NOVARTIS

Clinical Development

VAY736

CVAY736X2201

A single dose, double-blind, placebo-controlled, parallel study to assess the pharmacodynamics, pharmacokinetics and safety and tolerability of VAY736 in patients with primary Sjögren's syndrome

TSc RAP Module 3: Detailed Statistical Methodology

Personal Data

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1 Introduction to RAP documentation

1.1 Scope

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial ***"CVAY736X2201".***

Module 3 (M3) provides the description of the statistical methodology used to analyze the data, **Module 7** (M7) details the presentation of the data, including shells of summary tables, figures and listings, and **Module 8 (**M8) contains programming specifications e.g. for derived variables and derived datasets, to support the creation of CSR outputs.

1.2 Changes to RAP documentation (M3)

Refer to corresponding guidances and Translational Sciences (TSc) RAP Addendum template for detailed information on the requirements of documenting changes to RAP documentation.

For the statistical methodology (M3), any major changes occurring before database lock to the statistical methodology should be reflected in the RAP M3 documentation via version control (new document version to be approved by the trial team as the original module.

Major changes include, but are not limited to, changes in protocol that affect study design and statistical methodology.

Minor changes to the RAP M3 documentation can be captured e.g. by a study note to file / note in RAP Addendum or within the CSR itself. Minor changes include, but are not limited to, change in statistical model. Corrections of typographical errors or modification of spelling (from English to American, for example) do not need to be incorporated into the RAP M3 documentation.

2 Study objectives and design

2.1 Study objectives

Primary Objectives

- To compare the effect of a single i.v. dose VAY736 versus placebo on the clinical disease activity of primary Sjögren's syndrome patients as measured by the change of a modified EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) between base line and Week 12.
- To assess the safety and tolerability of a single i.v. dose VAY736 in patients with primary Sjögren's syndrome as measured by adverse events (AEs).

Secondary Objectives

- To evaluate the effect of a single i.v. dose VAY736 versus placebo on self-reported outcomes in pSS patients at 12 weeks compared to baseline as measured by the EULAR Sjögren's Syndrome Patient Reported Intensity (ESSPRI), the Short Form (36) Health Survey (SF-36) and the Multidimensional Fatigue Inventory (MFI) Questionnaire.
- To determine the changes in the physician global assessment of the patient's overall disease activity between baseline and Week 12 as recorded by a visual analog scale (VAS)
- To determine the changes in the patients global assessment of their disease activity between baseline and Week 12 as recorded by a VAS
- To determine the pharmacokinetics following a single dose i.v. VAY736 in pSS patients

Exploratory Objectives

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- High resolution ultrasound of parotid salivary glands as measured by the following parameters:
  - Parotid thickness and staging
  - Parotid blood flow with contrast agent (optional)

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- Salivary gland function using the salivary flow (unstimulated and stimulated)

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- Lacrimal gland function using the Ocular Staining Score
- Serum evidence of B cell hyperactivity, Corporate Confidential Information

- To assess the immunogenicity following a single i.v. dose of VAY736 in pSS patients
- To measure the effect of a single i.v. dose VAY736 on leukocyte subsets,

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2.2 Study design and treatment

This is a double-blind, randomized, placebo-controlled, parallel-group, non-confirmatory study to assess the safety, tolerability, pharmacokinetics, immunogenicity, pharmacodynamics and clinical efficacy of VAY736 administered intravenously as a single dose in pSS patients. The patients will be enrolled in 2 sequential cohorts:

- 3 mg/kg cohort (Cohort 1): 6 patients randomized to receive a single dose of VAY736 at a starting dose of 3.0 mg/kg or placebo at a 2:1 ratio; approximately 4 patients in this cohort will receive a 3.0 mg/kg dose of VAY736 and approximately 2 patients will receive placebo.
- 10 mg/kg cohort (Cohort 2): 20 patients randomized to receive a single dose of VAY736 at a dose of 10.0 mg/kg or 3.0 mg/kg or placebo at a 6:1:3 ratio, respectively. Around 12 patients will receive 10 mg/kg of VAY736 in this cohort and around 6 will receive placebo. Approximately 2 patients will receive 3.0 mg/kg in this cohort to maintain a level of blinding regarding the dose received.

