NOVARTIS

Clinical Development

ADPT15

CADPT15A12201 / NCT06097663

A randomized, placebo-controlled, parallel-group, investigator- and participant- blinded Phase 2a study to investigate, the safety efficacy and tolerability of DFV890 and MAS825 for inflammatory marker reduction in an adult population with coronary heart disease and Clonal Hematopoiesis of Indeterminate Potential (CHIP)

Statistical Analysis Plan (SAP)

Document type:	SAP Documentation
Document status:	Amendment 2
Release date:	11-Feb-2025
Number of pages:	32

Template Version 6.0, Effective from 23-Nov-2022

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
19-Jan-2024	Prior to FPFV	Creation of final version	N/A - First version	NA
04-Oct-2024	Prior to interim analysis (IA)	Considering new information arising during the course of the trial	Improved the definition of non-adherence to study treatment	1.2.1
			More details on the definition of the timeframe related to each dosing period	2.1.1.3
			More details on the management of final visits in participants discontinued from the study drug	2.1.1.11
			Added a note to highlight that analyses by treatment sequence may be used to investigate potential period/carry-over effects	2.5.1
			Removed the reporting of some variables which even if included in the study administration form are not part of the database	2.4.1
			More details on management of AEs with a day of onset on the edge between two dosing periods	2.7.1
			Added box plots for vital signs	2.7.4
			Added a section for immunogenicity analysis	2.9.1
			Added details related to exploratory analyses	2.11 and 2.12
			Added details related to the interim analysis	2.13
			Updated section on exclusion criteria considering protocol deviations occurred so far	5.5
11-Feb-2025	Post IA and prior to DBL	Considering new information arising from dry-run and from the completion of the protocol deviation process	Included more details on re-mapping process, covering the case of participants discontinuing the study treatment but still attending all the visits	2.1.1.11
			Harmonize analysis sets definition	2.2
			Definition of further baseline characteristics	2.3.2
			Included summary tables on concomitant medications and pre treatment procedures	2.4.2
			Added a reference to plots on individual data	2.5.1
			Updated further details on supplementary analyses	2.5.6
			Updated section on AE analyses	2.7.1
			Added new supplementary analyses	2.5.6

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			Improved the description of analysis of laboratory data	2.7.3
			Updated section on ECG analysis including information regarding flagging	2.7.4.1
			Updated section on Vital sign analysis including information regarding flagging and a box-plot by treatment	2.7.4.2
			Included further details concerning biomarkers analysis	2.11
			Included further details on other exploratory analyses	2.12
			Included details on management of partial dates in MH form	5.1.3.3
			Included further details on criteria for exclusion of participants/sessions from analysis sets	5.5

This list does not include minor cosmetic changes like correction of typos and terms added to the list of abbreviations.

Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse Event
ADA	Anti-drug antibodies
ASC	Apoptosis-associated speck-like protein containing a caspase recruitment domain
CHIP	Clonal Hematopoiesis Indeterminate Potential
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
CV	Coefficient of Variation
DNMT3A	DNA MeThyltransferase 3 Alpha gene
CXCL9	C-X-C Motif Chemokine Ligand 9
CXCL10	C-X-C Motif Chemokine Ligand 10
EOS	End of Study visit
EOT	End of Treatment visit
FPFV	First Patient/Participant First Visit
HDL-C	High Density Lipoprotein cholesterol
hsCRP	High-sensitivity C-reactive protein
hsIFN-γ	High-sensitivity Interferon gamma
ICH	International Council for Harmonization
IA	Interim Analysis
ICF	Informed Consent Form
IE	Intercurrent Event
IL-1β	Interleukin 1 beta
IL-6	Interleukin 6
IL-18	Interleukin 18
LDL-C	Low Density Lipoprotein cholesterol
Lp(a)	Lipoprotein alpha
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MI	Myocardial Infarction
PBMC	Peripheral blood mononuclear cells
PDS	Programming Data Set specifications
PK	Pharmacokinetics
QD	Once daily
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Standard deviation
SNP	Single Nucleotide Polymorphism
TET2	Tet methylcytosine dioxygenase 2 gene
TFL	Tables, Figures, Listings
VAF	Variant allele frequency
vWF	Von Willebrand Factor
WLIMS	Watson Laboratory Information Management System

