Clinical Development

VAY736

CVAY736A2201 / NCT02962895

# A randomized, double-blind, placebo-controlled multicenter phase 2 dose-ranging study to assess the safety and efficacy of multiple ianalumab doses administered subcutaneously in patients with moderate to severe primary Sjögren's Syndrome

Statistical Analysis Plan (SAP)

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| 17-May-2017 | Prior to DB lock | Creation of final version | N/A - First version | NA |
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| 27-Jul-2019 | Prior to DB lock | Amended based on comments on dry run | Remove some baseline characteristics; Correct significance level of confidence intervals; Add dose response analysis of ESSPRI dryness, fatigue, and pain subscores; [redacted] Add CTC grade for Lymphocytes; Add steroid conversion table. | Section 2.3, 2.5.1, 2.6.4, 2.10, 5.3 and 5.6 |

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## List of abbreviations

| | |
|---|---|
| AE | Adverse event |
| ATC | Anatomical Therapeutic Classification |
| AUC | Area Under the Curve |
| bid | bis in diem/twice a day |
| CSR | Clinical Study report |
| CTC | Common Toxicity Criteria |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DMC | Data Monitoring Committee |
| DMARD | Disease modifying anti-rheumatic drug |
| FAS | Full Analysis Set |
| eCRF | Electronic Case Report Form |
| IVR | Interactive Voice Response |
| IWR | Interactive Web Response |
| MedDRA | Medical Dictionary for Drug Regulatory Affairs |
| NCI | National Cancer Institute |
| o.d. | Once Daily |
| OS | Overall Survival |
| PFS | Progression-Free Survival |
| PK | Pharmacokinetics |
| PPS | Per-Protocol Set |
| PRO | Patient-reported Outcomes |
| qd | Qua'que di'e / once a day |
| QoL | Quality of Life |
| RAP | Report and Analysis Process |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAP | Statistical Analysis Plan |
| SOC | System Organ Class |
| TFLs | Tables, Figures, Listings |
| WHO | World Health Organization |

# 1 Introduction

The purpose of this Statistical Analysis Plan (SAP) is to describe the implementation of the statistical analysis planned in the data analysis section 9 of the study protocol.

This SAP will be used in executing the final CSR for this study. It can also be used to execute primary efficacy analysis when all patients complete Week 24.

## 1.1 Study design

This is a randomized, double-blind, placebo-controlled, multicenter, parallel-group trial in approximately 180 patients with active pSS. The study is divided into 4 study periods:

**Period 1:** A screening period of 4 weeks to assess patient eligibility. Patients can be re-screened only once and no study-related re-screening procedure should be performed prior to written re-consent by the patient.

**Period 2:** At baseline, eligible patients will be randomized to one of three VAY736 dose arms (VAY736 5 mg, 50 mg or 300 mg s.c.) or a placebo arm. Blinded study drug will be administered every four weeks for a 24-week period. Approximately 45 patients will be randomized per treatment group. [redacted], randomization will be stratified by:

- baseline ESSDAI score (<10 or ≥10 based on weighted scores)

[redacted]

The primary endpoint will be assessed at the end of period 2 (week 24).

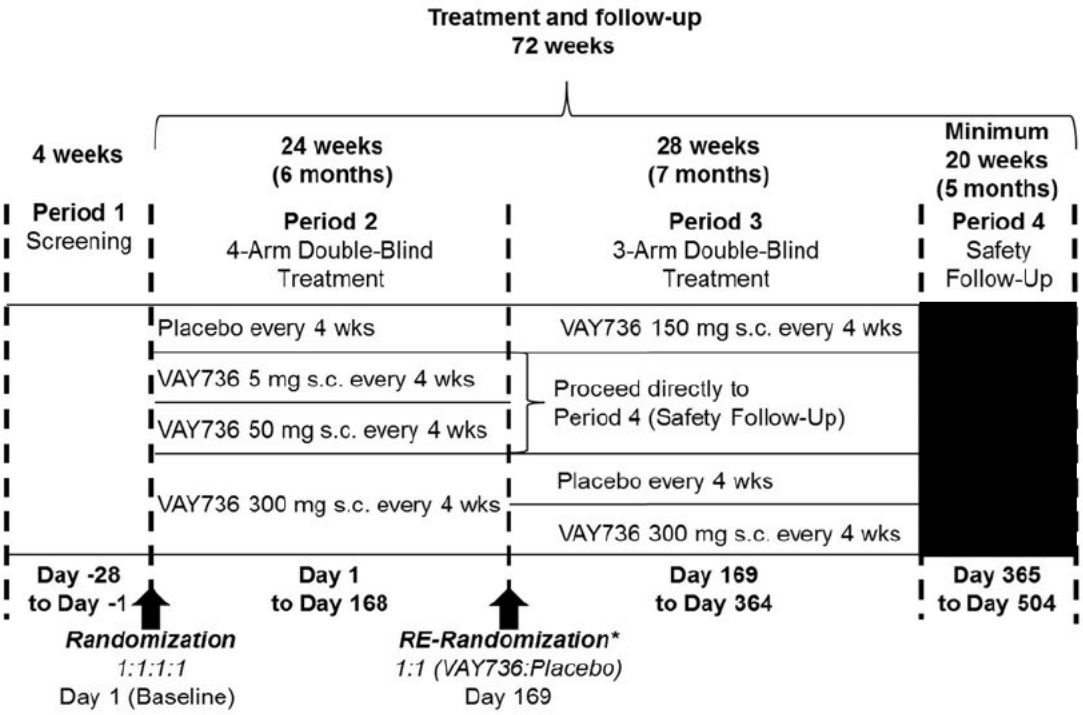
Treatment assignment in period 2 will remain double blinded until the end of period 3.

**Period 3:** After week 24 assessments, patients in the VAY736 300 mg arm will be re-randomized in a 1:1 ratio to either continue VAY736 300 mg s.c. every four weeks or switch to [redacted] placebo up to week 52. Patients who received placebo during period 2 will be switched to VAY736 150 mg s.c every four weeks up to week 52. Patients who received 5 mg and 50 mg s.c. in period 2 will proceed directly to period 4. Treatment assignment in period 3 will remain double blinded until the end of the study period.

**Period 4**: The safety follow-up period lasts for a minimum of 20 weeks from last dose administration of VAY736, or longer (with reduced visit frequency) [redacted] whichever occurs first (Figure 1-1) (van Vollenhoven 2012; Emery 2014, Genovese 2008). Patients who have not yet recovered their B-cell counts two years after last VAY736 dosing, will be discharged from the study and undergo their End of Study (EoS) visit. Patients who will be treated with another immunmodulatory or immunsuppressive treatment (e.g. azathioprine, cyclophosphamide, high dose glucocorticosteroids) after completion of the minimum 20 week safety follow-up period are excluded from further safety follow-up.

The primary efficacy analysis will be performed when all patients have completed the week 24 study visit.

