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Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

DFV890

CDFV890A12201 / NCT04868968

An open-label, single arm phase II study of DFV890 to assess the safety, tolerability and efficacy in participants with familial cold auto-inflammatory syndrome (FCAS)

Statistical Analysis Plan (SAP)

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1 Introduction

1.1 Scope of document

The Reporting and Analysis Plan (RAP) documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial **"*CDFV890A12201*".**

The Statistical Analysis Plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

1.2 Study reference documentation

Final study protocol amendment (v04) is available at the time of finalization of SAP.

1.3 Study objectives

1.3.1. Primary objective

Primary objective	***Endpoint for primary objective***
• To assess the efficacy of DFV890 to reduce cold-induced inflammation in participants with FCAS	• Ratio of fold change from pre-challenge to the highest post-challenge value of white cell count (WCC) between treatment and screening period

1.3.2. Secondary objective

Secondary objective	***Endpoint for secondary objective***
• To assess safety and tolerability of DFV890	• Safety endpoints (including vital signs, ECG parameters, safety laboratory assessment and adverse events)

• To assess the efficacy of DFV890 to improve the signs and symptoms of FCAS	• Change from pre-challenge to post-challenge between treatment and screening period in:
	  • Physician global assessment of autoinflammatory disease activity
	  • Physician's severity assessment of autoinflammatory disease signs and symptoms

• To assess the effect of DFV890 on patient reported outcomes	• Change from pre-challenge to post-challenge between treatment and screening period in:

	• Patients global assessment of disease activity

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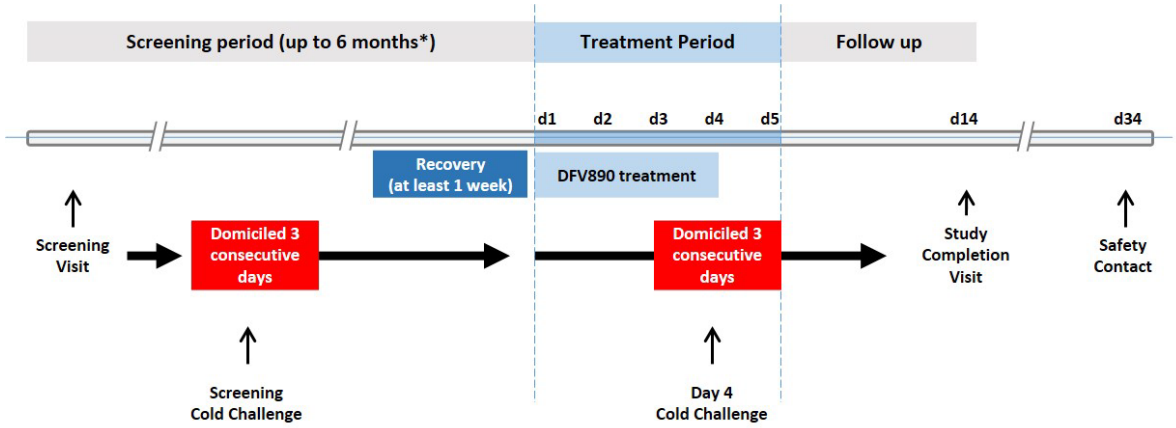
1.4 Study design and treatment

This is an open-label, single-arm, multiple dose, phase II study to assess safety, tolerability and efficacy of DFV890 in participants with FCAS who show evidence of inflammatory activity after the cold challenge performed during screening. Approximately 6 participants with FCAS and confirmed NLRP3 gain-of-function mutations will be enrolled in the study.

Figure 1-1 summarizes the study design and shows the steps that will be followed in the study. The study consists of three periods: screening, treatment and follow-up.

Figure 1-1 Study Design Schematic



* Up to 12 months for participants with a historical screening cold challenge prior to protocol amendment 04.

Screening period: A period of up to 6 months (and up to 12 months for participants with a historical screening cold challenge prior to protocol amendment 04), when the participant's eligibility will be assessed at a screening visit and a cold challenge will be performed. During the screening cold challenge, participants will be domiciled for three days following a minimum of one week of recovery from the cold challenge prior to enrollment and initiation of treatment. The screening cold challenge can be conducted any time during the screening period, provided that Day 1 is conducted within 6 months (and within 12 months for participants with a historical screening cold challenge prior to protocol amendment 04; see below) of the Screening visit and all inclusion and none of the exclusion criteria are met. Historical screening cold challenge conducted in this study under the previous protocol version is acceptable, provided that Day 1 is conducted within 12 months of the Screening visit, and all inclusion and none of the exclusion criteria based on this amendment are met.

