blind, placebo-controlled study with two parallel groups (S95011 750 mg and placebo).

1.1.4. Study plan

The study is divided into the following periods:

- **Screening period without study treatment:** from selection visit (ASSE within 28 days prior to W000) to inclusion visit (W000), after signing the ICF, in order to check eligibility of patients.
- **Randomised and double-blind treatment** period: from W000 to W013 (study drug administration at W000, W002, W004, W007, W010) with two-parallel groups (750 mg of S95011 and matching placebo), with stratification by baseline intake of oral corticosteroids (yes/no) and baseline intake of antimalarial (*e.g.* chloroquine, hydroxychloroquine, quinacrine) (yes/no).
- **Safety follow up period without study treatment**: 15 weeks with one visit at W019 and one at W028. This follow-up period will allow sufficient time for monitoring safety until 5 half-lives of S95011. In addition, it is anticipated that more than 97% of patients have RO < 95% at W028 (meaning that almost no pharmacological effect of the product is expected).

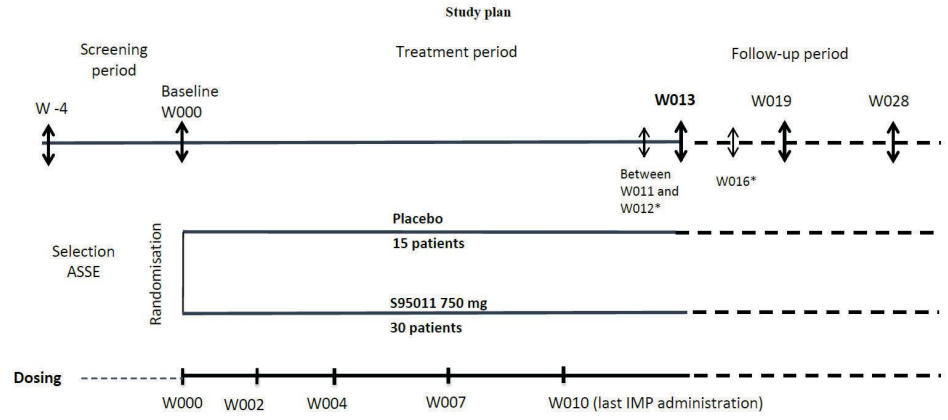
The expected duration of patient participation will be 32 weeks maximum.

Study treatments are supplied as follows:

- **During the screening period (from ASSE to W000),** no treatment will be dispensed.
- **From the day after inclusion until the day of W013 visit**, patients take one (1) IV infusion of 750 mg of S95011 or matching placebo every two weeks (q2w) for the first month (W000, W002, W004) and then every 3 weeks (q3w) until W010 (W007, W010). S95011/matching placebo will be provided to the site in 2 mL extractable volume vials containing 100 mg of S95011/matching placebo (50 mg/mL) concentrate for solution for intravenous administration. As treatment is dispensed during a double-blind period, the appearance and form of S95011 vials and placebo vials as well as the solutions to be administered will be similar: a colourless to slightly yellow, clear to slightly opalescent aqueous solution.
- **From the day after W013 visit until the day of W028 visit**, follow-up period.

The study plan is shown in Figure (1.1.4) 1.

Figure (1.1.4) 1 - Study plan



*One blood sample will be performed for PK assessment between W011 and W012 and at W16 (± 5 days), at site or not according to local facilities.

1.1.5. Type of randomization

The treatment randomization and allocation are centralized using an Interactive Web Response System (IWRS) procedure. The treatment (S95011 750 mg or placebo) is assigned at inclusion visit by a non-balanced 2:1 ratio, non-adaptive randomization with stratification by baseline intake of oral corticosteroids (yes/no) and baseline intake of antimalarials (*e.g.:* chloroquine, hydroxychloroquine, quinacrine) (yes/no).

1.2. Determination of sample size

The following efficacy criteria are defined:

- A statistically significant reduction in ESSDAI at W013 in the S95011 group compared to placebo, at the one-sided 10% significance level.
- An estimated mean reduction in ESSDAI in the S95011 group to be 3 points or greater than placebo. The decrease of 3 points was chosen because it is considered as clinically minimal relevant decrease (Seror *et al*, 2016).

Targeted sample size

With 45 patients in the primary analysis of the primary estimand (30 in the S95011 group and 15 in the placebo group), the study would have around 5% chance of having a false-positive result, *i.e.*, of meeting both the efficacy criteria when the true difference between S95011 and placebo is zero. Additionally, the chances of meeting both the efficacy criteria remain below 14% for true differences between S95011 and placebo of less than 1 point.

The study would have approximately 70% chance of meeting both the efficacy criteria, when the true difference between S95011 and placebo is 4 points. In case the true difference between S95011 and placebo is only 3 points, the study would have approximately 50% chance of meeting both the efficacy criteria. These calculations assume that the primary efficacy endpoint, change from baseline in ESSDAI, follows a normal distribution with a standard deviation of 6. This estimate of the standard deviation is based on some clinical studies (Fisher *et al*, 2020, UCB5857, RO5459072) in patients with primary Sjögren's syndrome in which the observed standard deviation ranged from around 4 to 6.

Blinded standard deviation reassessment

The similar operational characteristics (false-positive and right-positive rates) are obtained with 20 patients in S95011 group and 10 patients in placebo group under assumption of an overall standard deviation of primary efficacy endpoint of 5. So only if the recruitment is much longer than expected, when 30 patients will have completed the 13-week treatment period, the overall standard deviation of the primary endpoint on non-comparative data could be calculated. If the value is less or equal to 5, the sponsor could stop the patient recruitment, considering that the number of patients is sufficient to meet both efficacy criteria. This potential adaptation has very little or no impact on the probability of having a false-positive result (Kieser, 2003).

2. ANALYSIS SETS / TREATMENT GROUPS

2.1. Analysis sets

- **Randomised Set (RS):**
  All included patients to whom a therapeutic unit (TU) was randomly assigned using IWRS.
- **Safety Set (SS):**
  All patients having taken at least one dose of IMP.
- **Biomarker Set (BMKS):**
  All patients of the RS having at least one available result for any biomarker.

2.2. Treatment groups

Treatment groups considered will be S95011 (750 mg) and placebo.

They will correspond to treatment received at inclusion visit.

In the unlikely event of a patient receiving an incorrect Therapeutic Unit (TU) at a particular post-W000 visit on the 13-week double-blind treatment period, which would result in a switch of treatment group, the patient will be considered in the treatment group corresponding to their TU(s) received until the switch. Their data recorded from the switch will be managed according to the considered estimand. All safety data and IMP administration data of the patients with a switch of treatment group will be listed separately.

3. GENERAL STATISTICAL CONSIDERATIONS

3.1. Descriptive statistics

Descriptive statistics will be provided by treatment group, and all treatment groups pooled (for analyses on disposition of patients, baseline characteristics and patient follow-up, and on adverse events).

For **qualitative data**, number of observed values, number and percentage of patients per class will be presented. Unless otherwise specified in the TLG, no class "Missing" is considered.

For **quantitative data**, number of observed values, mean, standard deviation, median, first and third quartiles, minimum and maximum will be presented.

For **event data**, number of patients having experienced the event (n) and number of events that occurred (for AE analyses only) (NAE) will be presented.

3.2. General definitions

Patients having taken at least one dose of IMP correspond to patients with at least one date of first and/or last IMP intake complete or partially complete.

Analysable value will be defined as any non-missing value, except for:

- Laboratory parameters:
  - A laboratory value is considered as analysable if non-missing and not flagged in the ClinTrial database as "not analysable".
  - Vital signs value is considered as analysable if collected under appropriate circumstances (corresponds to the item of the source database).

Baseline value will be defined as the last analysable value prior to the first IMP intake. In case of patient included and/or randomised but not having taken at least one dosage of IMP: value at baseline is defined as the last analysable value prior or equal to date of inclusion visit.

Considered periods are:

- ASSE-W013 period.
- ASSE-W028 period.

Last post-baseline value under treatment of the period will be defined as the last post-baseline analysable value under treatment during the considered period.

Change from baseline to post-baseline visit is calculated as: Value at the post-baseline visit - Value at baseline.

Change from baseline to post-baseline visit under treatment is calculated as: Value at the post-baseline visit under treatment - Value at baseline.

Change from baseline to last post-baseline value under treatment is calculated as: Last post-baseline value under treatment - Value at baseline.
For safety endpoints (except adverse events), the following definition will be applied:

- **High emergent abnormal value under treatment according to the laboratory reference** ranges is defined as value ≤ ULN (Upper Limit of Normal laboratory reference range) or missing at the baseline of the treatment period and > ULN under treatment.
- **Low emergent abnormal value under treatment according to the laboratory reference** ranges is defined as value ≥ LLN (Lower Limit of Normal laboratory reference range) or missing at baseline of the treatment period and < LLN under treatment.

- **High emergent abnormal value under treatment according to the cut-offs for PCSA** values is defined as value ≤ ULS (Upper Limit used to define potentially clinically Significant abnormal values) or missing at baseline of the treatment period and > ULS under treatment.
- **Low emergent abnormal value under treatment according to the cut-offs for PCSA** values is defined as value ≥ LLS (Lower Limit used to define potentially clinically Significant abnormal values) or missing at baseline of the treatment period and < LLS under treatment.

Other calculation rules for general definitions (such as value prior to treatment / under treatment, first and last IMP intake dates…), are provided in Appendix 7.1.

4. STATISTICAL ANALYSES

Specific definitions and calculation rules are provided in Appendix 7.2

4.1. Study participant

4.1.1. Disposition

The size of each analysis set, and reasons for exclusion will be described.

Disposition of patients, including reasons for withdrawal, will be summarized during the study, overall and by visit, in the RS.

4.1.2. Protocol deviations

Protocol deviations before or at inclusion, as well as after inclusion, will be described in the RS for each considered period.

For the description of important protocol deviations, the 6 following categories are considered in accordance with ICH E3 guideline and ICH E3 Q&A:

- Selection/inclusion criteria not fulfilled.
- Patient having withdrawal criteria but not withdrawn.
- Incorrect treatment or dose received.
- Forbidden concomitant treatment.
- Endpoint assessment possibly affected.
- Safety possibly affected.

4.1.3. Demographic data and baseline characteristics

Demographic characteristics and other baseline characteristics will be summarized as follows, by treatment group and overall, in the RS:

- Demographic characteristics:
  - Age (years).
  - Sex: male / female.
  - Race: White / American Indian or Alaska Native / Asian / Black or African American / Native Hawaiian or other Pacific Islander / Other.
  - Ethnicity: Hispanic or Latino / not Hispanic or Latino.
  - Life habits:
    - Smoking (excluding e-cigarette): Never / Has stopped smoking / Current smoker.
    - E-cigarette: Yes / No.
    - Alcohol: No / Has stopped drinking / Currently drinking.
    - Caffeine: Yes / No.
- Baseline characteristics:
  - History of the primary Sjögren's syndrome:
    - Disease duration (years) and by class: ≤ 7 years / > 7 years.
    - Specific treatment for pSS for which a stratification was done at baseline Nothing / Oral corticosteroid / Antimalarial / Oral corticosteroid and antimalarial.
  - Relevant medical and surgical history other than the PSS symptoms (by SOC and PT).
  - Specific previous treatment (by ATC code and preferred name).
  - Non-specific previous treatment (by ATC code and preferred name).
  - ESSDAI total score overall and in severity classes: Mild < 5 / Moderate [5 – 14[/ Severe ≥ 14.