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the Clinical Study Report (CSR) of study CADPT15A12201, a randomized, placebo-controlled, parallel-group, investigator- and participant-blinded Phase 2a study to investigate the efficacy, safety, and tolerability of DFV890 and MAS825 for inflammatory marker reduction in adult participants with coronary heart disease and Clonal Hematopoiesis of Indeterminate Potential (CHIP).

The content of this SAP is based on protocol version 00 dated 28-Jul-2023 and Case Report Form (CRF) version 1.0 dated 09-Nov-2023.

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 and potential Interim Analysis (IA) outputs.

1.1 Study design

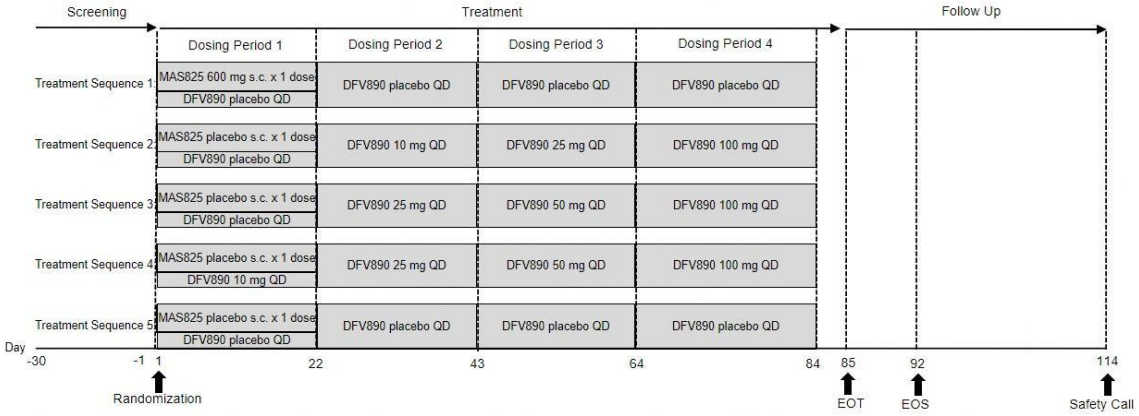
This is a multi-center, randomized, placebo-controlled, participant- and investigator-blinded study to evaluate the efficacy, safety, and tolerability of intra-individual dose escalation of DFV890 or a single s.c. dose of MAS825 for inflammatory marker reduction in participants with coronary heart disease and *TET2* or *DNMT3A* CHIP (VAF ≥2%). The study consists of a screening period up to 30 days; a treatment period of approximately 12 weeks with an end of treatment (EOT) visit on Day 85, which is one day after the last dose of DFV890 or placebo; a follow-up period of approximately 1 week; and a standard safety follow-up call approximately 30 days following the last dose. The overall study duration is approximately 21 weeks.

Approximately 28 participants will be randomized into the trial, of which a minimum of approximately 40% of randomized participants will be CHIP with *TET2* somatic mutations. For subgroup allocation, patients with *TET2* or *DNMT3A* CHIP will be determined based on their most common mutation (e.g., patients with mutations in both *DNMT3A* + *TET2* will be allocated to the subgroup based on the mutation with the highest VAF). Blood samples collected for CHIP genotyping on Day 1 and at the EOT visit will be analyzed at a central laboratory at EOS to explore changes in VAF, and will not be used for eligibility or subgroup allocation purposes.

Participants meeting all eligibility criteria will be randomized in a 4:4:4:1:1 ratio to one of the five treatment sequences as shown in Figure 1-1 (1 MAS825+placebo sequence, 3 DFV890+placebo sequences, and 1 placebo-only sequence). Within each DFV890+placebo sequence, participants will start on either oral placebo or DFV890 10 mg QD.

