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VAY736/ianalumab & CFZ533/iscalimab

CVAY736X2208 / NCT03656562

A placebo-controlled, patient and investigator blinded, randomized parallel cohort study to assess pharmacodynamics, pharmacokinetics, safety, tolerability and preliminary clinical efficacy of VAY736 and CFZ533 in patients with systemic lupus erythematosus (SLE)

Statistical Analysis Plan (SAP)

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1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial "CVAY736X2208".

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol for the purpose of the interim analyses and clinical study report.

Tables, Figures, Listings (TFL) details the presentation of the data, including shells of summary tables, figures and listings, and Programming Datasets Specification (PDS) contains programming specifications e.g. for derived variables and derived datasets, to support the creation of CSR outputs.

1.2 Study reference documentation

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1.3 Study objectives

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	Endpoint(s) for primary objective(s)
• To determine the effect of VAY736 and of CFZ533 versus their respective placebo on disease activity in SLE patients at Week 29 compared to baseline	• SRI-4 response status at Week 29 with reduced steroid dose maintained between Weeks 17 and 29
Secondary objective(s)	Endpoint(s) for secondary objective(s)
• To assess safety and tolerability of VAY736 and of CFZ533 in patients with SLE	• Adverse events and other safety data such as vital signs, ECG and laboratory results recorded during study
• To determine the change from baseline in the Physicians' Global Assessment (PhGA) at Week 29 in VAY736-, CFZ533- or their respective placebo-treated arms	• Changes between baseline and Week 29 in the PhGA visual analog scale (VAS) assessing patient's overall disease activity
• To determine the change from baseline in the Patient's Global Assessment (PGA) at Week 29 in VAY736, CFZ533 or their respective placebo-treated arms	• Changes between baseline and Week 29 in the patients' VAS assessing their global disease activity
• To determine the pharmacokinetics (PK) of multiple doses of VAY736 (s.c.) and CFZ533 (i.v.) in SLE patients	• PK Cohort 1 (VAY736): free VAY736 serum concentration (Ctrough). PK Cohort 2 (CFZ533): free CFZ533 concentration in plasma (Cmax, Ctrough).
• To assess the effect of VAY736 and of CFZ533 versus their respective placebo to prevent disease flares in SLE patients	• Flare rate and time to first flare, with flare defined as one new 'A' score or two or more 'B' score using BILAG -2004

Objective(s)	Endpoint(s)
• To evaluate the immunogenicity of multiple doses of VAY736 (s.c.) or CFZ533 (i.v.) in SLE patients	• Anti-VAY736 (Cohort 1) or anti-CFZ533 (Cohort 2) antibodies and incidence of ADA-positive patients.
• To evaluate the pharmacodynamics (PD; rate, extent and duration of target engagement) of multiple doses of CFZ533 in SLE patients	• PD Cohort 2 (CFZ533): total soluble CD40 in plasma
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**

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1.4 Study design and treatment

This is a randomized, patient- and investigator-blind, placebo-controlled, parallel-group, non-confirmatory study to assess the safety, tolerability, pharmacokinetics, immunogenicity, pharmacodynamics and preliminary clinical efficacy of multiple doses of VAY736 or of CFZ533 in patients with active SLE (see Figure 1-1).

Figure 1-1 Study design

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Key study design features are as follows:

- Patient randomization into one of two treatment cohorts (VAY736 or CFZ533) and to either active or placebo
- Seven-month, placebo-controlled, blinded treatment
- Guided corticosteroids taper from Study Week 5 to Study Week 17
- A 5-month, open label treatment followed by a final outcomes assessment
- Four-month follow up for safety/PK/PD, with additional follow up for VAY736-treated patients until B cell recovery criteria are met

Screening and randomization

The study will randomize approximately 120 patients to test two active treatments against their matching placebo in parallel cohorts. After a 28-day screening period, eligible patients will be enrolled and stratified according to serum extractable nuclear antigens (ENA) status (positive or negative) and baseline SLEDAI-2K score (<10, ≥10). At the baseline visit, patients who are eligible for both cohorts will be randomly assigned to one of the four treatment arms. Patients who are eligible for only one cohort will be randomly assigned to either of the two treatment arms in that cohort. Randomization across the cohorts will be implemented via central randomization aiming for randomization ratio of 1:1:1:1.