**Figure 1-1 Study design**




**Only patients in the period 2 VAY736 300 mg arm will be eligible for period 3 re-randomization. Patients who were randomized to Pbo in period 2 will receive double blind VAY736 150mg s.c. every 4 weeks, but will not be re-randomized in period 3. All other patients will proceed directly from period 2 to period 4 (Safety Follow-Up period).*

## 1.2 Study objectives and endpoints

**Table 1-2 Objectives and related endpoints**

| Objective | Endpoint |
|---|---|
| Primary | |
| To demonstrate a dose response of VAY736 defined as change in ESSDAI from baseline at 24 weeks | Change in ESSDAI score from baseline over 24 weeks as compared to placebo |
| Secondary | |
| To assess a dose response of VAY736 in the change from baseline of ESSPRI at 24 weeks | Change in ESSPRI score from baseline over 24 weeks as compared to placebo |
| To assess a dose response of VAY736 in the change from baseline of the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F) at 24 weeks | Change in FACIT-F from baseline over 24 weeks as compared to placebo |
| To assess a dose response of VAY736 in the change from baseline of SF-36 at 24 weeks | Change in SF-36 physical component (PCS) and mental component (MCS) from baseline over 24 weeks as compared to placebo |

| Objective | Endpoint |
|---|---|
| To assess changes from baseline in PhGA of the patient's overall disease activity at week 24 | Change from baseline in PhGA of patient's overall disease activity (recorded by VAS) over 24 weeks as compared to placebo |
| To assess change from baseline of ESSDAI, ESSPRI, PhGA, PaGA, FACIT-F, SF-36 at weeks 4, 8, 12 and 16. | Change in ESSDAI, ESSPRI, PhGA, PaGA, FACIT-F, and SF-36 from baseline at weeks 4, 8, 12, and 16 as compared to placebo |
| To evaluate the effects of VAY736 on salivary gland function at 24 weeks | Change from baseline in salivary flow rate (unstimulated and stimulated) at 24 weeks as compared to placebo |
| [redacted] | |
| To assess safety and tolerability of VAY736 | AEs, SAEs, and routine safety laboratory tests |
| To assess immunogenicity (IG) of VAY736 | Serum anti-VAY736 antibodies (ADA assay) during treatment and follow up period |
| To assess PK of VAY736 after multiple s.c. doses | Monthly and follow up PK measurements at the four dose levels |

[redacted]

# 2 Statistical methods

## 2.1 Data analysis general information

The analyses will be performed in SAS 9.3 or later (SAS Institute, Cary NC).

Descriptive statistics on continuous data will include mean, standard deviation, median, 25$^{th}$ and 75$^{th}$ percentiles, minimum and maximum, while categorical data will be summarized as frequencies and percentages.

Inferential modeling for primary and key secondary variables will include geographic region, and stratification factor baseline ESSDAI score <10 or ≥10.

**Table 2-1 Geographic Regions**

| Region | Countries |
|---|---|
| 1 | Argentina, Spain, Chile, France, Portugal, Italy |
| 2 | US, UK |
| 3 | Austria, Germany, Israel, Belgium, Netherlands |
| 4 | Romania, Russia, Hungary, Poland |
| 5 | Japan, Taiwan |

### 2.1.1 General definitions

**Study treatment**

The following grouping scheme / data selection will be used for reporting of safety summary:

Grouping Scheme 1 (short term summary, up to 24 weeks): only data on or before the end of treatment (defined below) in period 2 will be tabulated. The treatment used will be according to the treatment groups initially received:

Placebo

VAY736 5 mg

VAY736 50 mg

VAY736 300 mg

Any VAY736

Grouping Scheme 2 (long term summary, all study periods):

VAY736 5 mg

VAY736 50 mg

VAY736 150 mg

VAY736 300 mg 24 Weeks (this group includes patients receiving VAY736 300 mg and stopping treatment in period 2, as well as those receiving placebo in period 3)

VAY736 300 mg 52 Weeks

Any VAY736 300 mg

Any VAY736

**Study day**

Day 1 is defined as the date of first dose of study drug (VAY736 or Placebo). Study day is defined as the number of days since the date of first dose of study treatment (Day 1).

Therefore, for a particular date, study day will be calculated as follows:

- For dates on or after the date of first administration of study treatment,

  Study day = Assessment date – Date of first dose of study treatment + 1;

- For dates prior to the date of first administration of study treatment,

  Study day = Assessment date – Date of first dose of study treatment.

**Baseline**

The baseline value is defined as the last assessment prior to first dose administration. In case the scheduled baseline assessment value is missing, the screening value will be used instead.

**Treatment-emergent adverse event**

A treatment-emergent adverse event (AE) is definded as any adverse event started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term (PT).

**End of Treatment Date (EoT)**

The end of treatment date is the date of EoT disposition on CRF page for patients who complete the study treatment(s) as per protocol, or the date of the last dose plus 27 days if patients early discontinue the treatment. Therefore, the end of treatment date (EoT) in period 2 is defined as below:

1) patients who complete period 2 treatment and enter period 4 directly: EoT = the date of period 2 disposition on CRF page
2) patients entering period 3: EoT = the date of the first dose in period 3
3) patients early discontinue the treatment in Period 2: EoT = the date of the last dose in period 2 plus 27 days .

The end of treatment date (EoT) in period 3 is defined as below:

1) patients who complete period 3 treatment: EoT = the date of period 3 disposition on CRF page
2) patients early discontinue the treatment in Period 3: EoT = the date of the last dose in period 3 plus 27 days .

**Period**

The period 2 starts from the first dose on Day 1 visit; the period 2 end date is the end of treatment date in period 2. The period 3 starts from first dose in period 3; the period 3 end date is defined as the end of treatment date in period 3. The period 4 starts on the day after the end of treatment in period 2/3. Assignment of events to each period will be based on date and time. When time is missing or not reported, the assignment will be based on date only; in that case, events starting on the date of first dose in period 3 will be assigned to the period 3 for those who are entering period 3, or to the safety follow-up period.

**Visit windowing**

For the efficacy analysis, when visit windows are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows. E.g., if the *Week 4* visit of a subject is delayed and occurs on Day 46 instead of on Day 28, it will be re-aligned to visit window *Week 8*. In the case of major deviations from the visit schedule, or due to unscheduled visits, several assessments of a subject may fall in a particular visit window (either scheduled or unscheduled). The rule to derive the visit windows are given in the Appendix 5.1.

## 2.2 Analysis sets

**Enrolled set (ENR):** All subjects who signed the informed consent are included in the Enrolled Set. The enrolled set will be used when screening information needs to be presented.

**Randomized set (RAN):** All patients randomized are included in the Randomized Set. Patients will be analyzed according to the treatment assigned to at randomization. Unless otherwise

specified, mis-randomized patients (randomized in IRT by mistake ) will be excluded from the randomized set. The RAN will be used for summaries of patient disposition and analysis sets.