On Day 1, participants will receive the first oral dose of DFV890 or placebo and the single s.c. dose of either MAS825 or placebo. None of the treatment sequences include a combination of both active DFV890 and active MAS825. After initial dosing, assessments will be conducted at site. Participants will then be provided with a sufficient amount of DFV890/DFV890 placebo doses for daily dosing until their next scheduled visit.

Figure 1-1 Study design



If applicable, the dose of DFV890 will be uptitrated (according to the specific treatment sequence to which the participant is assigned) approximately every three weeks at the scheduled visits on Days 22, 43 and 64 as shown in the study design figure. At these visits, efficacy, safety and tolerability assessments will be performed. Participants will take oral daily doses of DFV890 or placebo for a total of approximately 12 weeks. Participants will return for an EOT period visit on Day 85.

After the EOT visit, participants will return approximately 1 week later on Day 92 for an End of Study (EOS) visit.

1.2 Study objectives, endpoints and estimands

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the effect of various dose levels of DFV890 versus placebo to reduce circulating levels of inflammatory markers in participants with coronary heart disease and CHIP	• Serum levels of IL-6 and IL-18 at 3 weeks after the start of a DFV890 dosing period
• To evaluate the effect of MAS825 versus placebo to reduce circulating levels of inflammatory markers in participants with coronary heart disease and CHIP	• Serum level of IL-6 at 3 weeks after a single s.c. dose of MAS825
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the safety and tolerability of DFV890 and MAS825 in participants with coronary heart disease and CHIP	• Adverse events, and parameters from safety assessments, including vital signs, electrocardiograms (ECGs), and laboratory assessments (urine and blood)
• To assess the PK of DFV890 in participants with coronary heart disease and CHIP	• Plasma trough concentrations (Ctrough) of DFV890 at steady-state
• To assess the PK of MAS825 in participants with coronary heart disease and CHIP	• Serum concentrations of MAS825 after a single s.c. dose of MAS825

Objective(s)	Endpoint(s)
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
• To assess the PK of IBW042 a metabolite of DFV890 in plasma	• Plasma Ctrough of IBW042 at various dose levels of DFV890
• To explore whether individual variation in the CYP2C9 gene related to drug metabolism confer differential PK response to DFV890	• Plasma Ctrough of DFV890 and its metabolite, IBW042, as well as CYP2C9 genotype
• To assess the effect of DFV890 and MAS825 on PD and inflammation-related, and CVD-related biomarkers (including PK/PD relationships)	• PD and inflammation-related markers may include but are not limited to hsCRP, soluble ASC, total IL-1β, CXCL9, CXCL10, hsIFN-γ, vWF, total count and percentage of myeloid/lymphoid cells in peripheral blood by flow cytometry, and total IL-18 (MAS825 only) • CVD-related biomarkers may include but are not limited to lipid parameters • DFV890 and MAS825 concentrations at or up to corresponding time point

• To explore genetic and proteomic drug-related response mechanisms, to understand the disease and/or the safety and efficacy of DFV890 and MAS825	• Exploratory genetic and proteomic endpoints may include but are not limited to:
	  • Presence of genetic polymorphisms
	  • Presence of somatic mutations (CHIP) and their change from baseline
	  • Serum or plasma proteins and their change from baseline serum or plasma

• To explore the effect of DFV890 on changes to the skin microbiome	• Skin microbiome at various visits

1.2.1 Primary estimand(s)

The primary clinical question of interest is: What is the effect of DFV890 and MAS825 in addition to SoC CVD prevention medication in patients with known coronary heart disease and presence of CHIP on the inflammatory markers IL-6 and IL-18 (IL-18 applicable for DFV890 only), assuming patients continue treatment with reasonable adherence and there are no new major cardiovascular events, initiations of prohibited medication, or febrile infections, but without regard to changes in SoC CVD prevention medication.

The justification for the estimand is that it will capture the effect of the investigational treatments versus placebo under research-like conditions, where participants adhere to their assigned treatment regimen and there is no impact of other intercurrent events on the primary endpoints (aside from potential changes in SoC CVD prevention medication).