- ESSDAI by domain: Constitutional / Lymphadenopathy and lymphoma / Glandular / Articular / Cutaneous / Pulmonary / Renal / Muscular / PNS / CNS / Haematological / Biological.
- ESSPRI total score overall and in classes: < 5 / ≥ 5.
- ESSPRI by symptom: Dryness / Fatigue / Pain.
- SF-36 physical and mental scores.
- MFI by domain: General fatigue / Physical fatigue / Reduced activity / Reduced motivation / Mental fatigue.
- NRS: PhGA score and PGA total score.
- Schirmer test for the most affected eye and mean of both eyes.
- OSS for the most affected eye and mean of both eyes.
- Sialometry (stimulated and unstimulated salivary flow score).
- Weight (kg).
- Body temperature (°C).
- BMI (kg/m2) and by class: < 18.5, [18.5-25[, [25-30[, ≥ 30.
- SBP (mmHg).
- DBP (mmHg).
- HR (b.p.m).

4.2. Treatments of patients

4.2.1. Extent of exposure and treatment compliance

Number and percentage of patients by total number of infusions and time between two IMP administrations by visit will be described by treatment group in the RS and SS (if different).

4.2.2. Concomitant treatments

All specific (resp. non-specific) concomitant treatments taken at inclusion, during the W000-W013 period, and after the last IMP intake will be described in the RS and the SS (if different), by ATC code and preferred name and by treatment group.

4.3. Efficacy analyses

Calculation rules for efficacy endpoints and other specific definitions are provided in Appendix 7.2.2.

4.3.1. Primary efficacy estimand

The primary estimand of interest is the effect of the treatments on the clinical disease activity in all patients assuming non-occurrence of intercurrent events (IE). The motivation for this choice is to assess at this proof-of-concept stage the full efficacy potential, that is, the pharmacologic effect of the S95011 if all patients adhere to it (without any intercurrent events).

The attributes of the primary estimand are defined as follow:

- Treatment: S95011 or placebo.
- Population: RS.
- Variable: change in ESSDAI total score from baseline to W013 (primary efficacy endpoint).
- Summary measure: difference in means between treatments.
- Intercurrent events (IE):
  - IE1: Study drug discontinuation for major worsening of primary Sjögren's syndrome.
  - IE2: Increase or initiation of authorized medication for pSS.
  - IE3: Study drug discontinuation for AE related to study drug.

- IE4: Study drug discontinuation for other reasons (non-medical reason, AE not related…).
- IE5: Switch of treatment group (error of dispensation).
- IE6: Decrease or stop of authorized medication for pSS.

The rate of IEs is assumed to be below 10%. They will be handled by a hypothetical strategy to estimate what the outcome would have been at the designated time point if no IE would have occurred through that time point, considering that patients with IE would have efficacy outcomes as patients, in their treatment group, who continue their treatment without IE.

Note: In case a patient is concerned by several IEs, the first event will be considered. If several IE occurred the same day, IE will be considered to be more conservative in the following order: IE1; IE2; IE3; IE4; IE5, IE6.

4.3.1.1. Primary analysis

Primary analysis will be done on RS.

Definition: the primary efficacy endpoint is defined as the change from baseline to W013 in ESSDAI total score. The ESSDAI total score is calculated as the weighted sum of 12 items of the scale in ClinTrial database.

Primary analysis: to assess the efficacy of S95011 (750 mg) as compared to Placebo on change from baseline to W013 in ESSDAI total score after a 13-weeks treatment, using a General Linear Model including the fixed, categorical effect of treatment and randomisation stratification factors (rando_factor) as well as the continuous fixed covariate of baseline value. The randomisation stratification factors are baseline intake of oral corticosteroids (yes/no) and baseline intake of antimalarial (yes/no)

GENERAL LINEAR MODEL: change = baseline rando_factors treatment [1]

The assumptions underlying the model, as for instance, the normality and homoscedasticity of residuals and detection of outliers will be checked. The assumptions of normality and homoscedasticity of residuals will be investigated using some graphs and descriptive statistics. The detection of outliers will be done using graphics.

If the model is not running due to too few patients in the stratas, the model mentioned above will be modified. Thus, the two stratification factors in the model will be replaced by the following composite factor: baseline intake of oral corticosteroids or antimalarial or both (yes/no). If the model is still not running with the stratification factor in two classes, then the stratification factor will not be considered.

Statistical hypotheses:
Let μ_0 and μ_1 be the population means of the change from baseline in ESSDAI total score at W013 (primary endpoint) under placebo and S95011, respectively.

The statistical hypotheses that will be tested are:

$$H_0: \mu_0 \geq \mu_1 \text{ (S95011 is not superior to placebo)}$$
versus
$$H_1: \mu_0 < \mu_1 \text{ (S95011 is superior to placebo)}$$

The type I error of the statistical tests will be set at 10% for unilateral situation, which is consistent with the objective of demonstrating the superiority versus placebo.

Missing data/intercurrent events handling: the primary analysis for the primary estimand will be conducted using only data obtained prior to IEs. Observed post IE values will not be used in the primary analysis. Post IE values will be imputed according to the MAR assumption (multiple imputation by treatment group). This is aligned with the primary estimand and the hypothetical strategy. Missing data not linked to intercurrent events will be imputed according to the MAR assumption with a multiple imputation by treatment group. The imputation method is detailed below and in Appendix 7.3.1. A patient with all visits missing or only baseline missing will not be considered in the analysis.

Multiple imputation inference involves 3 consecutive phases.
1/ Imputation step:
A total of 100 imputed complete data sets will be generated.

The imputation step for missing data as well as data considered as missing for the primary analysis due to the strategy used to handle intercurrent event will be the same and applied to data with a monotone pattern. For all patients, the regression method (adjusted on randomisation stratification factors, baseline and considering all longitudinal data of planned visits) will be used separately for each treatment arm to impute missing data (*i.e.* based on patient completers under corresponding treatment arm) under MAR approach.

It is of note that for missing data with an arbitrary missing pattern, the first imputation step might be preceded by one MI approach based on MCMC method using baseline and all longitudinal data by treatment groups.

If the regression method for imputation is not running due to too few patients in the stratas, the model mentioned above will be modified. Thus, the two stratification factors in the model will be replaced by the following composite factor: baseline intake of oral corticosteroids or antimalarial or both (yes/no). If the model is still not running with the stratification factor in two classes, then the stratification factor will not be considered.

2/ Analysis step:
The same model as [1] (described above) will be applied to each of the 100 imputed datasets.

3/ Combination step:
Statistical inferences will be generated by combining results from the 100 analyses using Rubin's formulae. The multiple imputation estimator of the difference between S95011 and placebo is the average of the individual 100 estimators. The variance of the estimator is the combination of the between- and within-imputation variability (Carpenter and Kenward, 2007).

Multiplicity handling: there is no multiplicity issue.

Statistical elements: Finally, the following elements will be provided in a summary table:
- Estimate (standard error) of the difference between adjusted treatment arm means.
- Two-sided 80% CI of the estimate.
- Two-sided 95% CI of the estimate.
- One-sided p-value.

4.3.1.2. Sensitivity analyses

Sensitivity analysis will be done on RS.

Sensitivity analysis: the same analysis as the primary analysis will be performed using model [1] except the fact the missing data/ intercurrent event handling will be different.

Missing data/intercurrent events handling: in order to assess the sensitivity to the missing at random (MAR) assumption, values post the following IEs:

- IE1: Study drug discontinuation for major worsening of primary Sjögren's syndrome.
- IE2: Increase or initiation of authorized medication for pSS.
- IE3: Study drug discontinuation for AE related to study drug.

will not be taken into account and will be imputed according to the missing not at random (MNAR) assumption.

The other IEs and missing data will be handled as in the primary analysis. The imputation method is detailed below and in Appendix 7.3.2. A patient with all visits missing or only baseline missing will not be considered in the analysis.

Note: In case a patient is concerned by several IEs, the first event will be considered. If several IE occurred the same day, IE will be considered to be more conservative in the following order: IE1; IE2; IE3; IE4; IE5, IE6.Multiple imputation inference involves 3 consecutive phases.

1/ Imputation step:

A total of 100 imputed complete data sets will be generated.

The imputation step for missing data with a monotone pattern will be:

- For all data following study drug discontinuation for major worsening of primary Sjögren's syndrome (IE1), the values of outcome will be imputed using a reference based multiple imputation ("jump to placebo" approach) for S95011 group and using multiple imputation (MAR) for the placebo group. This approach assumes that patients from S95011 mean's response distribution is that of the placebo group patients (Carpenter *et al*, 2013). The imputed value will reflect the fact that these IEs are considered a bad outcome (worst case scenario).
- For all data following increase or initiation of authorized medication for pSS (IE2) or study drug discontinuation for AE related to study drug (IE3), the values of outcome will be imputed using a reference based multiple imputation ("copy increments in placebo" approach) for S95011 group and using multiple imputation (MAR) for the placebo group. This approach assumes that patients from S95011 will exhibit an evolution of the disease similar to patients in the placebo group but starting from the benefit already obtained (Carpenter *et al*, 2013). The imputed value will reflect the fact that these IEs are considered a moderately bad outcome.
- For all data following another type of IE or missing data due to other reason, imputation will be done as in the primary analysis.

It is of note that for missing data with an arbitrary missing pattern, the first imputation step might be preceded by one MI approach based on MCMC method using baseline and all longitudinal data by treatment groups. If a patient has missing data before an intercurrent event, all data of this patient will be imputed using the method according to the intercurrent event.

2/ Analysis step:

The same model as [1] (described above) will be applied to each of the 100 imputed datasets.

3/ Combination step:

Statistical inferences will be generated by combining results from the 100 analyses using Rubin's formulae. The multiple imputation estimator of the difference between S95011 and placebo is the average of the individual 100 estimators. The variance of the estimator is the combination of the between- and within-imputation variability (Carpenter and Kenward, 2007).

Multiplicity handling: there is no multiplicity issue.

Statistical elements: Finally, the following elements will be provided in a summary table:
- Estimate (standard error) of the difference between adjusted treatment arm means.
- Two-sided 80% CI of the estimate.
- Two-sided 95% CI of the estimate.
- One-sided p-value.

4.3.1.3. Supplementary analyses

Supplementary analysis will be done on RS.

Definition: the efficacy endpoint is defined as the proportion of responders in ESSDAI total score at W013.

Supplementary analysis: to assess the efficacy of S95011 (750 mg) as compared to Placebo on proportion of responders in ESSDAI after a 13-weeks treatment. Responders in ESSDAI at W013 defined as patients having improvement from baseline in ESSDAI total score of at least:
- 3 points
- 5 points
- 7 points

will be analysed separately using a logistic regression model including the fixed, categorical effect of treatment and randomization stratification factors (*rando_factor*) as well as the continuous fixed covariate of baseline value.

LOGISTIC REGRESSION MODEL: responder = baseline rando_factors treatment [2]

The assumptions underlying the model, as for instance, independence of errors, linearity in the logit for continuous variables, absence of multicollinearity, and lack of strongly influential outliers will be checked.

If the model is not running due to too few patients in the stratas, the model mentioned above will be modified. Thus, the two stratification factors in the model will be replaced by the following composite factor: baseline intake of oral corticosteroids or antimalarial or both (yes/no). If the model is still not running with the stratification factor in two classes, then the stratification factor will not be considered.

Missing data/intercurrent events handling: the handling of IEs and missing data will be the same as the primary and sensitivity analysis. Thus, imputation will be done on the change and then the imputed change values will be turned into responder/non-responder.

Multiplicity handling: there is no multiplicity issue.

Statistical elements: Finally, the following elements will be provided in a summary table:
- Estimate (standard error) of the difference between adjusted treatment arm proportions.
- Two-sided 80% CI of the estimate.
- Two-sided 95% CI of the estimate.
- One-sided p-value.

4.3.1.4. Subgroup analysis

Not applicable.

4.3.2. Secondary efficacy estimand

The secondary estimand of interest is the effect of the treatments on symptoms reported by the patients in all patients assuming non-occurrence of IEs. The motivation for this choice is the same as the primary estimand.