**Full analysis set (FAS)**: comprises all patients in the RAN to whom study treatment has been assigned. Following the intent-to-treat principle, patients will be analyzed according to the treatment assigned to at randomization, but actual stratum. FAS will be used for all efficacy variables, unless otherwise stated.

**Per Protocol set (PPS)**: includes all FAS patients who are not excluded due to major protocol deviations (see Section 5.6).

**Safety set (SS)**: includes all patients who received at least one dose of study medication. Patient will be analyzed according to treatment received and the actual stratum at baseline. The safety set will be used in the analysis of all safety variables.

### 2.2.1 Subgroups of interest

Subgroups of interest are listed below. These will not necessarily be applied to all analyses but used as specified in the protocol or this SAP.

- stratification factor baseline ESSDAI score <10 or ≥10
- geographic region

## 2.3 Patient disposition, demographics and other baseline characteristics

The analyses described in this section will be based on RAN and presented by the treatment groups initially randomized.

Summary statistics will be presented for continuous demographic and baseline characteristic variables for each treatment group and for all patients in the randomized set. The number and percentage of patients in each category will be presented for categorical variables for each treatment group and all patients.

The following demographic variables and baseline disease characteristics will be summarized by treatment group:

- Demographics:
  - Continuous variables: age, weight, height, BMI, time since diagnosis

- Categorical variables: Gender, race, ethnicity

- Baseline Disease Characteristics:
  - Continuous variables: ESSDAI , ESSPRI (pain, fatigue, dryness), PhGA (physician-assessed global VAS score), PaGA (patient assessed VAS score for global disease) , stimulated and unstimulated salivary flow, [redacted], Immunoglobulin level (IgG and IgM), SF-36 score (PCS and MCS), FACIT-F score, [redacted]
  - Categorical variables: ESSDAI stratum (<10 or ≥10), use of DMARDs (split by type – to be defined further in PDS), [redacted] history of prior biologics treatment use (Yes/No), [redacted] Hypergammaglobulinemia (Yes if above ULN of IgG or IgM), Systemic signs (Glandular, Pulmonary, Neurologic or Articular, where 0=no sign), Steroid therapy (Yes/No) (A steroid conversion table is provided in Section 5.6 to calculate the amount of steroid use if needed)

### Medical history

Any significant prior or active medical condition at the time of signing informed consent will be coded using the MedDRA dictionary. These medical conditions will be summarized by primary system organ class and preferred term.

### 2.3.1 Patient disposition

The RAN will be used for summaries of patient disposition and analysis sets.

The patient disposition will be summarized by treatment group for different study periods (Period 2, Period 3 and Period 4). The following treatment group will be used for each period:

- Period 2: Placebo, VAY736 5 mg, VAY736 50 mg, VAY736 300 mg, Any VAY736, All
- Period 3: VAY736 150 mg, VAY736 300 mg -> Placebo, VAY736 300 mg -> VAY736 300 mg, Any VAY736
- Period 4: Placebo, VAY736 5 mg, VAY736 50 mg, VAY736 150 mg, VAY736 300 mg, VAY736 300 mg -> Placebo, VAY736 300 mg -> VAY736 300 mg, All

The number and percent of patients screened, randomized, completed and discontinued from the study will be summarized with reasons for discontinuation.

The number of patients with major protocol deviations and protocol deviations leading to exclusion from per-protocol set will be tabulated by category and deviation for the Randomized set.

The number of patients included in each analysis set will be tabulated. Patient exclusion from analysis populations will be listed for all patients with reasons for exclusion.

## 2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

### 2.4.1 Study treatment / compliance

The analysis of study treatment data will be based on the safety set.

The analysis will be summarized by the following treatment:

- Placebo
- VAY736 5 mg
- VAY736 50 mg
- VAY736 150 mg
- VAY736 300 mg
- Any VAY736

Duration of exposure of a treatment will be defined as following:

Duration of exposure (days) = end of treatment date – date of first dose + 1

Duration of exposure (weeks) = duration of exposure (days)/7

Note: Specifically in the calculation of duration of exposure, for VAY736 300 mg ->Placebo patients, end of treatment date is the end of treatment date (EoT) in period 2;

For Placebo->VAY736 150 mg patients, end of treatment date for placebo is the the end of treatment date (EoT) in period 2. The date of first dose for VAY736 150mg is the date of first administration of VAY736 150mg .

The cumulative duration of exposure to study treatment (the number and percentage of patients) will be summarized by treatment group (any, ≤ 4 Weeks, 5 - 8 Weeks, etc. up to 49 - 52 weeks).

### 2.4.2 Prior and concomitant medication

Prior medications are defined as treatments taken and stopped prior to first dose of study treatment. Any medication given at least once between the day of first dose of randomized study treatment and the date of the last study visit will be a concomitant medication, including those which were started pre-baseline and continued into the period where study treatment is administered.

Prior and concomitant medications will be summarized in separate tables for SAF. Medications will be presented in alphabetical order, by Anatomical Therapeutic Classification (ATC) codes and grouped by anatomical main group. Tables will show the overall number and percentage of patients receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

The number and percentage of patients receiving systemic therapies for pSS as prior and concomitant background medication will be presented separately by preferred term.

## 2.5 Analysis of the primary objective

### 2.5.1 Primary endpoint

The following estimand framework is adopted for the primary analysis.

- Population: FAS
- Variable of interest: Change from baseline in ESSDAI total score after 24 weeks of VAY736 or placebo administration every four weeks. This will be defined as the Week 24 ESSDAI value minus the baseline ESSDAI value with negative values indicating improvement in disease status.
- Intercurrent events: Regardless whether early termination from the study, interruption of study treatment, or intensified concomitant treatment (local and systemic) has occurred.
- Summary measure: Adjusted mean change from baseline in ESSDAI total score at Week 24 will be calculated from MMRM.

#### Statistical hypothesis, model, and method of analysis

The primary analysis will be based on FAS.

The primary objective of this study is to demonstrate a dose response of VAY736 defined as change in ESSDAI from baseline at 24 weeks. [redacted]

[redacted]

### 2.5.2 Handling of missing values/censoring/discontinuations

The planned primary repeated measures mixed effects model assumes that missing values are missing at random. The reasonableness of this assumption will be checked during the blinded review of the data and if necessary further methods may be applied.

Sensitivity analyses of imputing might be considered to test the robustness of the results to the missing data assumptions. The following approaches could be explored:

- impute data based on the placebo treatment group data;
- impute data based on patients' data who discontinued treatment but continued study visits in case a sufficiently high number of such cases is observed.

### 2.5.3 Supportive analyses

**Per Protocol Analysis**

To assess the potential influence of adherence to study procedures on the results of the primary analysis, the full dose response modeling analysis as described in Section 2.5.2 will be repeated based on per protocol set.