The estimand is defined by the following attributes:

1. Population: participants with known coronary heart disease and *TET2* or *DNMT3A* CHIP (VAF ≥2%) and potential SoC CVD prevention medication
2. Endpoints: Change from baseline (day 1) in log transformed Serum levels of IL-6 and IL-18 at 3 weeks after the start of a dosing period for DFV890 and serum level of IL-6 at Week 3 for MAS825
3. Treatment of interest: MAS825 or placebo single dose, DFV890 QD or DFV890 placebo QD

4. Handling of intercurrent events: see Table 1-2
5. Summary measure: the model-based difference in variable means between treatments.

Table 1-2 Intercurrent events for the primary estimand

Intercurrent event	Details (if necessary)	Handling of event
Permanent discontinuation of study treatment (DFV890 only)	Potential data collected during an EOT visit will be only used if collected within 1 day from the last dose and if the treatment duration is of at least 17 days in the dosing session affected.	Data collected after this intercurrent event will not be used for this estimand and set to missing
Incidence of a new major CVD event (e.g., myocardial infarction, stroke, etc.)	-	Data collected after this intercurrent event will not be used for this estimand and set to missing
Change in SoC CVD prevention medication	-	All data collected after this intercurrent event will be used for this estimand
Initiation of a prohibited medication for a comorbid condition	Unforeseen use of any medication expected to have a sustained effect on the primary endpoints (i.e., any systemic corticosteroids)	Data collected after this intercurrent event will not be used for this estimand and set to missing
	Unforeseen use of medication expected to have a limited effect on the primary endpoints (i.e., any other prohibited medications)	Only the assessment immediately following the event will be excluded for the purpose of this estimand and set to missing
New-onset febrile infection	Febrile infection around time of assessment classified as protocol deviation OTH02.	Only the assessment immediately following the event will be excluded for the purpose of this estimand and set to missing
Nonadherence to study treatment (DFV890 only)	Greater than 20% of missed daily doses within 3 weeks prior to an assessment or a treatment duration < 17 days	Only the assessment immediately following the event will be excluded for the purpose of this estimand and set to missing
	Any missed dose within the 2 days prior to an assessment	Only the assessment immediately following the event will be excluded for the purpose of this estimand and set to missing

The handling of each intercurrent event specified in Table 1-2, with the exception of changes in SoC CVD prevention medication, reflects what is referred to as the hypothetical strategy, which aims to mimic a scenario in which the intercurrent event did not actually occur and all participants had adhered to the randomized treatment throughout the course of the study. To enable this strategy, data from various assessments taking place after the event will be excluded from the primary analysis, as described in the table. The exception to this is changes to SoC CVD prevention medication, which will be handled by a treatment policy strategy, in which any occurrence of the event is ignored and the subsequent data are included in the analysis.

1.2.2 Secondary estimand(s)

Not applicable.

2 Statistical methods

A CSR will be prepared following the completion of the study. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

2.1 Data analysis general information

The final CSR analysis will be performed by Novartis. SAS version 9.4 or later software will be used to perform all data analyses and to generate tables, figures and listings.

General analysis conventions

Unless otherwise specified: categorical data will be presented as frequencies and percentages; continuous data will be presented as n, mean, standard deviation (SD), median, minimum, and maximum.

For PK concentration and PK parameters, coefficient of variation (CV) (%), geometric mean, and geometric CV% will be presented in addition to the previously mentioned summary statistics.

CV% is calculated as follows:

100*(SD/arithmetic mean).

Geometric CV (%) is calculated as follows:

sqrt (exp (variance for log transformed data)-1)*100.

Unscheduled assessments

The following points summarize the rules for unscheduled assessments:

- Baseline: All unscheduled assessments before the first dose may be included for consideration when calculating the baseline value.
- In summary tables by visit, unscheduled assessments should not be included unless they qualify as baseline.
- In shift tables and table of abnormal values all unscheduled assessments are included.

Unscheduled assessments will be reported with the scheduled assessments in the listings.