Between Cohort 1 and Cohort 2 recruitment will be paused and a safety review will be conducted by the VAY736 project team and the principle investigators.

The single doses of 3 - 10 mg/kg are based on the two highest doses safely administered in Part 1 of the SAD phase I study recently completed in RA patients. This study will enroll around 26 patients with primary Sjögren's syndrome. At least 24 subjects are expected to complete the study.

Subjects that are prematurely withdrawn from the study for reasons other than safety will be replaced on a case by case basis. Data from the withdrawn patients will still be used in the primary analysis as much as possible but the sponsor will use replacement patients to obtain complete data on at least 24 patients.

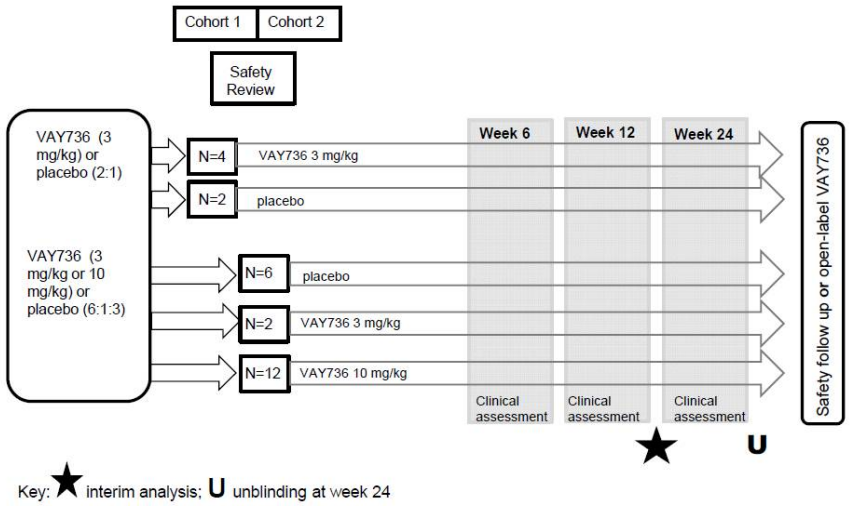
At Week 24 the blinding was broken to confirm treatment allocation. Investigators will follow the guidance below:

- If a patient received VAY736 and their B cell recovery was demonstrated at Week 24, then patients should have returned for their End of Study visit approximately 4 weeks later.
- Those patients who did not meet the criteria for B cell recovery at Week 24, will return to the site every 8 weeks until Week 52, then after Week 52, every 24 weeks until 2 years post dose (Week 100) and afterwards every 48 weeks, until B cell recovery is demonstrated and the End of Study visit may be scheduled.
- If a patient received placebo, at Week 24 they were offered the option of receiving open-label VAY736 (10 mg/kg) in a separate treatment arm.
  - Patients that consented to open-label VAY736 treatment would have restarted the study at Day 1 (within 4 weeks [+ 2 week window] of Week 24 visit);
  - Patients that did not consent to receive open-label VAY736 treatment would have returned to the site for End of Study visit as per Assessment schedule.

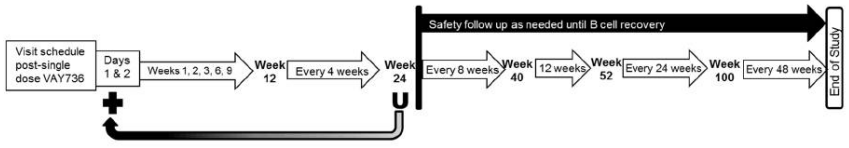
Patients will not be informed of their treatment allocation until after all of the assessments scheduled for Week 24 have been completed.