**Responder Analysis**

Responder status in ESSDAI will be assessed at week 12 [redacted]

[redacted]

## 2.6 Analysis of the secondary objective

### 2.6.1 Secondary endpoint

The following secondary variables will follow same estimand definition as primary efficacy endpoint.

The secondary variables include change from baseline in ESSPRI, FACIT-F, SF-36 (PCS and MCS), PhGA, PaGA and salivary flow rate (unstimulated and stimulated) over 24 weeks.

### 2.6.2 Statistical hypothesis, model, and method of analysis

The same dose-response analysis using MCPMod for primary endpoint will be done on the ESSPRI and FACIT-F score.

[redacted]

### 2.6.3 Handling of missing values/censoring/discontinuations

For the secondary analyses, missing data will not be imputed. If missing data occurs in a domain the corresponding total measurement will be set to missing. If a baseline assessment is missing (and there is no the screening value available to replace it) the corresponding change from baseline value will be missing.

[redacted]

## 2.7 Safety analyses

All safety variables will be analyzed on based on the safety set.

### 2.7.1 Adverse events (AEs)

The number (and proportion) of patients with treatment emergent adverse events (events started after the first dose of investigational drug or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class (SOC) and preferred term (PT).
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation.

As appropriate, the exposure-adjusted event rate (EAER) defined as below will be presented:

$$EAER = \frac{\sum \#\ of\ events}{\sum \min(study\ cutoff, end\ of\ study)}$$

A graphical display of relative frequencies within system organ classes and relative risks, as appropriate, will be presented.

**Compound specific safety evaluation**

Safety topics of interest, such as risks defined in the Safety Profiling Plan (SPP), Risk Management Plan (RMP) or topics of interest regarding signal detection or routine analysis are defined in the Program Case Retrieval Strategy (CRS).

The crude incidence and exposure-adjusted incidence rates for SPP risks will be summarized. In addition, listings will be provided presenting which subjects experienced which risk.

Important note: For the evaluation of SPP risks, primary and secondary system organ classes and preferred terms of the MedDRA dictionary will be considered, as defined in the Program CRS and RMP.

**Clinical Trial Safety Disclosure**

(see references)

[redacted]

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

### 2.7.2 Injection reactions

Injection reactions will be summarized by type of injection reaction (overall, local and systemic), by grading, and by visit.

### 2.7.3 Laboratory data

The summary of laboratory evaluations will be presented for [redacted] of laboratory tests [redacted]

Descriptive summary statistics for the change from baseline to each study visit will be presented by test group, and laboratory test.

Shift tables based on the normal laboratory ranges will also be provided. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for worst post-baseline relative to the baseline. These summaries will be presented by laboratory test category.

The number and percentage of patients with clinically notable laboratory results after baseline will be presented.

### 2.7.4 Immunogenicity

A listing of immunogenicity (anti-VAY736 antibodies) will be provided.

### 2.7.5 ECG data

Summary statistics will be presented for ECG variables by visit.

### 2.7.6 Vital signs

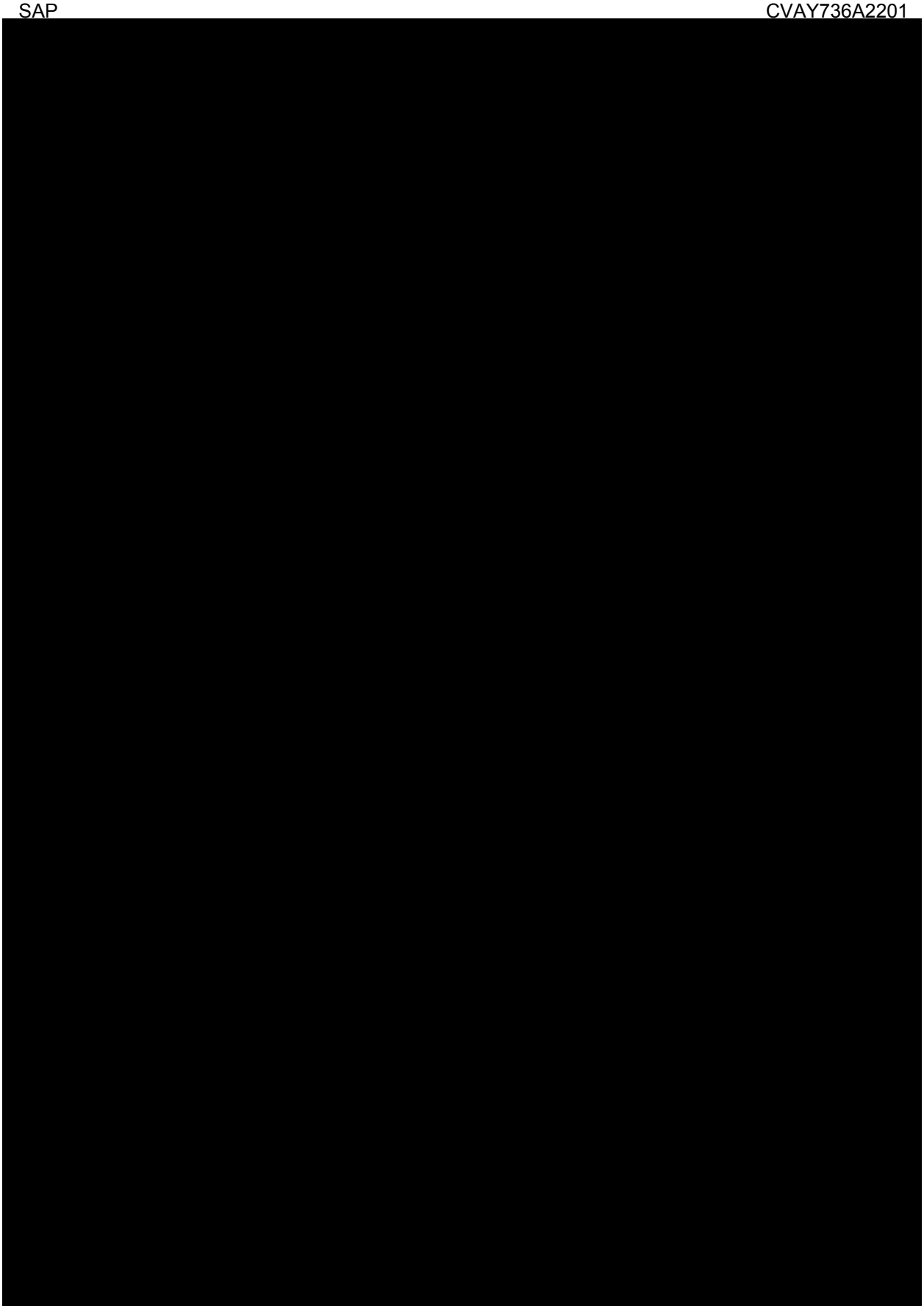
Analysis of the vital sign measurements using summary statistics for the change from baseline for each post-baseline visit will be performed. These descriptive summaries will be presented by vital sign.