Compared to the primary estimand, only the *variable* attribute is different and is defined as the change in ESSPRI total score from baseline to W013 (secondary efficacy endpoints). The ESSPRI total score is derived as the mean of 3 items. The other attributes, main and sensitivity analyses are the same as for the primary estimand.

In the same line as for the primary estimand, the supplementary analyses will be performed on the responders ESSPRI at W013 defined as patients having improvement from baseline in ESSPRI total score of at least:

- 1 point
- 2 points
- 3 points

using the same model as for responders ESSDAI.

4.3.3. Additional estimands based on ESSDAI and ESSPRI

Treatment policy estimands

Treatment policy estimands are defined in order to assess the treatment effect on the clinical disease activity (ESSDAI total score) and also on the symptoms reported by the patients (ESSPRI total score) regardless of whether or not the IE occurs.

The attributes of the additional estimands are defined as follow:

- Treatment: S95011 or placebo.
- Population: RS.
- Variable 1: change in ESSDAI total score from baseline to W013.
- Variable 2: change in ESSPRI total score from baseline to W013.
- Summary measure: difference in means between treatments.
- Intercurrent events: The occurrence of IEs (see list in primary estimand) is irrelevant in defining the treatment effect of interest. All observed values will be used regardless of occurrence of an IE.

Missing data not due to IE will be handled according to the MAR assumption as in the primary analysis.

Main analysis is the same as for the primary estimand. Supplementary analysis will be performed as for the primary estimand but considering the responders in ESSDAI at W013 defined as patients having improvement from baseline in ESSDAI total score of at least:

- 3 points

as well as on the responders in ESSPRI at W013 defined as patients having improvement from baseline in ESSPRI total score of at least:

- 1 point

using the same model as for responders ESSDAI for the primary estimand (Section 4.3.1.3).

Other estimand

This estimand of interest is the effect of the treatments on the composite response to treatment taking into account a double dimension - clinical disease activity from ESSDAI and symptoms reported by the patients from ESSPRI - in all patients assuming non-occurrence of IEs. The motivation for this choice is the same as the primary estimand.

The attributes of this estimand are defined as follows:

- Treatment: S95011 or placebo.
- Population: all randomised patients (RS).
- Variable: Number of responders defined as patients with ≥ 3 points of improvement in ESSDAI and with ≥ 1 point of improvement in ESSPRI from baseline at W013.
- Summary measure: difference in proportion between treatments.
- Intercurrent events (IE):
  - IE1: Study drug discontinuation for major worsening of primary Sjögren's syndrome.
  - IE2: Increase or initiation of authorized medication for pSS.
  - IE3: Study drug discontinuation for AE related to study drug.
  - IE4: Study drug discontinuation for other reasons (non-medical reason, AE not related…).
  - IE5: Switch of treatment group (error of dispensation).
  - IE6: Decrease or stop of authorized medication for pSS.

Note: In case a patient is concerned by several IEs, the first event will be considered. If several IE occurred the same day, IE will be considered to be more conservative in the following order: IE1; IE2; IE3; IE4; IE5, IE6.S95011 will be compared to placebo on the responders in the RS using a logistic regression model including the fixed, categorical effect of treatment and randomization stratification factors (*rando_factor*) as well as the continuous fixed covariate of baseline value of each score.

LOGISTIC REGRESSION MODEL:

responder = baseline_ESSDAI baseline_ESSPRI rando_factors treatment *[3]*

The assumptions underlying the model, as for instance, independence of errors, linearity in the logit for continuous variables, absence of multicollinearity, and lack of strongly influential outliers will be checked.

If the model is not running due to too few patients in the stratas, the model mentioned above will be modified. Thus, the two stratification factors in the model will be replaced by the following composite factor: baseline intake of oral corticosteroids or antimalarial or both (yes/no). If the model is still not running with the stratification factor in two classes, then the stratification factor will not be considered.

The handling of IEs and missing data will be the same as the primary analysis of the primary estimand for continuous ESSDAI and ESSPRI respectively. Then, imputed change will be turned into responder/non responder separately for each score (ESSDAI 3 points and ESSPRI 1 point). Finally, the response to the composite endpoint will be derived. Sensitivity and supplementary analyses are not planned for this estimand.

4.3.4. Additional estimand based on STAR

This estimand aims at evaluating the effect of the treatments on Sjogren's Tool for Assessing Response (STAR): a composite score, in all patients assuming non-occurrence of IEs. The motivation for this choice is the same as the primary estimand.

The attributes of these estimands are defined as follows:

- Treatment: S95011 or placebo.
- Population: RS.

- Variable 1: proportion of responders in STAR score at W013 defined as patients with a STAR score ≥ 5.
- Summary measure: difference in proportion between treatments.
- Intercurrent events (IE):
  - IE1: Study drug discontinuation for major worsening of primary Sjögren's syndrome.
  - IE2: Increase or initiation of authorized medication for pSS.
  - IE3: Study drug discontinuation for AE related to study drug.
  - IE4: Study drug discontinuation for other reasons (non-medical reason, AE not related…).
  - IE5: Switch of treatment group (error of dispensation).
  - IE6: Decrease or stop of authorized medication for pSS.

Note: In case a patient is concerned by several IEs, the first event will be considered. If several IE occurred the same day, IE will be considered to be more conservative in the following order: IE1; IE2; IE3; IE4; IE5, IE6.S95011 will be compared to placebo on the responders in the RS using a logistic regression model including the fixed, categorical effect of treatment and randomization stratification factors (*rando_factor*).

LOGISTIC REGRESSION MODEL:

responder = rando_factors treatment *[4]*

The assumptions underlying the model, as for instance, independence of errors, linearity in the logit for continuous variables, absence of multicollinearity, and lack of strongly influential outliers will be checked.

If the model is not running due to too few patients in the stratas, the model mentioned above will be modified. Thus, the two stratification factors in the model will be replaced by the following composite factor: baseline intake of oral corticosteroids or antimalarial or both (yes/no). If the model is still not running with the stratification factor in two classes, then the stratification factor will not be considered.

The handling of IEs and missing data will be in the same line as the primary analysis of the primary estimand, but imputation will be done directly on the response variable. Sensitivity and supplementary analyses are not planned for this estimand.

4.3.5. Additional estimand based on CRESS

This estimand aims at evaluating the effect of the treatments on the Composite of Relevant Endpoints in Sjögren's Syndrome (CRESS): a composite score, in all patients assuming non-occurrence of IEs. The motivation for this choice is the same as the primary estimand.

The attributes of these estimands are defined as follows:

- Treatment: S95011 or placebo.
- Population: RS.
- Variable 1: proportion of responders in CRESS at W013 defined as patients with a response on ≥3 of the 5 items.
- Summary measure: difference in proportion between treatments.
- Intercurrent events (IE):
  - IE1: Study drug discontinuation for major worsening of primary Sjögren's syndrome.
  - IE2: Increase or initiation of authorized medication for pSS.

- IE3: Study drug discontinuation for AE related to study drug.
- IE4: Study drug discontinuation for other reasons (non-medical reason, AE not related…).
- IE5: Switch of treatment group (error of dispensation).
- IE6: Decrease or stop of authorized medication for pSS.

Note: In case a patient is concerned by several IEs, the first event will be considered. If several IE occurred the same day, IE will be considered to be more conservative in the following order: IE1; IE2; IE3; IE4; IE5, IE6.S95011 will be compared to placebo on the responders in the RS using a logistic regression model including the fixed, categorical effect of treatment and randomization stratification factors (*rando_factor*).

LOGISTIC REGRESSION MODEL:

responder = rando_factors treatment *[4]*

The assumptions underlying the model, as for instance, independence of errors, linearity in the logit for continuous variables, absence of multicollinearity, and lack of strongly influential outliers will be checked.

If the model is not running due to too few patients in the stratas, the model mentioned above will be modified. Thus, the two stratification factors in the model will be replaced by the following composite factor: baseline intake of oral corticosteroids or antimalarial or both (yes/no). If the model is still not running with the stratification factor in two classes, then the stratification factor will not be considered.

The handling of IEs and missing data will be in the same line as the primary analysis of the primary estimand, but imputation will be done directly on the response variable. Sensitivity and supplementary analyses are not planned for this estimand.

4.3.6. Additional estimands based on other efficacy endpoints

These estimands of interest are the effect of the treatments on global assessments of the disease activity reported by the physician (PhGA) and by the patient (PGA), and tear and salivary glands function (Schirmer test, OSS and salivary test), in all patients assuming non-occurrence of IEs. The motivation for this choice is the same as the primary estimand.

The attributes of these estimands are defined as follows:

- Treatment: S95011 or placebo.
- Population: RS.
- Variable 1: change in PhGA score from baseline to W013.
- Variable 2: change in PGA total score from baseline to W013.
- Variable 3: change in Schirmer test from baseline to W013 (on the most affected eye and mean of both eyes).
- Variable 4: change in OSS from baseline to W013(on the most affected eye and mean of both eyes).
- Variable 5: change in unstimulated salivary flow score from baseline to W013.
- Summary measure: difference in means between treatments.
- Intercurrent events (IE):
  - IE1: Study drug discontinuation for major worsening of primary Sjögren's syndrome.
  - IE2: Increase or initiation of authorized medication for pSS.

- IE3: Study drug discontinuation for AE related to study drug.
- IE4: Study drug discontinuation for other reasons (non-medical reason, AE not related…).
- IE5: Switch of treatment group (error of dispensation).
- IE6: Decrease or stop of authorized medication for pSS.

Note: In case a patient is concerned by several IEs, the first event will be considered. If several IE occurred the same day, IE will be considered to be more conservative in the following order: IE1; IE2; IE3; IE4; IE5, IE6.Main analyses are the same as for the primary estimand. Sensitivity and supplementary analyses are not planned for these estimands.

4.3.7. Descriptive analyses

For all efficacy endpoints, descriptive statistics will be provided at each visit, by treatment group and also for some efficacy endpoints (ESSDAI (total score, each domain, and responders (3,5, 7 points)), ESSPRI (total score, each symptom, and responders (1,2,3 points)), Schirmer test, unstimulated salivary flow), by treatment group according to the disease severity at baseline and background therapy in RS, on the W000-W013 period.

The ESSDAI score by domain and ESSPRI score by symptom will also be described at each visit and by treatment group (value and change).

The SF-36 score by domain and MFI score by domain will also be described at each visit and by treatment group (value and change).

The STAR and CRESS scores will be described by domain at W013 and by treatment group

The clinESSDAI total score will be described at each visit and by treatment group (value and change).

IGG will be described at each visit and by treatment group (value and change).

For ESSDAI, the number and percentage of patients changing disease severity class between two timepoints (between W000 and W004, between W004 and W013 and between W000 and W013) will be described: No change / From mild to moderate / From mild to severe / From moderate to severe / From severe to moderate / From severe to mild / Form moderate to mild.

In the same way, for Schirmer test, the number and percentage of patients changing class between two timepoints (between W000 and W013) will be described: No change / From normal to grey zone / From normal to dry / From grey zone to dry / From dry to grey zone / From dry to normal / Form grey zone to normal.

The ESSPRI score will be described in a contingency table comparing classes modalities (score < 5 vs score ≥ 5) at baseline with the same classes' modalities at W013 thus allowing to determine number and percentage of patients moving from one modality to another between baseline and W013.

4.4. Safety analysis

All safety analyses will be performed by treatment group in the Safety Set, on the ASSE-W013 and ASSE-W028 periods.