Treatment period: Eligible participants (defined as those participants who respond to the cold challenge) will then enter the treatment period where they will be administered oral DFV890 100 mg b.i.d. for 3 days, one last dose will be administered in the morning of Day 4 followed by a cold challenge. Participants will be admitted to the clinic in the morning of Day 3 (the day prior to cold challenge) and will be domiciled for a total of three days or longer (if needed). On the morning of Day 4, pre-challenge assessments will be performed, and then cold challenge

will last for 45 minutes. After the end of the cold challenge, participants will be monitored until the next morning (Day 5) and discharged after the last assessment on Day 5 or later.

Follow up period: Participants will be then followed-up for an end of study evaluation at the study competition visit, approximately 10 days after last dose and a post study safety contact will occur 30 days after last dose. The total study duration from screening until study completion is expected to be up to 7 months (and up to 13 months for participants with a historical screening cold challenge prior to protocol amendment 04).

Unscheduled visits: Participants will be instructed to contact the investigator if they develop rash or pruritus between visits from Day 1 to the Study completion visit. An unscheduled visit should be considered based on clinical findings and severity of rash or pruritus and related assessments performed. Unscheduled visits may be performed at an alternative Sponsor-approved site (e.g. satellite site that may be more convenient to the participant) if agreed by the PI who will maintain the investigator responsibilities, and only as permitted by local regulations.

2 First interpretable results (FIR)

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3 Interim analyses

No interim analysis is planned for this trial.

Interim analyses may be conducted to support decision making concerning the current clinical study, the sponsor's clinical development projects in general or in case of any safety concerns.

4 Statistical methods: Analysis sets

The safety analysis set will include all participants that received any study drug.

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The PD analysis set will include all participants with no protocol deviations with relevant impact on PD data.

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

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Participants are excluded from safety analysis in case of these PDs:		Exclude participant from safety analysis set
INCL01	Informed consent form not obtained	Yes

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Participants are excluded from PD analysis in case of these PDs:		Exclude participant from PD analysis set
INCL01	Informed consent form not obtained	Yes
INCL08	relative WCC increase <40% compared to pre-challenge after cold challenge at screening period	Yes

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

The number and percentage of participants in each analysis set will be summarized. Participants excluded from any analysis set(s) along with the reason(s) for their exclusion will be listed.

All protocol deviations will be listed by participant and the number and percentage of participants with protocol deviations will be summarized.

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6 Statistical methods for Pharmacodynamic (PD) parameters

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

6.1 Primary objective

The primary efficacy objective of this study is to assess the efficacy of DFV890 to reduce cold-induced inflammation in participants with FCAS.

6.1.1 Variables

Fold change from pre-challenge to the highest post-challenge value of total WCC is the primary efficacy variable. The highest post-challenge value is based only on post-challenge measurements within the cold challenge visit (up to and including 8 hours post-challenge). Lower induction of total WCC is considered a favorable outcome.

Fold change from pre-challenge to a post-challenge value of WCC is defined as the ratio of the post-challenge WCC value to the pre-challenge WCC value, i.e.:

$$\textbf{Fold change} = \frac{\textbf{post challenge WCC}}{\textbf{pre challenge WCC}}$$

6.1.2 Descriptive analyses

A geometric mean (SE) plot of fold change from pre-challenge to post-challenge over time will be provided by period.

6.1.3 Statistical model, assumptions and hypotheses

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The primary objective will be achieved and DFV890 will be considered efficacious in treating cold-induced inflammation in participants with FCAS if the estimated ratio of fold changes from pre-challenge to highest post-challenge WCC between treatment and screening period is:

(1) Statistically significant (p-value<0.10), and

(2) Less than 80%.

Note: The highest post-challenge WCC value per period will be considered in the primary model analysis. This implies that the highest post-challenge WCC value will not necessarily occur at the same post-challenge time point in both periods.

6.1.3.1 Handling of remaining intercurrent events of primary estimand

Interruption of study treatment for any reason will be ignored.

6.1.3.2 Handling of missing values not related to intercurrent event

Due to the limited sample size, all available data will be included in the model. This corresponds to assuming a missing at random strategy.

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6.2 Secondary objective

The secondary efficacy objectives of this study are:

- To assess the efficacy of DFV890 to improve the signs and symptoms of FCAS.
- To assess the effect of DFV890 on patient reported outcomes.