The number and percentage of patients with clinically notable vital signs after baseline will be presented.

## 2.8 Pharmacokinetics

PK data will be analyzed based on the FAS.

[redacted]



## 2.15 Interim analysis

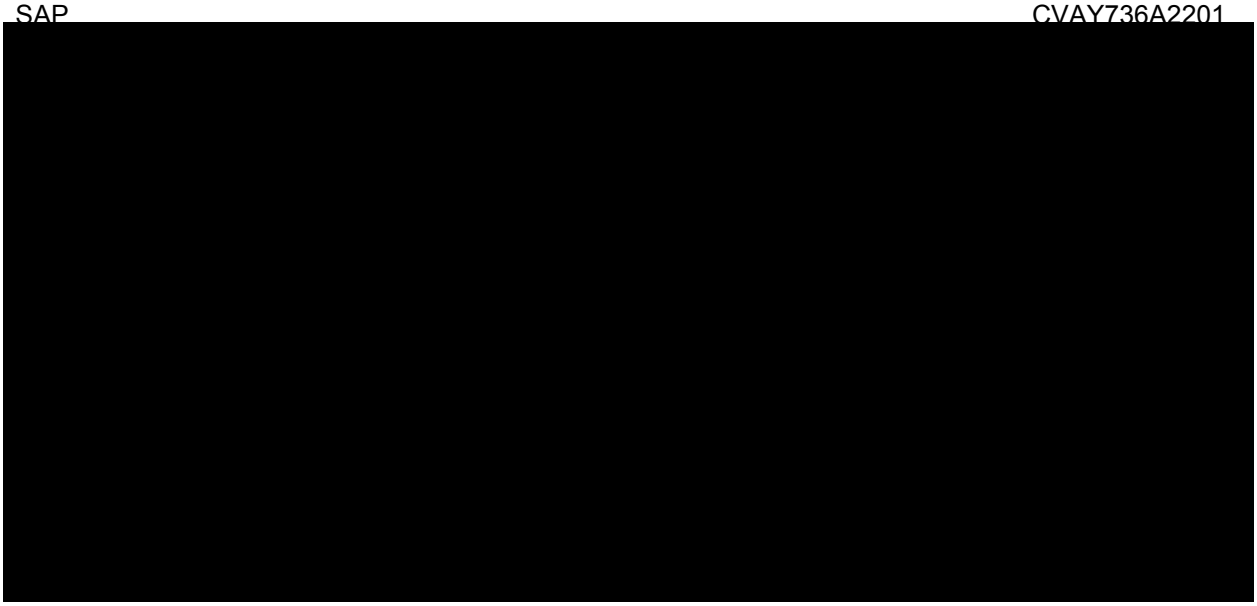
An interim analysis will be performed prior to the primary efficacy analysis in addition to regularly scheduled safety reviews of data performed by the DMC.

This interim analysis will occur when at least 100 of the randomized patients (~55% and ~25 per treatment group) will have reached the primary efficacy timepoint at week 24.

Further details of the interim analysis will be provided in a separate SAP.

### Primary efficacy analysis after all patients finished week 24

The primary efficacy analysis will be conducted when all randomized patients have finished period 2 (24 weeks of treatment). At this point the primary efficacy analysis and key secondary analyses will be conducted to allow planning activities for upcoming studies.



# 4 Change to protocol specified analyses

Not applicable.

# 5 Appendix

## 5.1 Visit Windows

When visit windows are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows. E.g., if the *Week 4* visit of a subject is delayed and occurs on Day 46 instead of on Day 28, say, it will be re-aligned to visit window *Week 8*. In the case of major deviations from the visit schedule, or due to unscheduled visits, several assessments of a subject may fall in a particular visit window (either scheduled or unscheduled).

The following rules are used to determine the window for an applicable visit post baseline: "Lower limit" = "upper limit of prior applicable visit" + 1. "Upper limit" = "target day of current visit" + integer part of ("target day of next applicable visit" – "target day of current visit")/2. Lower limit of the first applicable visit is always Day 2.

The mapping described in Table 5-1 applies to all visits (not just scheduled visits). Repeat and/or unscheduled visits (which will be numbered in the database according to NCDS standards) will be mapped for analysis purposes in the same way as scheduled visits. This leaves the possibility, then, for multiple measurements within an analysis window. The conventions in Table 5-2 will be used to determine the appropriate measurement to be summarized in the event of multiple measurements within a visit window.

**Table 5-1 Analysis Visit Windows**

| Period | Analysis Visit | Target Day | Visit Window for MMRM analysis | Visit Window for by-visit summary |
|---|---|---|---|---|
| | Baseline | 1 | ≤ 1* | ≤ 1* |
| 2 | Week 4 | 28 | 2-42 | 2-42 |
| | Week 8 | 56 | 43-70 | 43-70 |
| | Week 12 | 84 | 71-98 | 71-98 |

| | | | | |
|---|---|---|---|---|
| | Week 16 | 112 | 99-126 | 99-126 |
| | Week 20 | 140 | 127-154 | 127-154 |
| | Week 24 | 168 | 155-W24DT* if patient was dosed on Week 24<br>155-182 otherwise | 155-W24DT* if patient was dosed on Week 24<br>155-182 otherwise |
| 3 | Week 28 | 196 | | [W24DT**+1]-210 if patient was dosed on Week 24<br>183-210 otherwise |
| | Week 32 | 224 | | 211-238 |
| | Week 36 | 252 | | 239-266 |
| | Week 40 | 280 | | 267-294 |
| | Week 44 | 308 | | 295-322 |
| | Week 48 | 336 | | 323-350 |
| | Week 52 | 364 | | 351-378 |
| 4 | FU Week 4 | | | CRF visit |
| | FU Week 8 | | | CRF visit |
| | FU Week 12 | | | CRF visit |
| | FU Week 16 | | | CRF visit |
| | FU Week 24 | | | CRF visit |
| | FU Week 32 | | | CRF visit |
| | FU Week 44 | | | CRF visit |
| | FU Week 56 | | | CRF visit |
| | FU Week 80 | | | CRF visit |
| | FU Week 104 | | | CRF visit |

* W24DT is the date of week 24 dose
MMRM analysis: ESSDAI, PhGA, ESSPRI, FACIT-F, SF-36, PaGA, salivary flow, [redacted]