4.4.1. Adverse events

Definition:

- **Treatment Emergent Adverse Events (TEAE)** on the ASSE-W013 period are defined as all adverse events:
  - Which occur between the infusion start date/time of the first IMP intake (included) and the date of W013 visit (included) or the last IMP intake date + 21 days (included) if the W013 visit has not been done

or

  - Which occur before the infusion start date/time of the first IMP intake and which worsen (in terms of intensity) or become serious according to the investigator opinion between the infusion start date/time of the first IMP intake (included) and the date of W013 visit (included) or the last IMP intake date + 21 days (included) if the W013 visit has not been done.
    Of note, in case of multiple information of the same event before the first IMP intake date, the information nearest to the first IMP intake date is taken into account.
- **Treatment Emergent Adverse Events (TEAE)** on the ASSE-W028 period are defined as all adverse events:
  - Which occur between the infusion start date/time of the first IMP intake (included) and the last IMP intake date + 85 days (included),

or

  - Which occur before the infusion start date/time of the first IMP intake and which worsen (in terms of intensity) or become serious according to the investigator opinion between the infusion start date/time of the first IMP intake date (included) and the last IMP intake date + 85 days (included).
    Of note, in case of multiple information of the same event before the first IMP intake date, the information nearest to the first IMP intake date is taken into account.

Analysis:

Number of events, number and percentage of patients reporting at least one event, presented by primary system organ class, and/or preferred term (depending on the analysis), will be provided for:

- Serious adverse events (SAE) over the analysed period according to the investigator or sponsor opinion.
- Adverse events of special interest.
- Treatment Emergent Adverse Event (TEAE).
- TEAE leading to IMP withdrawal.
- TEAE requiring new treatment or increase of on-going treatment.
- TEAE requiring surgical or medical procedure.
- TEAE related to IMP.
- TEAE related to Pss.
- Serious TEAE.
- Serious TEAE related to IMP.
- TEAE of Grade 3-4 intensity.
- Non serious TEAE over the corresponding treatment period.

TEAE will be described according to the seriousness, the intensity, the relationship with the IMP, the action taken regarding the IMP, the requirement of added therapy and the outcome.
TEAE will also be described by time to onset according to the following classes: [0-4],]4,13] and > 13

4.4.2. Clinical laboratory evaluation

4.4.2.1. Blood samplings for haematology, biochemistry and coagulation

For each laboratory parameter, the following analyses will be performed:

- Descriptive statistics on value at baseline, on value at each post-baseline visit under treatment, on last post-baseline value under treatment and on change from baseline to last post-baseline value under treatment. These analyses will be performed on both periods (ASSE-W013 and ASSE-W028) only for haematology parameters and on ASSE-W028 for other parameters.
- Number and percentage of patients with at least one high/low emergent abnormal value under treatment, according to the laboratory reference ranges and to the cut-offs for PCSA values.
- Laboratory parameters classified (number and percentage of patients in each class) according to these reference ranges and cut-offs and using shift tables from baseline to the worst (high and/or low) values under treatment.

Moreover, listings of patients with out-of-range or PCSA analysable values emergent under treatment and of non-analysable values excluded from analyses will be provided.

4.4.2.2. Others laboratory parameters

For urinary biochemistry and cryoglobulins parameters, descriptive statistics on value at baseline, at each post-baseline visit under treatment and last post-baseline value under treatment will be performed.

4.4.3. Vital signs, clinical examination and other observations related to safety

4.4.3.1. Vital signs and clinical examination

Definition:
The following vital signs and clinical examination will be analysed:

- Weight (kg).
- BMI (kg/m²).
- Body temperature (°C).
- SBP (mmHg) before IMP infusion (and 2h after IMP infusion for W000 and W002).
- DBP (mmHg) before IMP infusion (and 2h after IMP infusion for W000 and W002).
- HR (b.p.m) before IMP infusion (and 2h after IMP infusion for W000 and W002).

Analysis:
Vital signs and clinical examination will be described, in terms of value at baseline, value at each post-baseline visit under treatment as well as in terms of change from baseline to each post baseline visit under treatment.

4.5. Antibody analysis

4.5.1. Auto-antibody analysis

Anti-Nuclear Antibodies (ANA) will be described in a contingency table comparing ANA modalities at baseline with ANA modalities at W013 thus allowing to determine number and percentage of patients moving from one modality to another between baseline and W013.

In a same way, Anti-Sjögren's Syndrome A Antibodies (Anti-SSA), subtype Anti-SSA RO52 and subtype Anti-SSA RO60 as well as Anti-Sjögren's Syndrome B Antibodies (Anti-SSB) will be described in a contingency table comparing Positive/Negative modalities at baseline with Positive/Negative modalities at W013.

Rheumatoid Factor (RF) will be described as value at baseline and W013 and change from baseline to W013.

4.5.2. Anti-Drug Antibody analysis

Number and percentage of patients having respectively positive or negative Anti-Drug Antibodies (ADA) will be described by treatment group at each visit on the W000-W028 period.

4.6. Exploratory analysis

Not applicable.

4.7. Biomarkers analysis

4.7.1. Biomarker endpoints: Interleukin 7 cytokine (IL7), cytokines and other proteins involved in pSS physiopathology

Interleukin 7 cytokine is evaluated at W000, W002, W004, W007, W010 W013, W019 and W028 by MSD Simplex. Pro-inflammatory panel (IL10, TNF-a, IFNg, IL2, IL6, IL8, IL4, IL1b, IL12p70 & IL13) is evaluated at W000, W002, W004 and W013 by MSD full multiplex. The cytokine panel (GM-CSF, IL1a, IL5, IL16, IL12/IL23p40, IL15, IL17A, TNF-b, VEGF) is evaluated at W000, W004 and W013 by MSD Multiplex. The chemokine panel (IP10 and MCP-1) is evaluated at W000, W004 and W013 by MSD multiplex. CXCL9, CXCL11 and CXCL13 is evaluated at W000, W004 and W013 by Quantikine ELISA kit.

In case of premature withdrawal, an evaluation is planned at this time-point and the evaluation will not be described in the following analysis.

Biomarker results will be described for patients of the Biomarker Set (BMKS).

For descriptive statistics, marker will be expressed in terms of concentration at baseline and at each post baseline visit and relative change from baseline to post baseline visit.

4.7.1.1. Qualitative analysis

Values of the marker will be expressed in class, according to the limits of quantification (Below Lower Limit, In Range, Above Upper Limit). The percentage of values of the marker in each class will be described overall.

If the out-of-range percentage (Below Lower Limit or Above Upper Limit) is above 30% then the quantitative analysis will not be performed. In this case, a more detailed qualitative analysis by treatment group and / or visit could be provided.

4.7.1.2. Quantitative analysis

4.7.1.2.1. Values out of limits of detection

For quantitative description of concentration of these biomarkers, missing values with a result flag not equal to “In ranges” will be substituted as follows:

Value	Substitued by
Missing and below quantification limit (based on the result flag)	LLOQ/$\sqrt{2}$
Missing and above quantification limit (based on the result flag)	ULOQ

If the lower (respectively upper) limit of quantification is missing, then it is replaced by the lower (respectively upper) limit of detection in the substitution rules. Change from baseline and percentage of reduction from baseline to post-baseline time point will be calculated using imputed values at the visits.

4.7.1.2.2. Description of biomarkers concentrations by arm

For each treatment group (S95011 and placebo), descriptive statistics of biomarker concentration will be provided (in terms of value at each visit and relative change from baseline to each post-baseline visit) using descriptive tables.

4.7.2. Biomarker endpoints: Immune panel (C3 and C4 complement fractions, CH50 (or CH100), quantitative immunoglobulins, protein electrophoresis and immunofixation)

Immune panel is evaluated at W000, W004 and W013 in blood. In case of premature withdrawal, an evaluation is planned at this time-point and the evaluation will not be described in the following analysis.

Biomarker results will be described for patients of the Biomarker Set (BMKS).

For descriptive statistics, marker will be expressed in terms of concentration at baseline and at each post baseline visit and relative change from baseline to post baseline visit.

4.7.2.1. Description of biomarkers concentrations by arm

For each treatment group (S95011 and placebo), descriptive statistics of biomarker concentration will be provided (in terms of value at each visit and relative change from baseline to each post-baseline visit) using descriptive tables.

4.7.3. Biomarker endpoints: β2 microglobulin

β2 microglobulin is evaluated at W000, W004 and W013 in blood. In case of premature withdrawal, an evaluation is planned at this time-point and the evaluation will not be described in the following analysis.

Biomarker results will be described for patients of the Biomarker Set (BMKS).

For descriptive statistics, marker will be expressed in terms of concentration at baseline and at each post baseline visit and relative change from baseline to post baseline visit.

4.7.3.1. Description of biomarkers concentrations by arm

For each treatment group (S95011 and placebo), descriptive statistics of biomarker concentration will be provided (in terms of value at each visit and relative change from baseline to each post-baseline visit) using descriptive tables.

4.8. Pharmacokinetic analysis and PK/PD analysis

Serum concentrations of S95011 will be analysed by a population modelling approach, described in a separated Data Analysis Plan (DAP), in order to assess the pharmacokinetics of the drug and to investigate potential sources of variability through a covariate analysis. This analysis will provide pharmacokinetic parameters and their associated variability in patients and will be the object of a separate report.

Exploratory assessment of the relationship between exposure and pharmacodynamics (as safety and efficacy including biomarkers, efficacy and/or safety endpoints) will be performed and if applicable, population pharmacokinetic pharmacodynamic (PK/PD) models will be developed and a DAP will be set up and reported separately. Mechanistic model-based approaches (such as physiologically based pharmacokinetic (PBPK) modelling, quantitative systems pharmacology (QSP) modelling, etc.) may be used to better describe the PK and/or PK/PD of S 95011. Those models would be the object of separate reports and a dedicated DAP would be set for PBPK models.

All the above-mentioned analyses may require pooling data from CL2-95011-001 study with data from other clinical trials or from literature.

5. INTERIM ANALYSIS

Except for the blinded standard deviation reassessment, no interim analysis is planned. Moreover, the blinded standard deviation reassessment was not performed as the recruitment was not much longer than expected.

6. CHANGES TO PROTOCOL-PLANNED ANALYSES

The definition of the Randomised Set has been modified as the set of all included patients to whom a therapeutic unit (TU) was randomly assigned using IWRS. Indeed, a patient non included has been randomised by mistake. According to the ICH E9 addendum, the population has to be defined according to the clinical question of interest. So, it has been judged relevant to define the analysis population as above.

The definition of treatment groups has been modified as the treatment received at inclusion visit for all analysis sets. Indeed, a patient has been randomised to one treatment but received the other one at inclusion (forced allocation). Thus, this patient has continued taking treatment received instead of randomised treatment for the following dispensations and it has been judged relevant to define the treatment groups as above.

As a patient received an incorrect Therapeutic Unit (TU) at a post-W000 visit on the 13-week double-blind treatment period, this patient has potentially switched treatment group. Thus, it has been decided to complete the definition of treatment groups by precising that in such cases, the patient will be considered in the treatment group corresponding to their TU(s) received until the switch. The switch being considered as an intercurrent event, data recorded from the switch will be managed according to the considered estimand.

Since the final version of the protocol, a new score for assessment of Sjögren has been constructed. It has been considered relevant to add this new score (STAR) in the statistical analyses. Thus, a new objective and associated secondary analyses have been added in this SAP.

In the same line, the CRESS score (a score similar to STAR) has been considered relevant to evaluate the efficacy of S95011. Thus, a new objective and associated secondary analyses have been added in this SAP for this score.

As descriptive statistics has been considered sufficient to evaluate the efficacy of S95011 on the MFI, SF-36 and stimulated salivary flow, the estimands and associated inferential analyses has been deleted.

The BMK set has been added to the list of analysis sets in order to perform Biomarker exploratory analyses.