Blinded treatment phase

Within the treatment cohort, blinded treatment with the investigational drug (VAY736 or CFZ533) or placebo will be administered on top of patients' stable standard of care therapy for SLE. Visits to assess safety and/or efficacy are scheduled at 4-week intervals. An additional safety visit is scheduled at Week 3 (within the placebo-controlled period) and Week 31 (within the open label period) where patients in Cohort 2 (CFZ533) will receive an additional treatment dose.

On the baseline visit Day 1, following patient eligibility confirmation and completion of all assessments, first dose of study drug/placebo will be administered. The last treatment in the blinded treatment period will be given at the Week 25 visit. The readout for the blinded treatment period will be performed at Week 29. Study drug will be administered every 4 weeks. Unless otherwise stated, all assessments must be completed BEFORE the next dose of study drug is administered.

Guided corticosteroid (CS) reduction

- Patients entering the study on a stable CS regimen are required to undergo a guided CS taper from baseline levels starting at Week 5 in order to achieve by Week 17:
  - a daily CS dose of ≤5 mg/day prednisone or equivalent,
  - or a CS dose that is less than the baseline dose, whichever is the lower dose.
- In addition, the patient should remain at the lowered CS dose achieved at Week 17 through to Week 29.
- Patients entering the study without background CS therapy should remain free of any CS regimen or increase in SoC DMARDs through to week 29.

- Patients exceeding the rescue therapy allowances may continue in trial but will be labeled a non-responder for primary endpoint.
- During the open label phase, further reductions in patients' SoC CS and DMARDs may be made on an individual basis as deemed appropriate by the investigator.

Open-label treatment phase

At the end of the Week 29 visit, after all assessments have been performed, the first open label treatment will be administered. Patients in Cohort 1 will receive VAY736 and patients in Cohort 2 will receive CFZ533. Study drug will be administered every 4 weeks. The last treatment will be given at the Week 49 visit, and the End-of-Treatment (EoT) visit will be performed 4 weeks thereafter, at Week 53.

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Follow-Up period

After completion of the open-label treatment period, all patients will enter a Follow-Up period in order to monitor safety and efficacy up to Week 69. The Week 69 visit is the End of Study (EoS) visit for patients in Cohort 2 (CFZ533). Study duration for patients in Cohort 2 will be approximately 18 months.

For Cohort 1 (VAY736). Patients who do not achieve B-cell recovery by Week 69 Visit will enter a Secondary Follow-Up period until achieving B cell recovery criteria (B-cell count is at 50 cells/µl or higher). Safety follow-up visits will be scheduled as deemed appropriate until the patient achieves the B cell recovery criteria, followed by an EoS 4 weeks later.

2 First interpretable results (FIR)

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3 Interim analyses

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4 Statistical methods: Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

All patients who received at least one dose of any study drug will be included in the safety analysis set.

The PK analysis set will include all patients 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.

All patients with evaluable PD parameter data and no major protocol deviations impacting PD data will be included in the PD data analysis "PD population".

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

Table 4-1 Protocol deviation codes and analysis sets

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5 Statistical methods: group presentations

The analyses will be performed on Cohort 1 and Cohort 2 separately unless otherwise specified.

For the analysis plan here onwards, treatment groups are defined as below and these groups will be followed for most summary tables by period and treatment group, unless otherwise stated.

- Blinded period (P1, up to and including Visit 190)

Treatment group for blinded period:

  - VAY736
  - VAY736 Placebo
  - CFZ533
  - CFZ533 Placebo

- Open label period (P2, from Visit 190 onwards) and post-treatment follow-up

Treatment sequence for the people participating in the extension:

- VAY736/VAY736,
- VAY736 Placebo/VAY736
- CFZ533/CFZ533
- CFZ533_Placebo/CFZ533

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Individual (Spaghetti) plots over time will be performed, unless otherwise stated, by sequence and will include the whole duration of the study.

6 Statistical methods for Pharmacokinetic (PK) parameters

All patients within the PK analysis set will be included in the PK data analysis.

6.1 Variables

The following pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.2 or higher): Cmax (only for CFZ533 cohort) - The highest concentration observed during a dosing interval and Ctrough - The trough observed analyte concentration at the end of a dosing interval.

