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Clinical Development

VAY736

Clinical Trial Protocol CVAY736X2203

A randomized, partial-blind, placebo-controlled trial evaluating the efficacy, safety, pharmacokinetics and pharmacodynamics of VAY736 in the treatment of patients with pemphigus vulgaris

TSc RAP Module 3: Detailed Statistical Methodology

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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 **"**CVAY736X2203**".**

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)

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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

2.1.1 Primary Objective

- To compare the efficacy of single i.v. doses of VAY736 relative to placebo in reducing clinical disease activity of pemphigus vulgaris patients, as determined by the change in Pemphigus Disease Area Index (PDAI) between baseline and 12 weeks

2.1.2 Secondary objective(s)

- To evaluate the safety and tolerability of VAY736 in patients with PV
- To evaluate the effect of VAY736 in PV patients as assessed by the Autoimmune Bullous Skin disease Intensity Score (ABSIS) at 12 weeks
- To evaluate the effect of VAY736 in PV patients as assessed by Investigator Global Assessment (IGA) at 12 weeks
- To evaluate VAY736 pharmacokinetics in serum in PV patients

2.1.3 Exploratory objective(s)

2.2 Study design and treatment

This is a non-confirmatory, randomized, partial-blind, placebo-controlled trial evaluating the efficacy, safety, pharmacokinetics and pharmacodynamics of VAY736 in the treatment of patients with pemphigus vulgaris.

Up to approximately 32 patients will be randomly assigned in a blinded fashion to one of three single dose treatment arms, and at least 24 patients are expected to complete the study. Recruitment will be staggered and progression between doses is dependent upon a safety review milestone (see Figure 2-1).

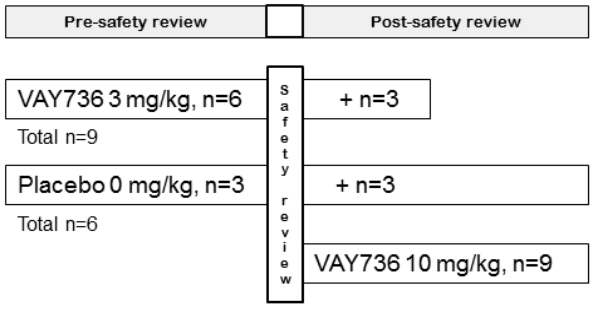
In the pre-safety review period, 9 patients will be randomized to a single dose of either 3 mg/kg VAY736 or placebo (6 dosed with VAY736 and 3 with placebo). After dosing of these 9 initial patients, recruitment will be paused and a safety review will be conducted by an internal Data Monitoring Committee (DMC), independent from the VAY736 project team.

The DMC will review all safety data available to the 9th patient achieving Week 6. If there are no safety signals identified by this safety review, recruitment will restart into the 3 mg/kgVAY736 and placebo treatment arms, and will commence to the 10 mg/kg VAY736 treatment arm. If there is a safety signal enrollment will be put on hold, pending a full data evaluation.

Following treatment on Day 1 with study medication, standard of care (SoC) medications are to be maintained at a stable dose level with minimal dose adjustments until "disease control" in signs/symptoms of PV. "Disease control" is defined as the time at which new lesions cease to form and established lesions begin to heal. A protocol-defined SoC medication taper begins once a patient reaches disease control, to safely deliver the patient to the lowest dose needed to maintain control of their disease.

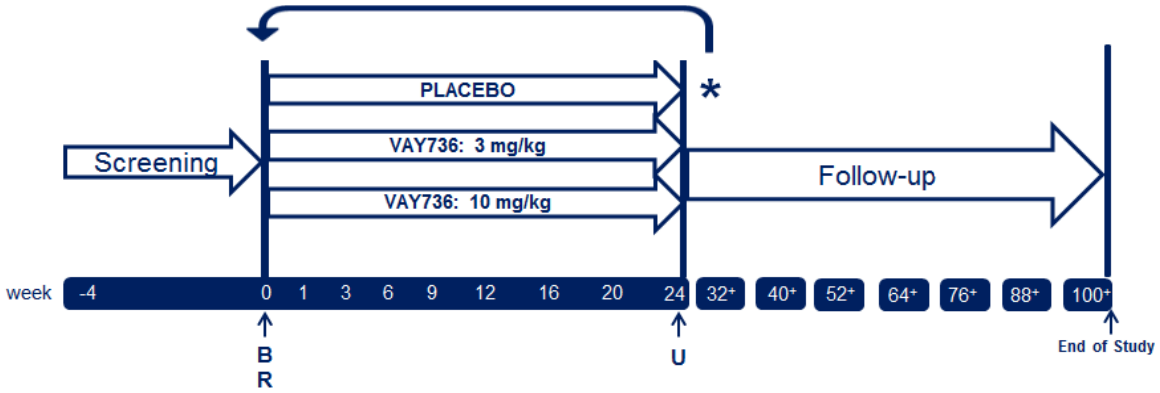
At study completion, it is intended that 9 patients will have been dosed with VAY736 at 3 mg/kg, 9 patients with 10 mg/kg, and 6 patients with placebo.