Regarding the estimand framework, some changes has been made between the protocol and the SAP on intercurrent events. Indeed, *"study drug discontinuation for major worsening of primary Sjögren's syndrome or AE related to study drug"* has been split into two independent IEs as *"study drug discontinuation for major worsening of primary Sjögren's syndrome"* (IE1) is considered more impacting than *"Study drug discontinuation for AE related to study drug"* (IE3). Thus, for sensitivity analyses, it is has been decided to handle data post the IE1 using a reference based multiple imputation ("jump to placebo" approach) while data post the IE3 are considered moderately bad outcome and will be handled using a reference based multiple imputation ("copy increment in reference" approach). In the same line, intercurrent event *"change or initiation of unauthorised medication"* from the protocol has been split into *"Increase or initiation of authorized medication for pSS"*(IE2) and *"Decrease or stop of authorized medication for pSS"* (IE6) (the unauthorized part being necessarily linked to discontinuation for major worsening this part is already handled by IE1). Here again, IE2 having more impact than IE6, post IE data will be handled using different method (respectively reference based multiple imputation "copy increment in reference" and MAR approaches) for sensitivity analyses. Finally, IE5 *"Switch of treatment group (error of dispensation)"* has been added to handle the case of the patient having a treatment switch discussed above (MAR approach).

For all efficacy analyses, it has been specified that if the regression or the imputation model does not run due to too few patients in the stratas, the four classes randomisation stratification factor will be replaced by a 2 classes composite factor: baseline intake of oral corticosteroids or antimalarial or both (yes/no). If the model is still not running, then the stratification factor will not be considered.

Finally, for the treatment policy efficacy analysis, it has been considered sufficient to consider only responders in ESSDAI defined as patients with an improvement of at least 3 points and responders in ESSPRI defined as patients with an improvement of at least 1 point.

The salivary gland tissue will not be described because of the very small number of available biopsies collected at W013.

Due to very low number of viable cells collected at each time point, no statistical analysis will be performed on PBMCs (cell subsets).

7. APPENDICES

7.1. General analytic definitions

Definitions below correspond to calculation rules for expressions defined in Section 4 as well as definition of value prior to treatment / under treatment, first and last IMP intake dates and other general definitions.

7.1.1. Value prior to treatment / under treatment

Table (7.1.1) 1 - Definition of value prior to treatment

General definition	
For assessments without time collected Corresponding assessment date ≤ date of the first IMP intake + $X1_{sup}$ days	$X1_{sup} = 0$
For assessments with time collected Corresponding assessment date/time ≤ infusion start date/time of the first IMP intake + $X1_{sup}$ days	
Specific definition	
For ESSDAI, ClinESSDAI and PhGA Corresponding assessment date = date of visit at W000 ≤ date of the first IMP intake + $X1_{sup}$ days	
For ESSPRI, MFI, PGA, SF-36 Corresponding assessment date = date of visit at W000 ≤ date of the first IMP intake + $X1_{sup}$ days	

Table (7.1.1) 2 - Definition of value under treatment

General definition	
For assessments without time collected	
On W000-W013 Period if W013 visit done Date of first IMP intake + $X1_{sup}$(*) days ≤ Corresponding assessment date ≤ Date of W013 visit+ $X2_{sup}$ days	$X2_{sup} = 0$
On W000-W013 Period if W013 visit not done Date of first IMP intake + $X1_{sup}$(*) days ≤ Corresponding assessment date ≤ Date of last IMP intake on the W000-W013 period + $X2_{sup}$ days	$X2_{sup} = 21$
On W000-W028 Period Date of first IMP intake + $X1_{sup}$(*) days ≤ Corresponding assessment date ≤ Date of last IMP intake on the W000-W028 period + $X2_{sup}$ days	$X2_{sup} = 85$
For assessments with time collected	
On W000-W013 Period if W013 visit done Infusion start date/time of the first IMP intake + $X1_{sup}$(*) days ≤ Corresponding assessment date/time ≤ Date of W013 visit + $X2_{sup}$ days	$X2_{sup} = 0$
On W000-W013 Period if W013 visit not done Infusion start date/time of the first IMP intake + $X1_{sup}$(*) days ≤ Corresponding assessment date/time ≤ Date of last IMP intake on the W000-W013 period + $X2_{sup}$ days	$X2_{sup} = 21$
On W000-W028 Period Infusion start date/time of the first IMP intake + $X1_{sup}$(*) days ≤ Corresponding assessment date/time ≤ Date of last IMP intake on the W000-W028 period + $X2_{sup}$ days	$X2_{sup} = 85$

(*) *cf. definition of value prior to treatment.*

7.1.2. First and last IMP intake dates

Because all IMP intake dates are complete, no substitution will be defined.

7.1.3. Other dates

If no specific management of dates is defined, missing information is substituted as defined below:

Table (7.1.3) 1 - Substitution rules of dates if no specific management is defined

Date to substitute		Substituted date
Date	../mmm/yyyy	01/mmm/yyyy
	../…/yyyy	01/JAN/yyyy
	../.../….	No substitution

Note:
../mmm/yyyy = missing day
../.../ yyyy = missing day and month
../.../.... = missing date

For assessments with time also collected and useful for the analysis, substitution rules are as follows:

Table (7.1.3) 2 - Substitution rules of dates and times if no specific management is defined

Date and time to substitute		Substituted date and time
Date	dd/mmm/yyyy hh-…	dd/mmm/yyyy hh:00
	dd/mmm/yyyy …-…	dd/mmm/yyyy 00:00
	../mmm/yyyy …-…	01/mmm/yyyy 00:00
	../…/yyyy …-…	01/JAN/yyyy 00:00
	../.../…. …-…	No substitution

Note:
hh-... = missing minutes
...-... = missing time
../mmm/yyyy = missing day
../.../ yyyy = missing day and month
../.../.... = missing date

7.2. Specific analytic definitions and data handling conventions

7.2.1. Study participants

7.2.1.1. Demographic data and other baseline characteristics

7.2.1.1.1. Demographic data

Age (years) is calculated in the ClinTrial database as:
Year of selection visit (ASSE) – Year of birth

7.2.1.1.2. History of the Sjögren's disease

The duration of the disease (years) is defined as:
(Date of selection visit (ASSE) – Date of diagnosis) / 12.
The result is rounded to the nearest integer.

7.2.1.1.3. Relevant medical and surgical history other than the PSS symptoms

The existence of a history (Yes/No) is defined from the presence, or not, of a Primary system organ class and/or Preferred term.

7.2.1.1.4. Previous treatments

Previous treatments are all treatments received and stopped within 12 months before screening visit (including vaccinations). All vaccinations deemed necessary by the investigator for the patient should be up to date before inclusion. Therefore, the corresponding last vaccinations and last boosters will be considered and reported as previous treatment (even if administered more than 12 months prior to the screening visit).

The anatomical therapeutic chemical classification (ATC code = 5 digits) is composed of 4 levels:

- The first (1 digit) represents the anatomo-physiological class.
- The second (2 digits) represents the pharmacological class.
- The third (1 digit) represents the pharmacological sub-class.
- The last (1 digit) represents the therapeutic class.

Previous treatment is defined as any treatment with associated stop date strictly inferior to the first IMP intake date.
Note: In case of patient included and/or randomised but not treated, previous treatment is defined as any treatment with associated stop date strictly inferior to date of inclusion visit.

Only treatment with an Anatomical therapeutic chemical classification and/or a Preferred name is considered.

The **rules for substitution** of missing or incomplete previous treatments stop dates are as follows:

Table (7.2.1.1.4) 1 - Substitution rules of previous treatments stop date

Date to substitute		Substituted date

Stop date	../mmm/yyyy	If patient died same month and year then
		Date of death
		Else
		Last day of the month/mmm/yyyy

	../…/yyyy	If patient died same year then
		Date of death
		Else
		31/DEC/yyyy

	../.../….	If patient died then
		Date of death
		Else
		No substitution
		(*i.e.*, treatment considered as still ongoing)

Note: ../mm/yyyy = missing day
../.../ yyyy = missing day and month
../.../.... = missing date

The lists of the considered ATC codes for specific previous treatments to Sjögren disease are the excel files:

- 2602.0 Systemic and local treatments containing corticosteroids DDB320221.
- 4306.0 Treatments containing antimalarial DDB320221.
- 4302.0 Treatments containing methotrexate DDB320221.
- 3700.2 Non-steroids antinflammatory drugs (NSAIDS) DDB320221.
- 4309.0 Treatments containing cevimeline and pilocarpine DDB320221.
- 4324.0 Ocular topics for S95011 DDB320221.
- 4382.1 Drugs known to induce dry mouth and dry eyes DDB320221.
- 1728.2 Treatments containing an alkylating agents DDB320211.
- 3432.1 Treatments containing rituximab or other B cell depleting agents DDB320221.
- 4299.0 Treatments containing Abatacept DDB320221.
- 4300.0 Treatments containing Belimumab DDB320221.
- 4303.0 Treatments containing Tumor Necrosis Factor (TNF) inhibitor DDB320221
- 4305.0 Treatments containing tocilizumab DDB320221
- 4308.0 Treatments containing specific immunosuppressants for 95011 DDB320221.
- 4618.0 Treatments containing Janus Kinase associated inhibitors DDB320221.

Other ATC codes in the ClinTrial database are for non-specific previous treatments.

7.2.1.2. Extent of exposure and treatment compliance

Number of infusions per patient is defined as:
Number of visits (among W000, W002, W004, W007, W010) with non-missing IMP intake date and the question “Did the patient receive the IMP infusion?” = Yes

Time between two IMP administrations (i and i+1) is derived as (days):
By visit i+1: Infusion stop date of the IMP intake at the visit i+1 – infusion stop date of the IMP intake at the visit i.

7.2.1.3. Concomitant treatments

The anatomical therapeutic chemical classification (ATC code = 5 digits) is composed of 4 levels:

- The first (1 digit) represents the anatomo-physiological class.
- The second (2 digits) represents the pharmacological class.
- The third (1 digit) represents the pharmacological sub-class.
- The last (1 digit) represents the therapeutic class.

The existence of a concomitant treatment (Yes/No) is defined from the presence, or not, of an Anatomical therapeutic chemical classification and/or Preferred name.

The **periods** considered **for the analysis** are:

- At inclusion for which treatments with start date ≤ inclusion date and stop date ≥ inclusion date or missing are taken into account.
- During the W000-W013 treatment period for which treatments:
  - With start date ≥ first IMP intake date and < last IMP intake date, or
  - With start date ≤ first IMP intake date and stop date ≥ first IMP intake date or missing

are taken into account.

- After the last IMP intake for which treatments with start date > last IMP intake date are taken into account

Concomitant treatments could be considered in one or several of the possible analysis periods.

The lists of the considered ATC codes for specific concomitant treatments to Sjögren disease are the excel files:

- 2602.0 Systemic and local treatments containing corticosteroids DDB320221.
- 4306.0 Treatments containing antimalarial DDB320221.
- 4302.0 Treatments containing methotrexate DDB320221.
- 3700.2 Non-steroids antinflammatory drugs (NSAIDS) DDB320221.
- 4309.0 Treatments containing cevimeline and pilocarpine DDB320221.
- 4324.0 Ocular topics for S95011 DDB320221.
- 4382.1 Drugs known to induce dry mouth and dry eyes DDB320221.

Other ATC codes in the ClinTrial database are for non-specific concomitant treatments.

The following **rules for substitution** of missing or incomplete start and stop dates are so that the concomitance period is maximised:

Table (7.2.1.3) 1 - Substitution rules of concomitant treatments intake dates

Date to substitute		Substituted date
Start date	../mmm/yyyy	**01/mmm/yyyy**
	../…/yyyy	**01/JAN/yyyy**
	../.../….	If stop date is non-missing and inferior to selection date then: **Stop date** Else: **Selection date**

Stop date	../mmm/yyyy	If patient died same month and year then
		Date of death
		Else
		Last day of the month/mmm/yyyy

	../…/yyyy	If patient died same year then
		Date of death
		Else
		31/DEC/yyyy

	../.../….	If patient died then
		Date of death
		Else
		No substitution
		(*i.e.*, treatment considered as still ongoing)

Note: ../mm/yyyy = missing day
../.../ yyyy = missing day and month
../.../.... = missing date

7.2.2. Efficacy

7.2.2.1. Intercurrent Event (IE)

IE1: Study drug discontinuation for major worsening of primary Sjögren's syndrome.
IE2: Increase or initiation of authorized medication for pSS.
IE3: Study drug discontinuation for AE related to study drug.
IE4: Study drug discontinuation for other reasons (non-medical reason, AE not related…).
IE5: Switch of treatment group (error of dispensation).
IE6: Decrease or stop of authorized medication for pSS.