A study design schematic is provided in Figure 2-1.

Figure 2-1 Study Design Schematic



Key: ★ interim analysis; U unblinding at week 24



Key: ✚ Placebo patients may enter into open-label VAY736 treatment and restart the study at Day 1;
U unblinding at week 24

An interim analysis is planned after all patients have completed the week 12 visit in order to assess the effect of VAY736 on the primary endpoint.

3 First interpretable results (FIR)

First interpretable results (FIR) will be provided for this trial.

The study FIR template can be found in CREDI in the study RAP folder [file name]

The template shows the analysis / results to be presented in the FIR. Study outputs required to be created at the time of the FIR will be marked as “Key” in the M9.1 Tracking sheet output list.

4 Interim analyses

Prior to this amended RAP two interim analyses have been performed, firstly when 25 and secondly when all 27 subjects had completed the Week 12 visit in order to assess the effect of VAY736 on the primary endpoints. For these subjects the efficacy endpoints (along with relevant safety data) were examined as a preliminary evaluation of therapeutic effects.

In addition, an interim safety review was performed between Cohort 1 and Cohort 2.

Additional interim analyses may be conducted to support decision making concerning the current clinical study.

4.1 Interim and Second CSRs

An interim CSR will be produced after all patients have completed up to Week 52 assessments or have completed the study before Week 52. Efficacy data up to each patients week 52 visit will be summarized in this interim CSR(see below for more details regarding the figures), while listings will have all data up to the DB freeze. All safety data will be listed and summarized up to the interim CSR freeze date. At the end of the study after all patients have had B cell recovery a second CSR will be produced describing the data from Week 52 onwards and including all end of study assessments.

The following rules will be used for the presentation of the data for the Week-52 interim CSR,

1) For the majority of PD summary figures (such as boxplots etc.), only data up to week 24 will be included. The exception includes B cell count data visualization which will show all the data.
2) For other PD visualizations such as overlaid individual plots, they will include all available PD data up to week 52.
3) For AEs and conmeds, the summaries where applicable will be done for the double-blinded period and open-label period separately.
4) For summary tables for PD/safety lab/VS/ECG the PD tables end at Week 52 visits; safety data may include data beyond.
5) For all outputs which include “uncleaned” data, a footnote will be added “All data up to 05Oct2016 (the last Week 52 visit) has been cleaned and data afterwards hasn’t been fully cleaned yet”.

5 Statistical methods: Analysis sets

For subjects for which the actual treatment received does not match the randomized treatment the treatment actually received will be used for the analysis.

All subjects that received study drug and with no protocol deviations with relevant impact on safety will be included in the safety analysis set.

The PK analysis set will include all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and experienced no protocol deviations with relevant impact on PK data.

The PD analysis set will include all subjects with any available PD data, who received any study drug and experienced no protocol deviations with relevant impact on PD data.

The analysis sets and protocol deviation codes are related as follows:

Table 5-1 Protocol deviation severity codes and analysis sets

Protocol deviation severity code		Safety analysis set	PK analysis set	PD analysis set
Code	Text			
5	Exclude subject from all safety analysis	-	-	-
8	*Exclude from all analyses*	-	-	-
20	Exclude subject from PK analysis set	+	-	+
22	Exclude subject from PD analysis set	+	+	-
23	Exclude subject from PK and PD analysis set	+	-	-
49	Report relevant protocol deviation – include subject in all analysis sets	+	+	+

+ = include in analysis set, - = exclude from analysis set, NA = not applicable

6 Statistical methods for Pharmacokinetic (PK) parameters

VAY736 plasma concentration data will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero. Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics. A geometric mean will not be reported if the dataset includes zero values.

Pharmacokinetic parameters will be listed by treatment and subject. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented.