## Table 5-2 Rules for flagging variables (values)

| Timing of measurement | Type of data | Rule |
|---|---|---|
| Baseline | All data | The last non-missing measurement made prior to or on the date of administration of the first dose of study treatment (the reference start date / Day 1). If a patient did not receive any dose of study treatment then the randomization date will be used. Only date part is considered if just one assessment on Day 1.<br>If there are multiple assessments on Day 1, following rules will apply:<br>(a) If assessment time exists,<br>- select the last available measurement prior to reference start date/time considering time;<br>- if no measurement prior to reference start date/time considering time, select the earliest measurement post reference start date/time considering time .<br>(b) If assessment time does not exist, select the available measurement from the lowest CRF visit number. |
| Post-baseline efficacy | All data | • The measurement closest to the target will be used. In the event two measurements are taken equally apart (e.g. 1 before target date and 1 after) the first one will be used.<br>• Cases where the same parameter is recorded more than once on the same date will be handled as follows:<br>o If time of completion exists the earliest measurement will be used;<br>o If time does not exist the measurement from the lowest CRF visit number will be used. |
| Post-baseline safety | Summary visit information [redacted] | • The measurement closest to the target will be used. In the event two measurements are taken equally apart (e.g. 1 before target date and 1 after) the first one will be used.<br>• Cases where the same parameter is recorded more than once on the same date will be handled as follows:<br>o If time of completion exists the earliest measurement will be used;<br>o If time does not exist the measurement from the lowest CRF visit number will be used. |

| Timing of measurement | Type of data | Rule |
|---|---|---|
| Post-baseline safety | Notable abnormalities (e.g. lab) | The most extreme measurement in the window will be used. Note this means a patient can have a notably high and notably low measurement within a window. |

## 5.2 Imputation rules

### 5.2.1 Study drug

No imputation will be made to the start date and end date of study treatment.

### 5.2.2 AE date imputation

The following missing dates will not be imputed:

- Missing AE start dates
- AE start dates missing the year
- Partial/missing AE end dates

For other type of partial missing start dates, rules specified in the following tables will be used.

| | Day | Month | Year |
|---|---|---|---|
| **Partial Adverse Event Start Date** | Not used | MON | YYYY |
| **Treatment Start Date** | Not used | TRTM | TRTY |

The following matrix explains the logic behind the imputation.

| | MON MISSING | MON < TRTM | MON = TRTM | MON > TRTM |
|---|---|---|---|---|
| YYYY MISSING | ( 1 ) No convention | ( 1 ) No convention | ( 1 ) No convention | ( 1 ) No convention |
| YYYY < TRTY | ( 2.a ) Before Treatment Start | ( 2.b ) Before Treatment Start | ( 2.b ) Before Treatment Start | ( 2.b ) Before Treatment Start |
| YYYY = TRTY | ( 4.a ) Uncertain | ( 4.b ) Before Treatment Start | ( 4.c ) Uncertain | ( 4.c ) After Treatment Start |
| YYYY > TRTY | ( 3.a ) After Treatment Start | ( 3.b ) After Treatment Start | ( 3.b ) After Treatment Start | ( 3.b ) After Treatment Start |

Impute AE start date -

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
    a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).

b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).

3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
    a. If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).
    b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), treatment start date + 1 day).
4. If the AE start date year value is equal to the treatment start date year value:
    a. And the AE month is missing the imputed AE start date is set to the treatment start date + 1 day.
    b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
    c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), treatment start date + 1 day).

If AE end date is available and the imputed AE start date is greater than the AE end date, then imputed AE start date should be set to the AE end date.

[redacted]

## 5.3 Parameters derivations

[redacted]

### Notable vital signs abnormalities in adult patients (≥18 years of age)

Post-baseline vital signs will be flagged as notable abnormalities as follows:

1. Systolic/Diastolic blood pressure: ≥25% decrease or ≥25 % increase from baseline
2. Pulse: ≥110 bpm with ≥15% change from baseline, or <50 bpm with ≥15% change from baseline

## 5.4 Statistical models

### 5.4.1 Primary analysis

The primary endpoint will be analyzed using a 3-step approach. An overview of the approach is shown in Section 2.5.2 . In the following sections, some details on MMRM and DR model families are provided, followed by the MCPMod methodology.

#### 5.4.1.1 Repeated measures analysis

As a first step in the dose-response characterization a repeated measures model will be fitted to the changes from baseline in ESSDAI up to week 24. The change from baseline in ESSDAI is assumed to be normally distributed.

An MMRM model will be fitted to the changes from baseline in ESSDAI including all time points until week 24 including the following fixed factors

- treatment group
- (analysis) visit
- treatment group by visit interaction
- stratification factor baseline ESSDAI score <10 or ≥10
- geographic region

as well as baseline ESSDAI as a continuous covariate. An unstructured variance-covariance matrix will be fitted to model the dependency between repeated observations. Graphical checks on the model assumptions of normality of the data will be provided.
The mean treatment effects will be estimated at week 24. Together with the estimated covariance matrix, they will be used in the dose-response modeling as described below.

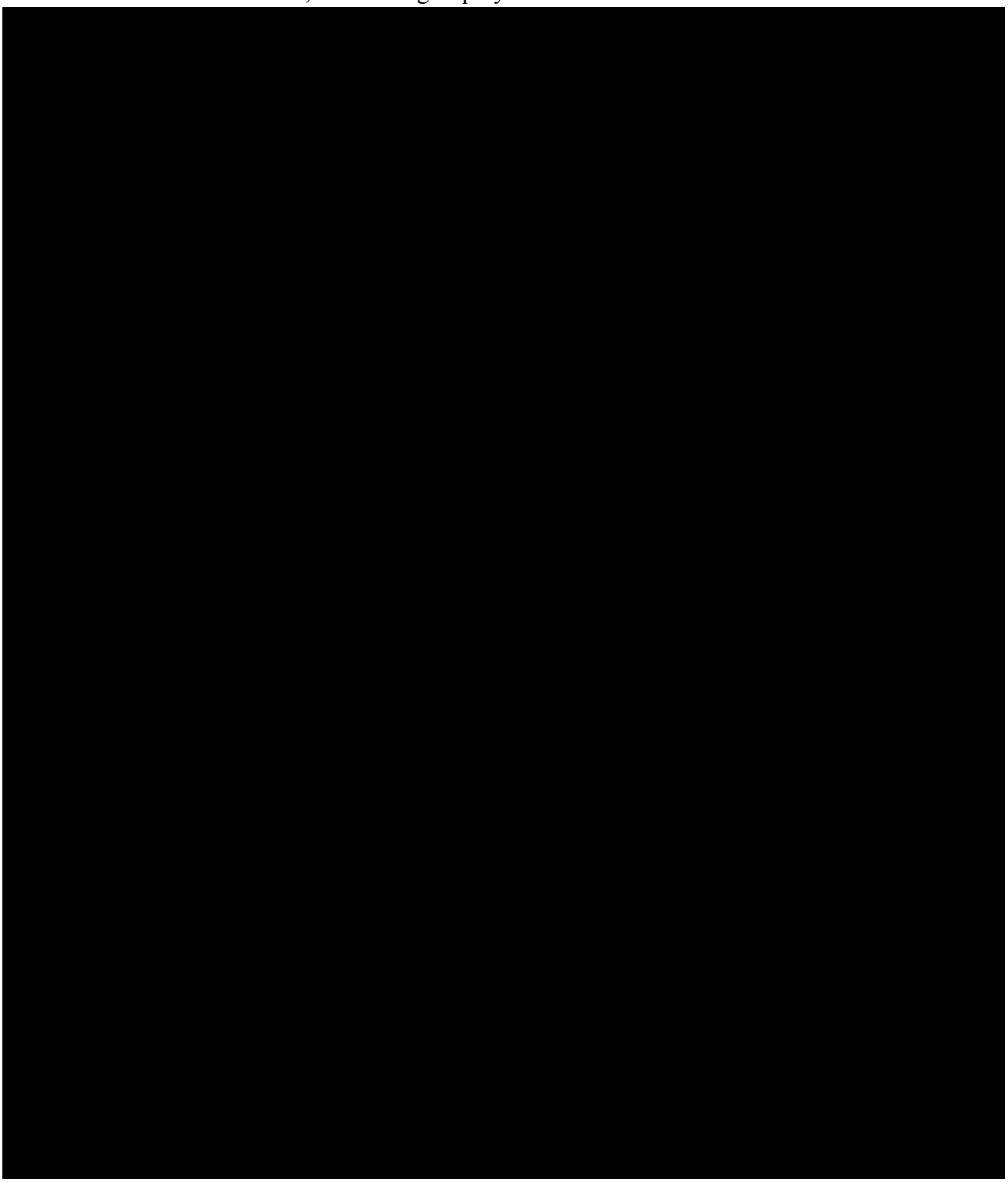
To allow adjustment for correlations between time points within patients, this MMRM approach is adopted to obtain the least squares means (LSM) fits.