Figure 2-1 Study design: Staggered recruitment



The study will consist of the following Phases (see Figure 2-2):

Figure 2-2 Study design: Visit Schedule



Key: B: Baseline; **R**: Randomization; **U**: unblinding of patient treatment; *: Placebo patients may enter into open-label VAY736 treatment and restart the study at Day 1;

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3 First interpretable results (FIR)

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4 Interim analyses

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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.

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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	
Code	Text			
5	Exclude subject from all safety analysis	-	-	Commercially Confidential Information
8	*Exclude from all analyses*	-	-	
20	Exclude subject from PK analysis set	+	-	
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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

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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.

7 Statistical methods for Pharmacodynamic (PD) parameters

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7.1 Analysis of the primary variable(s)

The primary aim of this study is to compare the efficacy of a single i.v. dose of VAY736 in reducing the clinical disease activity of pemphigus vulgaris patients as determined by the change in Pemphigus Disease Area Index (PDAI) between baseline and week 12.

7.1.1 Variable(s)

The primary efficacy variable is the total skin and mucous membranes activity score (PDAI score). The score is weighted for the number and size of lesions with a score of 0 (absent) to 10 given for skin (12 body locations), scalp and mucous membrane showing disease activity (erosions/blisters or new erythema). To be more precise at the lower end of the PDAI score the value of 1 that included 1-3 lesions on each anatomic region is split in intervals: 1

corresponds to one lesion (none greater than 2 cm); 1.3 corresponds to two lesions and 1.6 corresponds to three lesions.

Damage, such as post inflammatory hyperpigmentation or erythema from resolving lesion, is scored separately from the main score as absent (0) or present (1) for each body area or scalp resulting in a score of 0 to 12 or 0 to 1, respectively. Therefore the PDAI score ranges from 0 to 263, with 250 points representing disease activity (120 points for skin activity; 10 points for scalp activity; 120 points for mucosal activity) and 13 points representing disease damage.

7.1.2 Statistical model, hypothesis, and method of analysis

It is assumed that the PDAI skin and mucous membranes activity score will follow an approximate normal distribution.

Individual profile figures of PDAI and Mean (SD) plots by time and treatment will be produced for absolute and changes from baseline (including percentage changes from baseline). Similar Mean (SD) plots will be produced for the PDAI subscores: as detailed in Section 7.1.1. Summary statistics of absolute and changes from baseline (including percentage changes from baseline) by time and treatment will be presented.

Scatterplots of PDAI at 12 weeks versus total SoC use and also versus selected biomarkers will be presented.

7.1.3 Handling of missing values/censoring/discontinuations

Patients with missing PDAI 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.

7.1.4 Supportive analyses

Not applicable.

7.2 Analysis of secondary Commercially Confidential Information

Secondary efficacy variables supporting the secondary objectives are:

- PDAI total score recorded at baseline and weeks 3, 6, 9, 12, 16, 20 and 24.
- ABSIS recorded at baseline and weeks 3, 6, 9, 12, 16, 20 and 24.
- IGA recorded at baseline and weeks 3, 6, 9, 12, 16, 20 and 24.

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7.2.1 Variables

Autoimmune Bullous Skin disorder Intensity Score (ABSIS) is a quality- and quantity-based score for cutaneous and oral mucosal lesions combining the extent of the affected body surface area (BSA), the quality of the skin lesions and oral involvement, the ABSIS score ranges from 0 to 206 with 150 points for skin involvement, 11 points for oral involvement and 45 points for subjective discomfort during eating and drinking.

Investigator global assessment score (IGA) is a score on a 0-4 scale to assess each patient's PV disease activity.

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7.2.2 Efficacy / Pharmacodynamics

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The secondary Information efficacy variables will be analysed as follows:

The PDAI total score, ABSIS score will be analyzed following the same approach used for the primary efficacy variable.

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9 Statistical methods for safety and tolerability data

Open label VAY736 and the placebo data from before the patients were transferred to open label VAY736 will be presented as separate treatments in the outputs.

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group.

Subject disposition will be listed and summarized by treatment. In addition a figure displaying the subject disposition of all randomized subjects will be produced.

The number of subjects assessed by visit will be summarized in a frequency table and presented in a heatmap.

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

Adverse events

The number and percentage of subjects with adverse events will be tabulated by treatment, system organ class, and preferred term. Additionally the summary table with a breakdown by the severity of adverse events will also be provided. An adverse event starting at one time-point and continuing to another time-point will be counted only at the onset time-point. A

subject with multiple adverse events within a system organ class is only counted once towards the total of this system organ class.

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 will be listed by treatment, subject and visit/time. If normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Standard of care medication

Data will be summarized together with changes from baseline and presented graphically in mean (SD) profile plots.