2.1.1 General definitions

2.1.1.1 Investigational drug and study treatment

Investigational drug refers to DFV890, MAS825 or placebo.

Study treatment refers to sc single dose of MAS825, oral daily doses of placebo or DFV890 at various dose levels: MAS825, Placebo, DFV890 10 mg, DFV890 25 mg, DFV890 50 mg and DFV890 100 mg. The start and end of each study treatment refers to that of the dosing period.

2.1.1.2 Treatment sequence

In this study, participants are randomized to either of the five treatment sequences, each contains 4 dosing periods. The study treatment planned for each dosing period within each treatment sequence is shown below:

Treatment sequence 1: MAS825 – Placebo – Placebo – Placebo. Note that the effect of MAS825 is expected to persist over the entire 12-week treatment period. Therefore data collected in this sequence, after week 3 will be still assigned to MAS825.

Treatment sequence 2: Placebo – DFV890 10 mg – DFV890 25 mg – DFV890 100 mg

Treatment sequence 3: Placebo– DFV890 25 mg – DFV890 50 mg – DFV890 100 mg

Treatment sequence 4: DFV890 10 mg – DFV890 25 mg – DFV890 50 mg – DFV890 100 mg

Treatment sequence 5: Placebo – Placebo – Placebo – Placebo

2.1.1.3 Dosing period

A dosing period is defined as an approximate 3-week interval between scheduled visits as given in the study design figure (Figure 1-1). For example, dosing period 1 will begin at Day 1 (randomization) and it is expected to end on the Day 22 visit, at which point the next treatment will be administered according to the specific treatment sequence. All assessments will be done before the dosing of the next dosing period. Specifically:

Dosing period 1: Begins at Day 1 (randomization) and ends on max (Day 22 visit, last dose in dosing period 1) prior to next dosing level.

Dosing period 2: Begins immediately after the end of dosing period 1 and ends on max (Day 43 visit, last dose in dosing period 2) prior to the next dosing level.

Dosing period 3: Begins immediately after the end of dosing period 2 and ends on max (Day 64 visit, last dose in dosing period 3) prior to the next dosing level.

Dosing period 4: Begins immediately after the end of dosing period 3 and ends on max (Day 85 visit, last dosing in period 4).

The Follow-up period begins immediately after the last dosing period.

2.1.1.4 Date of first administration of investigational drug

The date of first administration of investigational drug is defined as the first date when a nonzero dose of investigational drug is administered and recorded on dose administration CRF. The date of first administration of investigational drug will also be referred as start of investigational drug. Date of first administration of investigational drug will also be defined at the dosing session level.

2.1.1.5 Date of last administration of investigational drug

The date of last administration of investigational drug is defined as the last date when a dose of investigational drug is administered and recorded on dose administration CRF. The date of last administration of investigational drug will also be referred as end of investigational drug.

Date of last administration of investigational drug will also be defined at the dosing session level.

2.1.1.6 Date of first administration of study treatment

See Section 2.1.1.4

2.1.1.7 Date of last administration of study treatment

See Section 2.1.1.5

2.1.1.8 Study day

Study Day 1 for all assessments is taken to be the date of first administration of study treatment.

The study day for all assessments will be calculated as follows:

1. If date of assessment occurred on or after the start of study treatment, then
   Study day = Date of assessment - Start of study treatment + 1.
2. If date of assessment occurred before the start of study treatment, then
   Study day = Date of assessment - Start of study treatment.

If an event starts before the reference start date, the study day will be negative

The study day will be displayed in the data listings and used in outputs, often in the form of planned study day, by treatment sequence.

Study day will also be defined at the dosing period level, that is to say, taking into account the date of first dosing within each treatment period. This alternative definition will be used in outputs by treatment.

2.1.1.9 Baseline

If not stated otherwise, the last available assessment prior to dosing on Day 1 is taken as baseline assessment. Each participant has one baseline value for each parameter.

All unscheduled assessments before the first dose should be included for consideration when calculating the baseline value.