Modeling of the PK data may be performed as appropriate. During modeling of the pharmacokinetics of the study drug, the broad principles outlined in the FDA Guidance for Industry: Population Pharmacokinetics will be followed. Subjects with missing PK parameters (e.g., Cmax, AUClast, AUCinf) in some but not all periods will be included in a mixed model

analysis assuming missing at random. This modelling of the PK data will be performed by the Novartis PKist.

PK/PD modeling will be used to explore the relationship between extent and duration of B cell depletion and the pharmacokinetic profile of VAY736. The PK/PD modelling will be performed internally at Novartis. Overlaid individual B cell counts with PK concentrations will be provided by Covance.

7 Statistical methods for Pharmacodynamic (PD) parameters

7.1 Primary parameter

The primary aim of this study is to evaluate the effect of a single i.v. dose VAY736 on the clinical disease activity of primary Sjögren's syndrome patients as measured by the ESSDAI at Week 12 compared to baseline. The statistical analysis model will include data on the ESSDAI from all timepoints at which it was recorded (baseline, Weeks 6, 12 and 24) but the primary comparison is made for Week 12.

The ESSDAI is an established disease outcome measure for Sjögren's syndrome that will be applied to the study patients at baseline and again at Weeks 6, 12 and 24. The instrument contains 12 organ-specific domains contributing to disease activity. For each domain, features of disease activity are scored in 3 or 4 levels according to their severity. These scores are then summed across the 12 domains in a weighted manner to provide the total score.

It is assumed that the ESSDAI will follow an approximate normal distribution. If, on blinded review of the data, this assumption appears to not be met, alternative statistical methods may be applied, e.g. data may be log transformed with changes from baseline in the log transformed data being analyzed.

A positive sign of therapeutic effects will be considered to be a difference of at least 5 points in the change from baseline between VAY736 and placebo with a moderate level of evidence. Additionally there should be a high level of evidence that is a difference between VAY736 and placebo. The two active doses will be pooled for the primary efficacy analysis (unless there is evidence of inferiority of the 3 mg/kg dose to the 10 mg/kg dose). These criteria will be evaluated by calculating Bayesian posterior probabilities as follows:

$\Pr(\theta_{VAY736,12w} - \theta_{placebo,12w} > 0 \mid data) > 90\%$ and
$\Pr(\theta_{VAY736,12w} - \theta_{placebo,12w} > 5 \mid data) > 50\%$
where θ means change from baseline in ESSDAI at 12 weeks.

It is assumed that Y_{ijt}, the observed change from baseline in ESSDAI for subject i receiving treatment j (VAY736 or placebo) at time t, follows a normal distribution $N(\theta_{jt}, \sigma^2)$, It is further assumed that θ_{jt} follows a standard non-informative prior Normal distribution, $p(\theta_{jt}, \sigma^2) = 1/\sigma^2$.

The statistical model will be a repeated measures fitting terms for treatment by timepoint and baseline by timepoint using the SAS procedure PROC MCMC. Estimates of the difference between VAY736 and placebo at each timepoint will be derived from this model and presented together with 95% credible intervals. The estimates of the posteriors probabilities of the efficacy criteria being met will be provided.

Patients with missing ESSDAI at baseline will not be included in the analysis. Patients with missing data at one or more timepoints post baseline will be included in the analysis. The planned 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.

Summary statistics will be provided for absolute and changes from baseline in ESSDAI by treatment and timepoint. Mean (SD) plots for absolute and changes from baseline in ESSDAI will also be provided. Overlaying individual profiles will also be provided by treatment.

7.2 Supportive analyses for the primary parameter

The primary analysis uses a standard mixed model repeated measures approach where timepoints are considered as factors. This was chosen since the time course of ESSDAI changes following a single dose of VAY736 or placebo is not known. Supportive analyses will attempt to model the time effect to better describe changes over time, the model may include the following covariates: baseline, treatment, time, treatment by time interaction, treatment by time square interaction, as well as a random intercept and a random slope for each patient. Time will be modeled as a continuous variable. The model may be simplified if there are problems with convergence. The treatment by time square interaction will be included if it improves the fit.