6.2.1 Variables

The secondary efficacy variables of this study are:

- Physician global assessment of autoinflammatory disease activity.
- Physician's severity assessment of autoinflammatory disease signs and symptoms.
- Patient's global assessment of disease activity.

6.2.2 Descriptive analyses

Summary tables, including absolute and relative (%) frequencies of the different categories, will be provided by period and time for each secondary variable.

Overlaying individual plots (line plots) with the screening and treatment periods in separate panels will be provided for each secondary variable. Data from -2 to 23 hours post-challenge will be considered.

6.3 Exploratory objectives

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7 Statistical methods for safety and tolerability data

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

The assessment of safety and tolerability of DFV890 is one of the secondary objectives of this study.

7.1 Variables

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

7.2 Descriptive analyses

Participant disposition, demographics and other baseline characteristics

The disposition information for each study phase will be listed by participant. The number and percentage (%) of participants who completed each study phase and who prematurely discontinued each study phase along with the primary reason for discontinuation will be presented by period.

All data for background and demographic variables including baseline disease characteristics and smoking status will be listed by participant and summary statistics will be provided. Summary tables for categorical data will include absolute and relative frequencies. The following variables will be included in the demographics and other baseline characteristics summary table:

- Age
- Age categories (<=65 years old & >65 years old)
- Sex
- Race
- Ethnicity
- Weight
- Height
- BMI
- Country

Other variables may also be considered, as needed.

Screening failures (and the reasons for those) will be listed separately.

Data on informed consent and withdrawal of informed consent will also be listed separately.

Relevant medical histories and current medical conditions at baseline will be listed and summarized by system organ class and preferred term.

Treatment

All data for study drug administration will be listed by participant. The duration of exposure to study treatment in days will be summarized. The duration of exposure to study treatment in days will be calculated as *study day of last non-missing dose – study day of first dose + 1*.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed according to the Anatomical Therapeutic Chemical (ATC) classification system. Concomitant medications will also be summarized by medication class and preferred term.

Vital signs

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

ECG evaluations

All single 12-lead ECG data (included but not limited to PR, QRS, QT, QTcF and RR intervals) will be listed by period, participant and time, abnormalities will be flagged. Summary statistics will be provided by period and time.

Clinical laboratory evaluations

All laboratory data will be listed by period, participant, and time and if normal ranges are available abnormalities will be flagged. A separate listing is provided presenting all parameters in a participant with any abnormal values.

Summary statistics will be provided by period and time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline (defined as Day 1 pre-first dose assessment) to the worst on-treatment value.

Adverse events

All information obtained on adverse events will be displayed by period and participant. Two separate listings for serious adverse events and adverse events leading to study discontinuation will also be provided.

The number and percentage of participants with adverse events will be tabulated by body system and/or preferred term with a breakdown by period. An adverse event starting in one period and continuing into the next period is counted only in the onset period. A participant with multiple adverse events within a body system and period is only counted once towards the total of this body system and period.

The number and percentage of participants with skin rash will be summarized by period. Skin rash data will also be listed.

Separate summaries will be provided for AEs by maximum severity, drug-related AEs, serious AEs, drug-related serious AEs and cold challenge-related AEs by body system and preferred term with a breakdown by period.

The overall incidence of AEs including the number of events and the number (and percentage) of participants under specific AE categories will also be summarized by period in a separate table.

For the legal requirements of ClinicalTrials.gov and EudraCT, two tables are required: on treatment emergent adverse events which are not serious adverse events with an incidence greater than 5% and on 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 analysis set.

If for a same participant, 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. All information obtained on deaths will be listed.

Other safety evaluations

Cold challenge

All cold challenge data (challenge start and end datetime, temperature of cold room at start and end time (^{o}C) and reason for interruption of the cold challenge) will be listed by participant.

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7.3 Graphical presentation

Scatterplots with overlaid median will be created to visualize trends in longitudinal safety data (vitals, ECG, lab parameter).

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10 Consideration due to COVID-19

Due to the COVID-19 pandemic, it may not be possible to perform some procedures as per protocol. All deviations due to COVID-19 will be listed separately to other deviations and may also be tabulated.

Observations that were impacted due to COVID-19, may be excluded from the primary analyses, for example including (but not limited to) observations taken at participant's house instead of site, and separately explored to identify if there is an impact of them on the analyses.