In rare cases where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied: If values are from central and local laboratories, the value from central assessment should be considered as baseline. If multiple values are from the same laboratory (local or central) or collected for ECGs or vital signs, then the median should be considered as baseline.

If participants have no value as defined above, the baseline result will be missing.

For hsCRP the baseline value will be derived as the mean of the two planned assessments before dosing, collected at screening visit and at day 1 pre-dose.

2.1.1.10 On-treatment period (safety analyses)

On-treatment period starts at day 1 and ends after 30 days from the last dosing.

2.1.1.11 Visit windowing and mapping

Analyses will be conducted according to the planned relative time associated to each visit, except for visits performed after a study drug discontinuation. Post discontinuation visits performed one day after the last dose will be mapped to the corresponding dosing period. Furthermore, if the visit is performed outside the limits described in Table 1-2, PD data collected at that visit will be excluded from the PD analysis set remaining eligible just for supplementary analyses

Other post discontinuation visits will be treated as EOS visits. In case of multiple EOS visits carried-out for the same participant, the visit occurred closer to the planned time (7 days from the last dose) will be considered into the analysis, while data collected in the other visit(s) will be just listed. This is also applicable to the case of participants who discontinued the study treatment still attending all the subsequent visits. Also in this case, visits attended after the study drug discontinuation will be mapped to the end of period, if performed within 1 day from the last dose, to EOS, the one closer to the expected threshold (7 days from the last dose) or excluded from the analysis.

The table below presents some examples:

Table 2-1 Post discontinuation visit mapping

Visit performed after a permanent discontinuation of the study drug	Mapping	Effect on PD analysis set
Within 1 day from the last dose, and after at least 17 days of treatment	Visit mapped to the corresponding dosing period	Data included in the PD analysis set
Within 1 day from the last dose and after < 17 days of treatment	Visit mapped to the corresponding dosing period	Data not included in the PD analysis set (eligible for supplementary analyses)
Not performed within 1 day from the last dose.	Visit mapped to EOS (the closer to the planned time), or excluded from summaries (the further away from the planned time)	Data not included in the statistical Emax/traditional model

2.2 Analysis sets

Participants will be analyzed according to either the treatment(s) received or to the assigned treatment sequence, depending on the analysis.

The enrolled set will include all participants who signed an ICF, including screen failures.

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

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

The PD analysis set will include all participants that received study treatment and had no protocol deviations with relevant impact on PD data.

Details on pharmacokinetic analysis

Concentrations that should not be included in the descriptive statistics (summaries or figures) may be flagged by the pharmacokineticist at the time of the final pharmacokinetic analysis. These concentrations will remain in the listings along with an explanation for the exclusions (provided by the pharmacokineticist).

Analysis set exclusions based on Protocol Deviations

Protocol deviations will be reviewed case by case to select any participant to be excluded from an analysis set taking also into account the rules defined in Table 1-2.

Withdrawal of Informed Consent

Any data collected in the clinical database after a participant withdraws informed consent from all further participation in the trial, will not be included in the analysis. The date on which a participant withdraws full consent is recorded in the eCRF.

2.2.1 Subgroup of interest

Participants will be divided into 2 subgroups of interest according to CHIP type (*TET2* or *DNMT3A*).

Summary statistics by subgroup will be provided for the main analyses.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

Disposition at screening, including those who completed screening and were treated, those who completed screening and were not treated, and reasons for those not completing screening will be displayed for the enrolled set.

Participant disposition will be presented using the Safety set for treatment sequence and all participants. The following summaries will be provided:

- Number (%) of participants who completed treatment and those who discontinued the study treatment phase along with the primary reason for study treatment discontinuation (based on the 'End of Treatment' disposition page)

Participant disposition data will be listed by treatment sequence.

2.3.2 Demographics and other baseline characteristics

The Safety analysis set will be used for all baseline and demographic summaries and listings. Demographic summaries will be presented by actual treatment sequence.