For all efficacy endpoints, a flag for each intercurrent event (IE) will be created to identify the values collected post-IE vs the values before or on the IE date. As a reminder, the IE date is the date of the start of IE.

One global IE flag will be derived to determine which IE occurs first. In case a patient is concerned by several IEs, the first event will be considered. If several IE occurred the same day, IE will be considered to be more conservative in the following order: IE1; IE2; IE3; IE4; IE5, IE6.

Study drug discontinuation for major worsening of primary Sjögren's syndrome (IE1) is defined as follow:

- AE related to pSS leading to study drug discontinuation.

Increase or initiation of authorized medication (IE2) is defined as follows:

- Any increase or initiation of a new dose of corticosteroids (oral prednisone or equivalent) within 4 weeks prior to W013 visit.
- Any intramuscular, IV, or intra-articular corticosteroids within 4 weeks prior to W013 visit.
- Any increase or initiation of new dose of topical corticosteroids within 2 weeks prior to W013 visit.

- Any increase or initiation of new dose of antimalarials (*e.g.* chloroquine, hydroxychloroquine, quinacrine) after randomisation (W000).
- Any increase or initiation of new dose of methotrexate after randomisation (W000).
- Any change in route of administration of methotrexate within 4 weeks prior to W013 visit.
- Any increase or initiation of new dose of regularly scheduled Non-steroidal anti-inflammatory drugs (NSAIDs) within 2 weeks prior to W013 visit.
- Any increase or initiation of new doses of cevimeline or oral pilocarpine within 2 weeks prior to W013 visit.
- Any increase or initiation of new doses of Ocular topics (excluding artificial tears, gels, lubricants, antibiotherapy) within 90 days prior to W013 visit.
- Required regular use of medications known to cause dry mouth/eyes as a regular and major side effect, and which have not been on a stable dose for at least 30 days prior to W013.

Study drug discontinuation for AE related to study drug (IE3) is defined as follow:
- AE related to IMP leading to study drug discontinuation.

Study drug discontinuation for other reasons (non-medical reason, AE not related…) (IE4) is defined as follow:
- Patients who did not receive IMP infusion neither at this visit nor at the following ones without any AE related to pSS or related to IMP leading to study drug discontinuation.

Decrease or stop of authorized medication for pSS (IE6) is defined using the same time windows and definitions as IE2.

The lists of the considered ATC codes for IE2 are the excel files:
- 2602.0 Systemic and local treatments containing corticosteroids DDB320221.
- 4306.0 Treatments containing antimalarial DDB320221.
- 4302.0 Treatments containing methotrexate DDB320221.
- 3700.2 Non-steroids antinflammatory drugs (NSAIDS) DDB320221.
- 4309.0 Treatments containing cevimeline and pilocarpine DDB320221.
- 4324.0 Ocular topics for S95011 DDB320221.
- 4382.1 Drugs known to induce dry mouth and dry eyes DDB320221.

7.2.2.2. ESSDAI total score

ESSDAI total score is calculated in the ClinTrial database as the weighted sum of the 12 domains (one decimal will be kept). The maximum theoretical score is 123. If one item is missing, then the total score is not calculated.

7.2.2.3. ESSPRI total score

The ESSPRI total score is derived as the mean of the 3 items (one decimal will be kept). If one item is missing, then the total score is not calculated. The maximum theoretical score is 10 (mean score of the 3 subscores).

7.2.2.4. STAR score

The STAR score (Sjogren's Tool for Assessing Response) is a composite responder index in primary Sjögren's syndrome (pSS). This score will not be computed in the ClinTrial database and will have to be derived. The STAR score should be calculated as follows:

- Systemic activity (/3points):
  - **3 points** if decrease of at least 3 points in clinESSDAI from baseline.
  - **0 points** otherwise.
- Patient reported outcome (/3points):
  - **3 points** if decrease of at least 1 point or at least 15% in ESSPRI from baseline.
  - **0 points** otherwise.
- Lachrymal gland function (/1point):
  - If abnormal Schirmer's test score at baseline (*i.e.* < 5 mm).
    - **1point** if increase of at least 5mm from baseline (on mean of both eyes).
    - **0 point** otherwise.
  - If normal Schirmer's test score at baseline:
    - **1point** if no change to abnormal value (on mean of both eyes).
    - **0 point** otherwise.

    Or
  - If abnormal OSS score at baseline (*i.e.* ≥ 3):
    - **1point** if decrease of at least 2 points from baseline (on mean of both eyes).
    - **0 point** otherwise.
  - If normal OSS test score at baseline:
    - **1point** if no change to abnormal value (on mean of both eyes).
    - **0 point** otherwise.
- Salivary gland function (/1point):
  - If unstimulated salivary flow score is > 0 at baseline:
    - **1 point** if increase of at least 25% from baseline.
    - **0 point** otherwise.
  - If unstimulated salivary flow score is equal to 0 at baseline:
    - **1 point** if any increase from baseline.
    - **0 point** otherwise.
- Biological (/1point):
  - **1 point** if decrease of at least 10% of serum IgG level or decrease of at least 25% of RF level.
  - **0 point** otherwise.

For the Lachrymal gland function domain, if the amelioration criterion is met for at least one of the two scores (Schirmer or OSS) on the mean of the two eyes then patient get 1 point for this domain. The STAR score is then the sum of the 5 previously mentioned domains. Finally, a patient is a candidate STAR responder if his STAR score is ≥ 5.

ClinESSDAI is defined as a sub score of the ESSDAI score taking into account all ESSDAI domains except the Biological one and considering new weights. The new weights for calculation of clin ESSDAI are: 4 for Constitutional domain, 4 for Lymphadenopathy domain, 2 for Glandular domain, 3 for Articular domain, 3 for Cutaneous domain, 6 for Pulmonary domain, 6 for Renal domain, 7 for Muscular domain, 5 for PNS domain, 5 for CNS domain, and 2 for Haematological domain.

If one domain cannot be calculated, then the STAR score will not be calculated. However, for the definition of responder:

- If the sum of the non-missing items ≥ 5, then the patient will be considered as responder.
- If the sum of the non-missing items + maximal potential sum of the missing items < 5 then the patient will be considered as non-responder.

7.2.2.5. CRESS score

The CRESS score (Composite of Relevant Endpoints in Sjögren's Syndrome) is a composite responder index in primary Sjögren's syndrome (pSS). This score will not be computed in the ClinTrial database and will have to be derived.
The CRESS score should be calculated as follows:

- Systemic activity (/1points):
  - **1 points** if clinESSDAI score at visit is < 5.
  - **0 points** otherwise.
- Patient reported outcome (/1points):
  - **1 points** if decrease of at least 1 point or at least 15% in ESSPRI from baseline.
  - **0 points** otherwise.
- Tear gland function (/1point):
  - If abnormal Schirmer's test score at baseline (*i.e.* < 5 mm):
    - **1point** if increase of at least 5mm from baseline (on mean of both eyes).
    - **0 point** otherwise.
  - If normal Schirmer's test score at baseline:
    - **1point** if no change to abnormal value (on mean of both eyes).
    - **0 point** otherwise.

    Or
  - If abnormal OSS score at baseline (*i.e.* ≥ 3):
    - **1point** if decrease of at least 2 points from baseline (on mean of both eyes).
    - **0 point** otherwise.
  - If normal OSS test score at baseline:
    - **1point** if no change to abnormal value (on mean of both eyes).
    - **0 point** otherwise.
- Salivary gland function (/1point):
  - If unstimulated salivary flow score is > 0 at baseline.
    - **1 point** if increase of at least 25% from baseline.
    - **0 point** otherwise
  - If unstimulated salivary flow score is equal to 0 at baseline:
    - **1 point** if any increase from baseline.
    - **0 point** otherwise.
- Serological (/1point):
  - **1 point** if decrease of at least 10% of serum IgG level or decrease of at least 25% of RF level.
  - **0 point** otherwise.

For the Tear gland function domain, the patient is responder if the amelioration criterion is met for at least one of the two scores (Schirmer or OSS) on the mean of the two eyes. The CRESS score is then the sum of the 5 previously mentioned domains. Finally, a patient is a candidate CRESS responder if his CRESS score is ≥3.

ClinESSDAI is defined in the previous section.

If one domain cannot be calculated, then the CRESS score will not be calculated. However, for the definition of responder:

- If the sum of the non-missing items ≥ 3, then the patient will be considered as responder.
- If the sum of the non-missing items + maximal potential sum of the missing items < 3 then the patient will be considered as non-responder.

7.2.2.6. MFI total score

The MFI (Multidimensional Fatigue Inventory) is a self-report measure designed to evaluate five dimensions of fatigue: general fatigue, physical fatigue, reduced motivation, reduced activity, and mental fatigue.

The MFI is a 20-item scale ranging from 1 to 5 to indicate how aptly certain statements regarding fatigue represent the individual experiences. For each of the 5 scales (general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue) a total score is calculated by summation of the scores of the individual items. Scores can range from the minimum of 4 to the maximum of 20. Higher total scores correspond with more acute level of fatigue.

Each of the 5 dimensions will be described but the total score will not be considered as not recommended.

Before calculating total scores of each of the 5 scales, one need to be careful about some items that have to be recoded. Indeed, as written above, higher total score of a specific domain correspond with more acute level of fatigue. Nevertheless, some items are coded reversely. For example, item 2 “Physically, I feel only able to do a little” is scored 1 for “yes, that is true” and 5 for “No that is not true”. Thus, for this item, a higher score is associated to a less acute level of fatigue. This is the case for items 2, 5, 9, 10, 13, 14, 16, 17, 18 and 19. For those 10 items, sores will be recoded as follows: 1=5, 2=4, 3=3, 4=2, 5=1.

Once the 10 reverse items have been recoded, the 5 scales total scores can be calculated as follows:

- General Fatigue is the sum of the patient’s score on items 1, 5, 12 and 16.
- Physical Fatigue is the sum of the patient’s score on items 2, 8, 14 and 20.
- Reduced activity is the sum of the patient’s score on items 3, 6, 10 and 17.
- Reduced Motivation is the sum of the patient’s score on items 4, 9, 15 and 18.
- Mental Fatigue is the sum of the patient’s score on items 7, 11, 13 and 19.

7.2.2.7. SF36 physical and mental scores

The SF-36 physical score corresponds to the SF-36 physical component summary and the SF-36 mental score corresponds to the SF-36 mental component summary which are calculated according to the user’s manual for the SF-36v2 health survey – third edition, using a dedicated software and transferred in the ClinTrial database.

7.2.2.8. Schirmer test

The Schirmer test determines whether the eye produces enough tears to stay moist. This test results in a measure of the moisture on paper strips previously applied on eyes for five minutes. The results of the Schirmer test will be directly available in ClinTrial. The mean score of both eyes will be derived as the mean of right eye and left eye. The score will be evaluated on the mean of both eyes but also the most affected eye which means on the eye with the smallest score at baseline. If both eyes have the same Schirmer score at baseline, the right eye will be evaluated by default.

7.2.2.9. OSS

The Ocular Staining Score (OSS) uses lissamine green dye to grade the conjunctiva and fluorescein dye to grade the cornea. Total ocular staining scores of 0 to 12 *per* eye assess the range of severity of keratoconjunctivitis sicca.