6.2 Descriptive analyses

Plasma CFZ533 and serum VAY736 concentration will be summarized by treatment, and visit/sampling time point. Descriptive summary statistics will be provided, 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 and for PK parameter derivation. Zero values will be treated as missing data when calculating geometric mean and geometric CV.

Pharmacokinetic parameters will be summarized by treatment with descriptive statistics as above. Graphical methods will be employed to show mean and individual concentration-time profiles over the whole study by treatment, with time defined as visit and actual day respectively.

7 Statistical methods for Pharmacodynamic (PD) parameters

All patients within the PD analysis set will be included in the PD data analysis.

7.1 Primary objective

The primary objective is to determine the effect of VAY736 and of CFZ533 versus their respective placebo on disease activity in SLE patients at Week 29 compared to baseline. The primary analysis will compare active treatment with its matching placebo based on the PD analysis set within either cohort independently.

7.1.1 Variables

The primary endpoint is a composite of SRI-4 response at Week 29 with sustained reduction in oral corticosteroid from Week 17 through Week 29.

SRI-4 response is defined as below:

- having ≥4 points reduction from baseline in SLEDAI-2K score AND
- no new BILAG-2004 A organ domain score and no more than one new BILAG-2004 B organ domain scores compared with baseline AND
- <0.3 mm or <10 mm point increase if scaled 0 to 3 or 0 to 100 mm, respectively in the physician's global assessment from baseline

Sustained reduction in oral corticosteroid is defined as below:

- ≤5 mg/day or ≤ baseline dose, whichever is lower, at Week 17
  AND
- no increase of that dose from Week 17 through Week 29

When all these criteria are met, the patient is considered as a responder. However, patients receiving CS dosing in addition to the baseline CS dosing levels or subsequent, reduced levels attained at Week 17 after completing the guided corticosteroid tapering period will be considered non-responder for primary endpoint:

- if total daily CS dose is >30 mg/d prednisone or equivalent, or
- increased daily CS dose is administered >2 days within a 4-week treatment cycle, or
- daily CS dose is increased within 2 weeks of Study Visit Week 29.

Patients who have taken other rescue medication or prohibited medication (Table 6-3 of study protocol, e.g., new immune suppressive agents or biologics) or drop out before Week 29 will also be considered non-responder for the primary endpoint. Where acute CS administration occurs for purposes other than the treatment of SLE disease activity, patient responder status will be discussed on a case-by-case basis.

7.1.2 Descriptive analyses

The SRI-4 response status, patients who successfully achieve steroid tapering, SRI-4 response status with sustained steroid reduction (primary variable) at Week 29 will be summarized by treatment. Descriptive statistics will include frequency and percentage.

7.1.3 Statistical model, assumptions and hypotheses

The primary endpoint will be analyzed using a Bayesian logistic regression model. The model will include treatment group, ENA status, baseline SLEDAI-2K (<10, ≥10) as fixed effects. Weakly informative priors will be used to obtain the posterior estimates. The primary analysis will be performed for each cohort separately.

Bayesian posterior probabilities will be used to assess the following criteria as a guide for decision making (Fisch et al 2015).

Efficacy criteria (for primary endpoint):

- Week 29 responder rate in active group better than that in placebo group with high confidence (90%), i.e., Prob (θ_active - θ _ placebo >0) >90%, AND
- Average magnitude of effect on Week 29 responder rate >15% over placebo, i.e., Prob (θ_active - θ_ placebo >15%) >50%.

Where θ is the Week 29 responder rate, i.e. the proportion of responders per definition.

The 15% threshold is chosen based on a study showing around 15% difference in responder rate based on SRI-4 with sustained reduction in oral corticosteroid at Week 24 between an active treatment and placebo (Furie et al 2017).

Futility criterion:

- Week 29 responder rate in active group worse than that in placebo with confidence higher than 60%, i.e., Prob (θ_active - θ _ placebo <0) >60%.

The posterior estimates of the treatment effect of VAY736 and CFZ533 compared to their matching placebos (along with the 90% credible intervals) at Week 29 will be provided. The results will be reported in terms of difference in probability of responders.