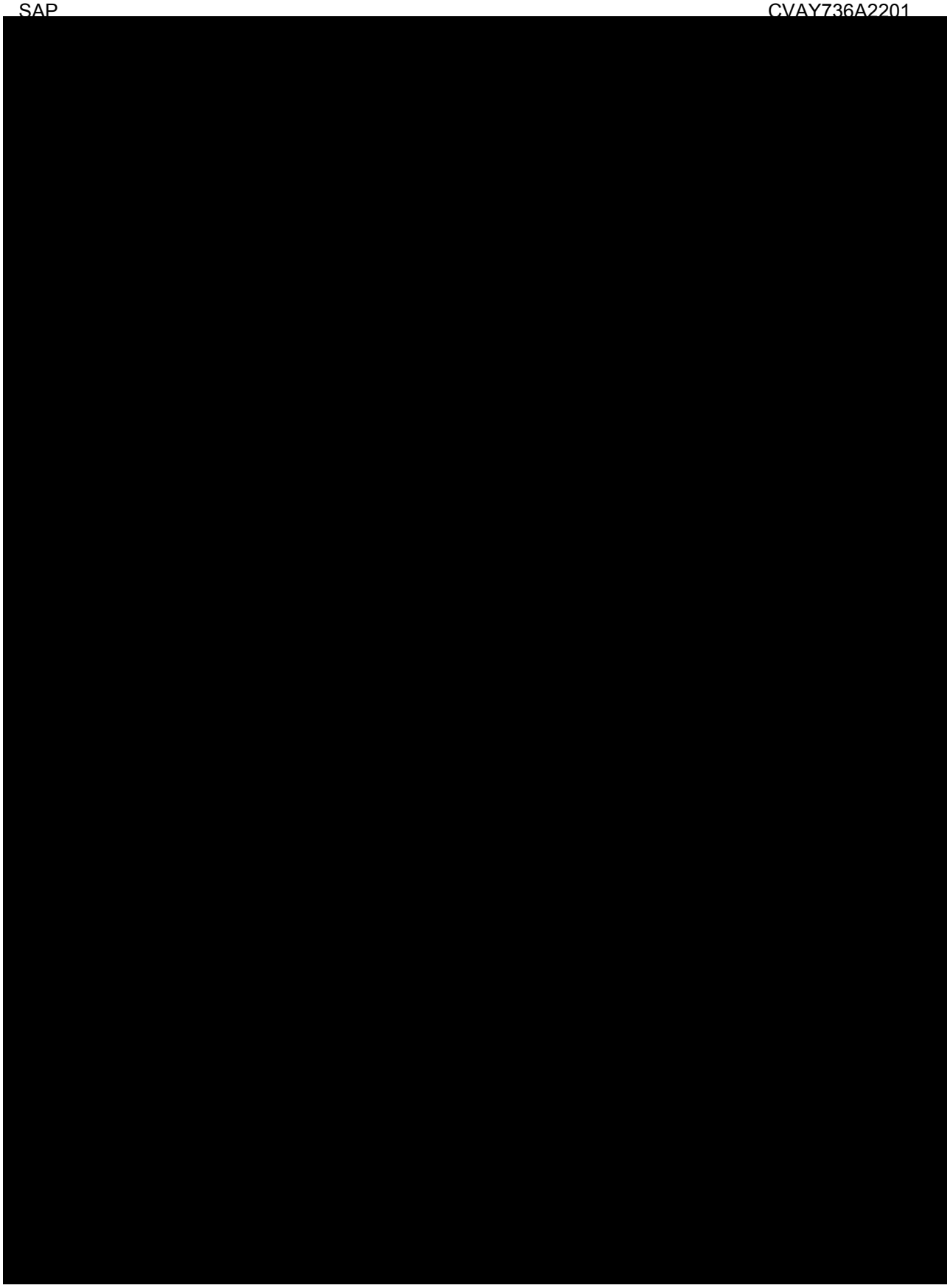
The mean responses at each individual dose will be obtained through covariate-adjusted treatment effects by modeling the primary efficacy variable using a mixed-effect model for repeated measures (MMRM). The model will contain terms (factors) given above. Treatment group, visit, and geographical region will be fitted as categorical variables and baseline score as a continuous covariate. The model will be fitted using the SAS procedure “PROC MIXED”. Unstructured covariance matrix will be used (TYPE = UN), thus allowing adjustment for correlations between time points within patients. In order to get the variance covariance matrix of treatment effects to be full rank matrix, no intercept option will be used (NOINT option in MODEL statement). Adjusted means and the corresponding variance covariance matrix will be estimated. The estimated treatment differences for all treatment comparisons will be tabulated along with the associated 90% confidence intervals (ALPHA = 0.1) and two-sided p-values. No adjustment for multiplicity will be made. The estimated treatment means along with 90% CIs will be presented graphically as well. For calculation of denominator degrees of freedom Kenwood-Rogers method would be used (DDFM=KR)