The total OSS for each eye is the summation of the fluorescein score for the cornea and the lissamine green scores for the nasal and temporal bulbar conjunctiva. The maximum possible score for each eye is 12. The mean score of both eyes will be derived as the mean of right eye and left eye. The score will be evaluated on the mean of both eyes but also the most affected eye which means on the eye with the highest score at baseline. If both eyes have the same OSS score at baseline, the right eye will be evaluated by default.

7.2.2.10. Sialometry under unstimulated and stimulated conditions

The results of the sialometry tests will be available in ClinTrial and the flow rate of saliva automatically calculated as Volume (mL)/minute.

7.2.3. Safety

7.2.3.1. Adverse events

Each **medical concept of adverse event coded according to the internal "multiple medical concept" process** is taken into account as a single adverse event in the statistical analysis. The modalities of the adverse event (onset and end dates, intensity, seriousness, action taken, additional therapy, relationship, outcome...) replicated by default to each medical concept are also taken into account in the statistical analyses.

Treatment Emergent Adverse Events (TEAE) are defined in Section 4.4.1.

Serious adverse events are defined as all adverse events upgraded by the sponsor during the IME or PharmacoVigilance (PV) process (upgrade of seriousness) or considered as "serious" from investigator assessment.

Serious adverse events from investigator assessment are defined as all adverse events fulfilling at least one of the following seriousness criteria for immediate notification at any time (before, during or after IMP intake): death, hospitalisation or prolongation of hospitalisation, medically important, life-threatening, disability/incapacity or congenital anomaly.

Severe adverse events are defined as adverse events of grade 3, 4 or 5.

A fatal adverse event corresponds to an adverse event with "Fatal" outcome.

Adverse events of special interest (AEOSI) are adverse events of scientific and medical interest or concern regarding the IMP for which recording rules, special documentation with detailed information such as hospital records is required. It may be a serious or non-serious AE that may require further investigation in order to characterize and understand.

AEOSI include:

- Allergic reaction grade 3 or higher according to CTCAE/v5.0 grading (Note: Humans administered foreign proteins are at risk of developing allergic reactions, including anaphylaxis).
- Cytokine release syndrome: No cytokine release has been observed in FIH study (IFNγ, IL12p70, IL4, IL5, IL6, IL8, TNFα, however, given the risk of cytokine release syndrome observed in certain therapeutic monoclonal antibodies, this event will be systematically collected and closely monitored in patients treated with S95011). In case of suspicion of cytokine release syndrome, a blood sample for cytokines assay will be performed and analysed locally.
- Infections grade 3 or higher according to CTCAE/v5.0 grading (Note: IL 7 receptor inhibition may induce immunomodulation, so patients should be monitored clinically for manifestations of infectious disease, and, if necessary, appropriately treated [*e.g.* with antibiotics]).
- Lymphopenia < $500x10_6$/L (grade 3 or higher according to CTCAE v5.0 Criteria)

The lists of the considered ATC codes for AEOSI are the excel files:

- 3736.0 PRE Infusion related reaction M251.
- 3847.0 Lymphopenia M250.
- 4314.0 Bacterial, viral, fungal, parasitic infections for 95011 M250.
- 4639.0 Cytokine release syndrome M250.

Adverse events related to IMP correspond to adverse events with relationship with IMP forced by the sponsor during the PV process (upgrade of relationship at least for adverse events assessed as serious according to investigator or sponsor opinion) or considered as "related" from investigator assessment.

The following information will be taken into account:

- For the analyses where the intensity of the adverse event is considered, the worst intensity from the day of emergence to the end of the studied period will be taken into account.
- For the analyses where the action taken regarding the IMP is considered, all the actions taken recorded from the day of emergence to the end of the studied period will be taken into account.
- For the analysis of recovered emergent adverse events during, an EAE is considered as recovered "during treatment period" if the associated outcome is "recovered" or "recovered with sequelae" and occurs between the first IMP intake date and the last IMP intake date.

The following rules are applied in case of missing intensity to define emergent adverse events:

Table (7.2.3.1) 1 - Adverse events - Rules in case of missing intensity

Intensity			Worsening of intensity
Nearest before the first IMP intake date	During studied period*		
Missing	Missing	⇒	Yes
Missing	Grade 1	⇒	No
Missing	Grade 2	⇒	Yes
Missing	Grade 3	⇒	Yes
Missing	Grade 4	⇒	Yes
Missing	Grade 5	⇒	Yes
Grade 1	Missing	⇒	Yes
Grade 2	Missing	⇒	Yes
Grade 3	Missing	⇒	Yes
Grade 4	Missing	⇒	Yes
Grade 5	Missing	⇒	No

** Studied period – cf Section 4.4.1*

The rules for substitution of missing or incomplete onset date, dates of modification of intensity, dates of action taken and/or dates of the six seriousness criteria are as follows:

Table (7.2.3.1) 2 - Substitution rules of AE dates

Date to substitute	Substituted date
dd/mmm/yyyyhh: ..	If same date and same hour as IMP intake date then: - **First intake date and time + 1 min** Else: **hh:00**
dd/mmm/yyyy …-…	If same date as IMP intake date then: - **First IMP intake date and time + 1 min** Else: - **dd/mmm/yyyy 00:00**
../mmm/yyyy..:..	If same month and year as IMP intake date then: **First IMP intake date and time + 1 min** Else: **01/mmm/yyyy 00:00**
../…/yyyy ..:..	If same year as IMP intake date then: **First IMP intake date + 1 min** Else: **01/JAN/yyyy 00:00**
../.../….	**First IMP intake date and time + 1 min**

Note: ../mm/yyyy = missing day
../.../ yyyy = missing day and month
../.../.... = missing date
dd/mmm/yyyyhh: .. = missing minutes
dd/mmm/yyyy.. : .. = missing time

The rules for substitution of missing or incomplete recovery dates, in case of AE outcome "recovered" or "recovered with sequelae" are as follows:

Table (7.2.3.1) 3 - Substitution rules of recovery date

Date to substitute	Substituted date
../mmm/yyyy	If same month and year than date of AE last information* then: **Date of AE last information** Else: **Last day of the month /mmm/yyyy**
../…/yyyy	If same year than date of AE last information* then: **Date of AE last information** Else: **31/DEC/yyyy**
../.../….	**Date of AE last information***

** Date of AE last information is defined as the maximum between onset date, dates of modification of intensity, action taken and dates of the six seriousness criteria for this adverse event.*

Note:

../mmm/yyyy = missing day,
../.../ yyyy = missing day and month,
../.../.... = missing date.

7.2.3.2. Clinical laboratory evaluation

Management of samplings

The following rules will be applied to define the visit associated to the sampling which is used in the analysis by visit (considering the date and the nature of the sampling):

- Each scheduled sampling is associated to the nearest visit where a sampling is expected according to the protocol (W000, W002, W004, W007, W010, W013, W019 and W028).
- Retests with a sampling date between two scheduled samplings n and n+1 are reported at the same report visit as the sampling n.

Note: The previous rules do not apply to unscheduled samplings (these latter are not taken into account in the analysis by visit).

Management of multiple samples

- For the description of the values at each planned post-baseline visit, only the first analysable one measured under treatment at the visit is taken into account.
- Otherwise, each post-baseline value (test, re-test, planned, unplanned) measured under treatment is taken into account for other analyses.

Management of values out of quantifiable limit

- For the quantitative analyses, values "less (resp. greater) than quantifiable limit" will be substituted by the quantifiable limit.
- For the qualitative analyses, the quantifiable limits will be used for classification according to the laboratory reference range and the cut-offs for PCSA values.

Management of reference ranges and cut-offs for PCSA values

In case of aberrant values of reference ranges as compared to PCS ranges, it will be managed as follows:

- If ULN > ULS (resp. LLN < LLS) then ULN value (resp. LLN value) will be imputed with ULS value (resp. LLS value).
- If ULN < LLS, then ULN value will be imputed with ULS value.

- If LLN > ULS, then LLN value will be imputed with LLS value.
- If ULN < LLN, then ULN value will be imputed with ULS value and LLN value will be imputed with LLS value.
- If ULN is missing, then ULN value will be imputed with ULS value.
- If LLN is missing, then LLN value will be imputed with LLS value.

For the qualitative analysis:

- If the limits of normal laboratory reference ranges (*i.e.* LLN and ULN) are optional (*i.e.* present in the database but not clinically relevant), they will not be taken into account and will be considered as missing.
  Same approach regarding the limits used to define PCSA values (*i.e.* LLS and ULS) when optional.
  So:
  - Only ULN and ULS will be considered as clinically relevant for Alanine Aminotransferase, Alkaline phosphatase, Amylase, Aspartate Aminotransferase, Basophils, Basophils/Leucocytes, Bilirubin, C reactive Protein, Cholesterol, Creatine Kinase, Direct Bilirubin, Eosinophils, Eosinophils/Leukocytes, Gamma Glutamyl Transferase, Indirect Bilirubin, Lactate dehydrogenase, Triglycerides.
  - Only LLN, ULN and ULS will be considered as clinically relevant for Creatinine, Monocytes, Monocytes/Leukocytes, Protein, Triacylglycerol Lipase, Uric acid.
  - Only LLN and ULN will be considered as clinically relevant for Activated partial thromboplastin time, Albumin (%) in total protein, Erythrocyte Sedimentation Rate, Prothrombin time, Urea.
  - Only ULN will be considered as clinically relevant for Rheumatoid Factor.
  - All limits (LLS, LLN, ULN and ULS) will be considered as clinically relevant for other parameters.
  - Note: For Glucose parameter, whatever the condition (fasting or not), the laboratory reference ranges and PCSA values of Glucose in fasting condition will be considered.
- For parameters with mandatory limits of normal laboratory reference ranges, in the situation where these limits are outside the limits used to define PCSA values, the normal laboratory reference limits will be substituted by the corresponding PCSA limits
- Each non missing value will be classified taking into account clinically relevant (reference/PCS) limit (*i.e.* the value will only be compared to the clinically relevant limit(s) and will be considered as normal if not out of this (those) limit(s)).

7.2.3.3. Vital signs and clinical examination

The Body Mass Index is calculated at a visit in the ClinTrial database as:
BMI (kg/m²) = Weight (kg) / (Height (cm) x 0.01)².
using the height measured at ASSE visit and the weight recorded at the corresponding visit.
The result is rounded to one decimal place.

7.3. Statistical methods details

7.3.1. General Linear Model

A model that will be used for this study is the General Linear Model studying treatment effect with baseline and randomisation stratification factors (baseline intake of oral corticosteroids (yes/no) and baseline intake of antimalarial (yes/no)) variable as covariates. The randomisation stratification factors will be considered in a unique variable with four modalities ("Nothing", "oral corticosteroids", "antimalarial" and "oral corticosteroids and antimalarial"):

$$Y_{ijk} = \gamma X_{ijk} + a_i + b_j + \varepsilon_{ijk}$$

Where:

- Y_{ijk} is the continuous response from the k^{th} patient, in strata j, that received treatment i.
- X_{ijk} is the baseline value of the analysed variable for the k^{th} patient, in strata j, that received treatment i.
- γ denotes the common slope of the baseline covariate.
- a_i denotes the intercept of the i^{th} treatment.
- b_j denotes the fixed effect of strata j.
- $\varepsilon_{ijk} \sim$ iid $N(0, \sigma_\varepsilon^2)$ denotes the experimental unit error associated with the k^{th} patient, in strata j, that received treatment i.

The model can also be written in matrix notation as:

$$Y = X\beta + \varepsilon$$

Where:

- Y is the vector of observations.
- X is the design matrix of the fixed effects and baseline factors.
- β is the unknown vector of the fixed effects and baseline factors.
- ε is the unobserved vector of independent and identically distributed random errors, such as $\varepsilon \sim N(0,R)$ where $R = \sigma_\varepsilon^2 I_n$.