7.1.3.1 Supportive analysis

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7.2 Secondary objectives

7.2.1 Variables

The secondary variables are:

- Physician's global assessment (PhGA) in VAS
- Patient's global assessment (PGA) in VAS
- Flare: flare determined by BILAG-2004 as below
  - Severe flare: developing a BILAG-2004 "A" score in any system due to items that are new or worse
  - Moderate flare: having two or more "B" scores due to items that are new or worse

7.2.2 Descriptive analyses

Physician's global assessment (PhGA) in VAS and the change from baseline will be summarized by period, treatment and visit. Summary statistics will include mean, SD, median, minimum and maximum. Patient's global assessment (PGA) in VAS will be analyzed in the same way as physician's global assessment (PhGA) in VAS.

The proportion of patients with moderate or severe flare will be summarized by period, treatment and flare severity. The time to first moderate or severe flare will be summarized for blinded period by treatment group.

7.2.3 Statistical model, assumptions and hypotheses

Bayesian mixed effect model for repeated measure (MMRM) will be applied to the change from baseline in Physician's global assessment (PhGA) in VAS, as continuous response variable. The model will include treatment group, ENA status, baseline SLEDAI-2K (<10, ≥ 10) and visit as fixed effects and baseline PhGA as continuous covariate. Weakly informative priors will be used to obtain the posterior estimates and unstructured covariance will be assumed. The posterior estimates of the treatment effect of VAY736 and CFZ533 compared to their matching placebos (along with the 90% credible intervals) at each visit will be provided. The results will be reported in terms of group estimate and treatment difference in PhGA in VAS. Patient's global assessment (PGA) in VAS will be analyzed in the same way as physician's global assessment (PhGA) in VAS. For both PhGA in VAS and PGA in VAS, data up to Week 29 will be used in the model.

7.2.3.1 Model checking procedures

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7.2.3.2 Graphical presentation of results

The arithmetic mean (± SD) or box plot of change from baseline in PhGA in VAS and PGA in VAS up to Week 29 will be plotted over time by treatment group. The individual plots for raw VAS scores over time will also be presented by treatment.

7.3 Exploratory objectives

7.3.1 Variables

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7.3.2 Descriptive analyses

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7.3.3 Statistical model

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7.3.4 Model checking procedures

Refer to section 7.2.3.1.

8 Statistical methods for safety and tolerability data

All patients within the Safety analysis set will be included in the safety data analysis.

8.1 Variables

Adverse events, vital signs (blood pressure, pulse rate, body temperature), ECG intervals, laboratory measurements, as well as subject demographics, baseline characteristics, and treatment information.

8.2 Descriptive analyses

Subject demographics and other baseline characteristics

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

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

Treatment

Use of concomitant medications and administration of study drug will be listed by treatment and patient.

Vital signs

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

When repeated assessments are collected in any visit, the average of the values at that visit will be used in the analyses.

ECG evaluations

All ECG data will be listed by treatment, patient and visit, and abnormalities will be flagged. Summary statistics will be provided by period, treatment and visit.

Clinical laboratory evaluations

All laboratory data will be listed by treatment, patient, and visit/time and if normal ranges are available abnormalities will be flagged.

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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.

Adverse events

All information obtained on adverse events will be displayed by treatment and patient.

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The number and percentage of patients with adverse events will be tabulated by body system and preferred term with a breakdown by period and treatment. A patient with multiple adverse events within a body system is only counted once towards the total of this body system and treatment. Separate tables and listings will be presented indicating event severity and study drug relationship.

The on-treatment/ treatment emergent period lasts from date of first administration of study treatment until end of study (EoS). Summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment emergent AEs).

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on <on-treatment/treatment emergent> adverse events which are not serious adverse events with an incidence greater than 5% and on <on-treatment/treatment emergent> serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

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.

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Injections Reactions

Injection reactions will be summarized by type of injection reaction (overall, local and systemic), by grading, and by visit. Injection reaction events will be listed by treatment, patient and visit/time.

Other safety evaluations

Pregnancy test results will be listed by treatment, patient and visit/time.

Immunogenicity

The frequency and proportion of ADA-positive patients will be displayed by treatment and visit. Immunogenicity results will be listed by treatment, patient and visit/time.

8.3 Graphical presentation

Boxplots to visualize trends in longitudinal safety data (vitals, ECG, lab parameter) will be created. Mean and overlaying individual figures will be presented for selected parameters from vital signs, ECG and lab as needed.

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10 Reference list

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Furie R, Khamashta M, Merrill J. T, et al (2017) Anifrolumab, an Anti–Interferon-α Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus. Arthritis & Rheumatology; 69(2): 376-386.

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11 Appendix

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