Potential differences in efficacy between the 3 mg/kg dose and the 10 mg/kg dose of VAY736 may be explored.

7.3 Secondary efficacy variables

Secondary efficacy variables supporting the exploratory objectives are:

- EULAR Sjögren's Syndrome Patient Reported Intensity (ESSPRI) change from baseline.
- Change in physician global assessment of the patient's overall disease activity between baseline and Week 12 as recorded by a visual analog scale (VAS)
- Change in the patient's global assessment of their disease activity between baseline and Week 12 as recorded by a VAS
- Change from baseline for each domain of the Short Form (36) Health Survey (SF-36).
- Change from baseline for each dimension of the Multidimensional Fatigue Inventory (MFI) Questionnaire.

The secondary efficacy variables will be analyzed using a repeated measures model with the same factors as the primary efficacy variable but will use a frequentist rather than Bayesian approach.

During the conduct of the study it has been noted that the ESSPRI score has been recorded as 1 to 10 rather than 0 to 10 which would lead to an underestimate of the outcomes. The Principal Investigator has confirmed that the scale still provides a reliable detection of relative changes.

The ESSPRI statistical analyses will be rerun after transforming the results as per the below to assess the impact:

1. Use a linear transformation to change the 1-10 scale to a 0-10 scale

   New scale score = 10 x (Old scale score – 1)/9

   (i.e. 1 becomes 0, 2 becomes 1.111, 3 becomes 2.222 etc.)

2. Recode 1 to 0 and leave the rest of the scores the same (the rationale is that a score of 1 indicates zero activity but for scores above 1 it is not possible to say what they really should be)

The statistical analysis will be provided for both the untransformed and transformed data (only untransformed data was used in the first 2 interim analyses).

7.4 Exploratory efficacy variables

Exploratory efficacy variables supporting the exploratory objectives are:

- Ultrasound parameters including gland thickness and staging (de Vita score), parotid blood flow with contrast agent (vascularization index and perfusion AUC) parotid elasticity from sonoelastography (shear wave and velocity). De Vita responders (defined as at least a 1 point reduction from baseline in the mean of the left and right values)
- Results of histological and the immunohistochemistry staining of lymphocyte subsets in salivary gland biopsies
- Salivary flow rates
- Ocular Staining Score
- Flow cytometry

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Time to B cell event endpoints will be summarized by treatment group, based on the results from the previous IAs there was no B cell depletion for placebo subjects therefore no Kaplan-Meier estimates or log-rank tests among treatment groups will be performed. The B cell depletion AUC (area under curve, calculated using the linear trapezoidal rule) over time at Week 12 and 24 will be explored for the relationship with change from baseline PRO parameters at corresponding time points. Baseline B cell count will also be explored for such relationship. The AUC and baseline B cell count will be log transformed prior to analysis.

For ultrasound parameters where both the left and right side of glands have been measured, the mean of the two sides will be taken for summary statistics and other planned statistical analyses, including the correlation among changes from baseline in ultrasound parameters and also correlation between changes from baseline in ultrasound parameters with changes from baseline in PRO parameters.

8 Statistical methods for safety and tolerability data

All data for background demographic variables will be listed and summarized by treatment.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed.

Data for study drug administration and concomitant therapies will be listed by treatment group and subject.

Boxplots to visualize trends in longitudinal safety data (vitals, ECG, lab parameters) will be created.

Vital signs

All vital signs data will be listed by treatment, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

ECG evaluations

All ECG data will be listed by treatment, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data, including pregnancy tests, will be listed by treatment, subject, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Adverse events

All information obtained on adverse events will be displayed by treatment and subject. The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A subject with multiple adverse events within a body system is only counted once towards the total of this body system. Boxplots to visualize trends in longitudinal safety data (vitals, ECG, lab parameters) will be created.

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