The restricted maximum likelihood (REML) approach for estimation of variance will be considered.

Estimate:

The estimate $\hat{\beta}$ of β is given by:

$$\hat{\beta} = (X'X)^{-1}X'Y$$
$$\text{with } Var(\hat{\beta}) = (X'\hat{R}^{-1}X)^{-1} = \hat{C}$$

Confidence interval and p-value:

The Sum of Squares using a Least-Squares-means contrast is used for computing the Sum of Squares under H0: $L\beta = 0$ (where $L\beta$ denotes a linear estimable combination of the fixed effects).

The 95% confidence interval of $\hat{\beta}$ is given by:

$$L\hat{\beta} \pm t_{\hat{\nu},0.975}\sqrt{L\hat{C}L'}$$

Where:

- $\hat{\nu}$ denotes the approximate degrees of freedom by the residual degrees of freedom, $n - rank(X)$, where n is the number of observations.
- $t_{\hat{\nu},0.975}$ is the 0.975^{th} quantile of the t-distribution with $\hat{\nu}$ degrees of freedom.

The Least-Squares approach provides estimates of the linear parameters that are unbiased and have minimum variance among linear estimators.
The treatment effect is estimated by the difference of the Least-Squares-means of each studied treatment group.

Validation of hypothesis:
For the validation of the model used, the following points will be studied:
a) Normality and homoscedasticity of residuals
The assumptions of normality and homoscedasticity of residuals will be investigated on the model using some graphs and descriptive statistics.

b) Detection of outliers
The detection will be done using graphics.

7.3.2. Logistic Model

Another model that will be used for this study for the responder analysis is the Logistic Model studying treatment effect with baseline and randomisation stratification factors (baseline intake of oral corticosteroids (yes/no) and baseline intake of antimalarial (yes/no)) variable as covariates. The randomisation stratification factors will be considered in a unique variable with four modalities ("Nothing", "oral corticosteroids", "antimalarial" and "oral corticosteroids and antimalarial").

Logistic regression is one of the generalized linear models with a logit link to model a binary dependent variable. Under logit setting, we can model our response as below:

$$log\frac{E[P(Y=1)]}{1-E[P(Y=1)]} = \beta_0 + \beta_1 * I_{treatment} + \beta_2 * X_2 + \beta_3 * X_3 + \beta_4 * X_4$$

Let L_p and L_T be the linear predictor for placebo and treatment, respectively

$$L_T = \beta_0 + \beta_1 + \beta_{T2} * X_2 + \beta_{T3} * X_3 + \beta_{T4} * X_4$$

$$L_p = \beta_0 + \beta_{p2} * X_2 + \beta_{p3} * X_3 + \beta_{p4} * X_4$$

Estimate:
The difference between two rates can be considered as a function of β:

$$E[P(Y=1|\mathrm{T})] - E[P(Y=1|\mathrm{P})] = h(\beta) = \frac{1}{1+\exp(-L_T)} - \frac{1}{1+\exp(-L_P)}$$

So the difference in percentages of responders between Treatment and Placebo will be given by:

$$diff_{\%}(T-P) = \frac{\exp(L_T)}{1+\exp(L_T)} - \frac{\exp(L_P)}{1+\exp(L_P)}$$

Then the standard error for rate difference can be derived by Delta method.

$$\sqrt{n}(\hat{\beta} - \beta) \sim N(0, \Sigma)$$

The delta method will be applied using the NLMIXED procedure of SAS on the results from the GENMOD procedure (Ke, 2022).

```
ods output AdditionalEstimates=output_nlmixed;
proc nlmixed data=data_analyse alpha=risk_alpha;
p = logistic(Intercept + b1*(class=1) + b2*(class=2) + b3*(class=3) + b4*baseline +
b5*(treatment=1));
model response ~ binary(p);
by _Imputation_;
estimate 'T-P' logistic(Intercept + 0.25*b1 + 0.25*b2 + 0.25*b3 + 12.146*b4 + b5) -
logistic(Intercept + 0.25*b1 + 0.25*b2 + 0.25*b3 + 12.146*b4);
run;
```

The values in green above are an example and will be replaced by coefficients extracted from proc genmod.

7.3.3. Imputation step for main analysis on primary endpoint

We will implement a standard multiple imputation method for handling missing data due to any kind of IE as well as missing data for other reasons.

Standard multiple imputation: this method (Rubin, 1987) replaces each missing value with a set of plausible values that represent the uncertainty about the right value to impute. Each value is a Bayesian drawn from the conditional distribution of the missing observation given the observed data, made in such a way that the set of imputation properly represents the information about the missing value that is contained in the observed data for the chosen model.
The multiply imputed data sets are then analysed by using standard procedures for complete data and combining the results from these analyses, based on the change from baseline.

Multiple imputation inference involves **3 consecutives phases** (phase 1: imputation step, phase 2: analysis step and phase 3: combination step).

Phase 1: Imputation step
To guarantee the reproduction of results, the seed will be fixed at 95011.

Step 1:
First, data collected post IE should be considered as missing (use flag derived in ADAM). In case of patient with several events (IE1="Y" and IE2="Y"…), the first one will be considered and all the values after (strictly) will be considered as missing. All intermittent missing data (*i.e.* with an arbitrary missing pattern) will be first imputed using a MI approach based on MCMC method using baseline and all longitudinal data by treatment groups, in case the initial dataset has not a strict monotone missing pattern.

A total of 100 imputed partially completed datasets will be generated. This dataset will serve as a basis for Step 2 (*DATA_BASIS*). For the following step, the entry dataset will be sorted by imputation, by treatment and by USUBJID.

Step 2:
In this sequence, remaining missing data of *DATA_BASIS* will be imputed. For all patients with missing data with or without an IE:

- To impute those missing data, all data (*DATA_BASIS*) will be considered in order to benefit of all data available at each visit.
- A regression method will be used to perform the imputation, using in this order: randomisation stratification factors, baseline, visit i-1, visit i in the model. Of note, for imputing data of visit i, data up to visit i-1 are to be considered for the imputation, even if the data of visit i-1 already results of an imputation (this is taken into account in PROC MI with the order of the variables put in the VAR statement).

Phase 2: Imputation step
The planned model will be applied to each of the 100 imputed datasets obtained at the previous step (*DATA_COMPLETE*). For each imputed dataset i (i=1,2…,m), the estimate of the difference between groups and the associated standard error will be stored.

Phase 3: Combination step
Statistical inferences will be generated by combining results from the 100 analyses using Rubin's formulae. The multiple imputation estimator of the difference between S95011 and Placebo is the average of the individual 100 estimators.

7.3.4. Imputation step for sensitivity analysis on primary endpoint

We will implement a hybrid approach using jump to placebo approach, copy increments in placebo approach and standard multiple imputation depending if:

- **Case a:** one of the following IE occurs:
  - IE1: Study drug discontinuation for major worsening of primary Sjögren's syndrome.
- **Case b:** the following IE occurs:
  - IE2: Increase or initiation of authorized medication for pSS.
  - IE3: Study drug discontinuation for AE related to study drug.
- **Case c:** data is missing due to another type of IE (IE4, IE5, IE6) or for other reasons.

Standard multiple imputation: this method (Rubin, 1987) replaces each missing value with a set of plausible values that represent the uncertainty about the right value to impute. Each value is a Bayesian drawn from the conditional distribution of the missing observation given the observed data, made in such a way that the set of imputation properly represents the information about the missing value that is contained in the observed data for the chosen model.

Copy increments in placebo: this method (Carpenter *et al*, 2013) involves imputing the missing values in the treatment arm under MNAR by a patient's mean profile similar to the mean profile in the control arm but starting from the benefit already obtained. On the other hand, the missing values in the control arm will be imputed under MAR.

Jump to placebo: this method (Carpenter *et al*, 2013) involves imputing the missing values in the treatment arm under MNAR by a patient's mean profile similar to the mean profile in the control arm, thus losing the potential effect of the under-treatment period. On the other hand, the missing values in the control arm will be imputed under MAR

The multiply imputed data sets are then analysed by using standard procedures for complete data and combining the results from these analyses, based on the change from baseline.

Multiple imputation inference involves **3 consecutives phases** (phase 1: imputation step, phase 2: analysis step and phase 3: combination step).

Phase 1: Imputation step
To guarantee the reproduction of results, the seed will be fixed at 95011.

Step 1:
First, data collected post IE should be considered as missing (use flag derived in ADAM). In case of patient with several events (IE1="Y" and IE2="Y"…), the first one will be considered and all the values after (strictly) will be considered as missing.

Thanks to Part1a and Part1b macros, all intermittent missing data (*i.e.* with an arbitrary missing pattern) will be first imputed using a MI approach based on MCMC method by treatment groups, in case the initial dataset has not a strict monotone missing pattern.

A total of 100 imputed partially completed datasets will be generated. This dataset will serve as a basis for the following.

Step 2:
In this sequence, remaining missing data of *DATA_BASIS* will be imputed. The nature of the IE has to be considered as the imputation rules will be different. The macro Part2a and Part2b of five macro will be used here. The methodV statement (*i.e.* a variable indicating for each record which imputation method should be used) will be used in Part2a macro. This variable would have been derived in the dataset. Then depending in IE and associated method the following will occur inside the macro:

- **Step 2a: for all missing data due to IE written in case a:**
  For this specified IE (IE1), imputation will be done according to jump to placebo approach. All data (*DATA_BASIS*) will be considered to benefit of all data available at each visit. Steps for imputation are the following:
  - For patients in treatment arm: use jump to placebo approach with non-missing data from the placebo arm to impute missing data post-IE1 in the treated arm (use SAS macro "five macros").
  - For patients in control arm: impute the missing values for each imputation separately under the assumption of MAR, taking into account the baseline and value at previous and current visits in this order from *DATA_BASIS.*
  - Keep only the imputed rows in the table (patients with IEFNUM=1).
- **Step 2b: for all missing data due to IE written in case b:**
  For those two specified IEs (IE2 and IE3), imputation will be done according to copy increments in placebo approach. All data (*DATA_BASIS*) will be considered to benefit of all data available at each visit. Steps for imputation are the following:
  - For patients in treatment arm: use copy increments in placebo approach with non-missing data from the placebo arm to impute missing data post-IE2/IE3 in the treated arm (use SAS macro "five macros").
  - For patients in control arm: impute the missing values for each imputation separately under the assumption of MAR, taking into account the baseline and value at previous and current visits in this order from *DATA_BASIS.*
  - Keep only the imputed rows in the table (patients with IEFNUM=2 or 3).
- **Step 2c: for all patients with missing data as mentioned in case c**
  - To impute those missing data, all data (*DATA_BASIS*) will be considered in order to benefit of all data available at each visit. However, at the end, only imputed data from this step will be considered.

- A regression method will be used to perform the imputation, using in this order: baseline, treatment, visit i-1, visit i in the model. Of note, for imputing data of visit i, data up to visit i-1 are to be considered for the imputation, even if the data of visit i-1 already results of an imputation (this is taken into account in PROC MI with the order of the variables put in the VAR statement).

Step 3:
Finally, the macro returns a complete data set with all patients with imputed data from Step2a, from Step2b, from Step2c and all Completers patients from Step1 (*DATA_COMPLETE*).

Phase 2: Analysis step
The planned model will be applied to each of the 100 imputed datasets obtained at the previous step (*DATA_COMPLETE*). For each imputed dataset i (i=1,2…,m), the estimate of the difference between groups and the associated standard error will be stored. This will be done with the Part3 macro.

Phase 3: Combination step
Thanks to Part3 macro, Statistical inferences will be generated by combining results from the 100 analyses using Rubin's formulae. The multiple imputation estimator of the difference between S95011 and Placebo is the average of the individual 100 estimators.

8. REFERENCES

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