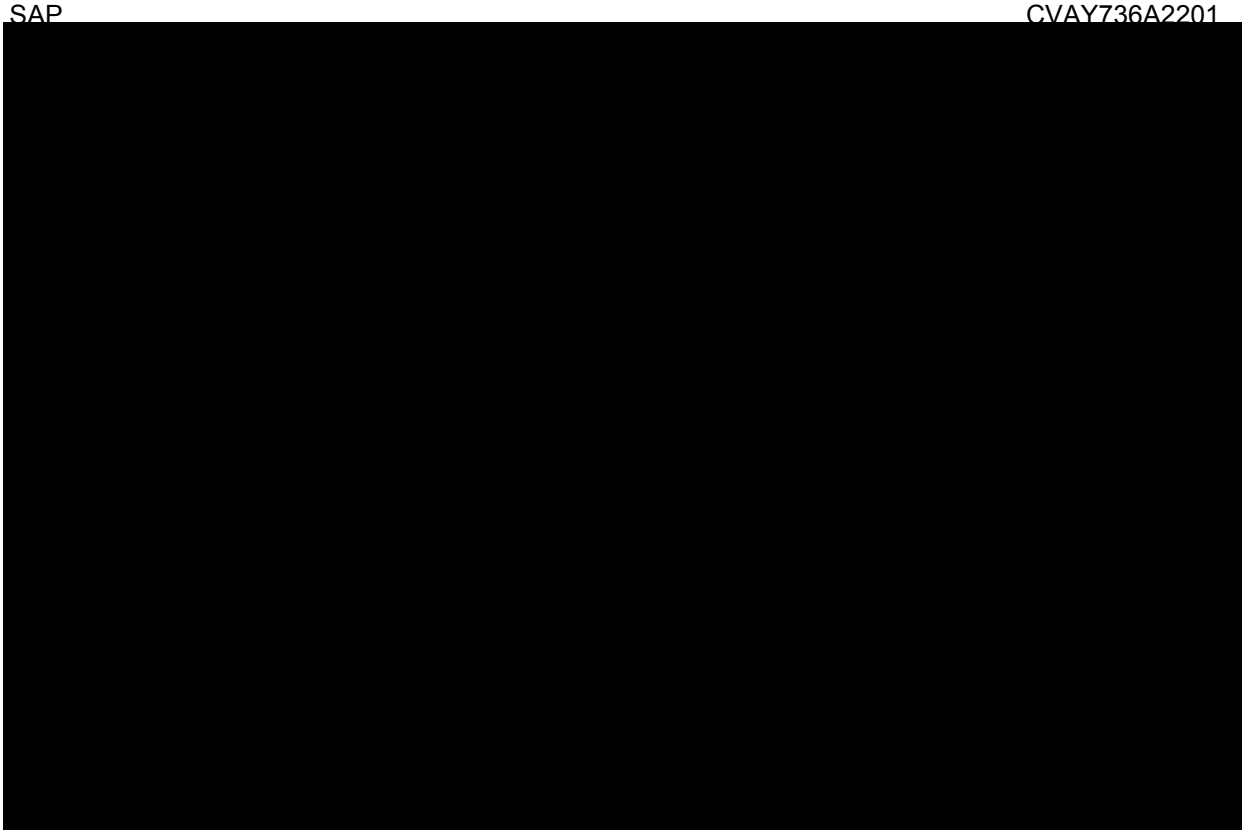
In case the MMRM model does not converge the following sequential steps will be used:

1. change ddfm=kr to ddfm=bw. If still no convergence, perform step 2.

2. change type=un to type=cs. If still no convergence, perform step 3.
3. remove covariates in the following order until convergence: geographic region, stratification factor, treatment group by visit interaction.







### 5.4.2 Secondary analysis

See Section 2.6.2.

In case the MMRM model does not converge the following sequential steps will be used:

1. change ddfm=kr to ddfm=bw. If still no convergence, perform step 2.
2. change type=un to type=cs. If still no convergence, perform step 3.
3. remove covariates in the following order until convergence:, geographic region, stratification factor, treatment group by visit interaction.

## 5.5 Rule of exclusion criteria of analysis sets

**Table 5-4 Protocol deviations that cause subjects to be excluded from PP analysis**

| Deviation ID | Description of Deviation |
|---|---|
| INCL03 & INCL06 | No histology biopsy and negative serology at screening for [redacted] |
| INCL04 | ESSDAI value <6 at screening, based on weighted scores of the 7 domains: biologic, hematologic, articular, cutaneous, glandular, lymphadenopathy and constitutional domains |
| INCL05 | ESSPRI value <5 at baseline |
| TRT01 | Patient did not receive at least one dose of study medication |
| TRT02 | Patient received wrong study medication |
| TRT03 | Patient missed two consecutive doses of study medication |
| CONC01 | Use of other investigational drugs within 5 half-lives of enrollment or within 30 days whichever is longer, or longer if required by local regulations |

| Deviation ID | Description of Deviation |
|---|---|
| CONC02 | Prior use of any B-cell depleting therapy (e.g., rituximab or other anti-CD20 mAb, anti-CD22 mAb or anti-CD52 mAb)<br>• within 1 year prior to randomization<br>• or as long as B-cell count <50 cells/µL |
| CONC03 | Prior treatment with any of the following within 180 days prior to randomization ([redacted] CTLA4-Fc Ig (abatacept); anti-TNF-α mAb; intravenous/subcutaneous Ig; plasmapheresis; i.v. or oral cyclophosphamide; oral cyclosporine<br>• Patients taking either hydroxychloroquine or methotrexate or azathioprine at consistent dose for ≥3 months prior to randomization are eligible if dose is maintained throughout the study<br>• If azathioprine is discontinued prior to enrollment, a minimum washout period of 30 days prior to randomization is required. |

## 5.6 Steroids Conversion

**Table 5-5 Steroids conversion factors**

| WHO drug code | Preferred term corticosteroid | Equivalent dose (mg) | Conversion factor |
|---|---|---|---|
| 000447xx | Prednisone | 5 | 1 |
| 000162xx | Prednisolone | 5 | 1 |
| 000496xx | Methylprenisolone | 4 | 1.25 |
| 012428xx | Meprednisone | 4 | 1.25 |
| 001867xx | Prednylidene | 5 5/7 | 0.875 |
| 000319xx | Triamcinolone | 4 | 1.25 |
| 000146xx | Cortisone | 25 | 0.2 |
| 000286xx | Hydrocortisone | 20 | 0.25 |
| 002131xx | Fludrocortisone | 2 | 2.5 |
| 000085xx | Betamethasone | 0.75 | 6 2/3 |
| 000664xx | Paramethasone | 2 | 2.5 |
| 000160xx | Dexamethasone | 0.75 | 6 2/3 |
| 008827xx | Deflazacort | 6 | 5/6 |
| 006445xx | Cloprednol | 3 | 1 2/3 |

# 6 Reference

## 6.2 External references

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Seror R, et al. (2016) Defining disease activity states and clinically meaningful improvement in primary Sjögren's syndrome with EULAR primary Sjögren's syndrome disease activity (ESSDAI) and patient-reported indexes (ESSPRI)Ann Rheum Dis; 75:382–389. doi:10.1136/annrheumdis-2014-206008.

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