Demographic parameters (Age, Sex, Race, Ethnicity, Height, Weight, and BMI) and main baseline characteristics: CHIP type, CYP2C9 genotype, hsCRP, IL-6, IL-18, Systolic and Diastolic Blood Pressure, LDL Cholesterol, Estimated GFR expressed in numerical and categorical (grades) terms will be summarized descriptively and listed.

Time (years) from last episode of Myocardial infarction (MI) will be derived as a further baseline characteristic, looking at data collected in the medical history form.

Episodes will be detected by considering events coded as 'Acute myocardial infarction/ Myocardial infarction and time in years from last MI will be derived as: (day 1 – date of MI +1)/365.25.

The following categories will be reported:

Not available, <= 1year, >1 to <=5 years, >5 to <=10 years, > 10 years.

Incomplete dates will be managed as indicated in Section 5.1.3.3

ST-elevation (not available / STEMI/ non STEMI) will also be reported looking at the lower level term code.

Relevant medical histories and current medical conditions at baseline will be listed by system organ class and preferred term, by treatment sequence and participant. A summary table by treatment sequence will also be provided.

2.3.3 Protocol deviations

All important protocol deviations will be listed. A summary table by treatment sequence and deviation category will be provided if appropriate.

2.3.4 Analysis sets membership

The number (%) of participants randomized and included in each analysis set (defined in Section 2.2) will be summarized by treatment sequence and treatment separately.

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

2.4.1 Study treatment / compliance

Study treatment compliance will be descriptively summarized by study treatment for the safety analysis set, including compliance in different percent categories, (< 20%, between 20% and < 40%, between 40% and <60%, between 60% and < 80%, >= 80%) as derived considering protocol deviation codes. This analysis will be performed in terms of dosing sessions considering a potential sample size of twenty-four 3-week dosing sessions with placebo. Note that treatments with MAS825 and DFV placebo won't be included in this analysis being assigned to MAS825 treatment.

Study treatment duration (in days), defined as last date of administration – first date of administration +1, will also be summarized by treatment.

Compliance data will also be listed by treatment sequence.

This analysis will be restricted to DFV890/DFV890 placebo sessions excluding the participants randomized to the first treatment sequence.

Details regarding MAS825, MAS825 placebo, DVF890 placebo administrations in participants treated previously with MAS825, will be only listed by treatment sequence and treatment.

2.4.2 Prior, concomitant and post therapies

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 classification system by treatment sequence for the safety analysis set.

Concomitant medications, defined as medications started before Day 1 and still ongoing at Day 1, will also be summarized by treatment sequence.

Pre-treatment (non-drug) procedures will be summarized by treatment sequence.

2.5 Analysis supporting primary objective(s)

The primary objective is to evaluate the effect of various dose levels of DFV890 versus placebo to reduce circulating levels of inflammatory markers (IL-6 and IL-18) in participants with coronary heart disease and CHIP. The effect of a single dose of MAS825 vs placebo, as well as a comparison between MAS825 and DFV890 (IL-6 only) will be also evaluated.

2.5.1 Primary endpoint(s)

The primary endpoints are the change from baseline in log transformed serum levels of IL-6 and IL-18 at 3 weeks after the start of a dosing period. Screening and follow-up assessments will be listed and summarized, while the statistical analysis, described in the next section, will include only the assessments taken at the end of each dosing period and the baseline as a covariate. Invidual plots by treatment and by treatment sequence will also be provided.

Summaries of descriptive statistics by time will be provided by treatment and by treatment sequence. Summary statistics by sequence will also be used to investigate the presence of potential period/carry-over effects.

Descriptive analyses will also be provided by subgroup (see Section 2.2.1).

The definition of the primary estimand is provided in Section 1.2.1

2.5.2 Statistical hypothesis, model, and method of analysis

The primary analysis will assess the effect of DFV890 on the change from baseline in log transformed IL-6 and IL-18 values, compared to placebo in a dose-response model, separately for the two biomarkers. In this analysis, MAS825 data are excluded from the analysis (including placebo sessions following a MAS825 dose).

For each biomarker, an E_{max} model will be fit to the change from baseline, with a random effect (reflecting between-participant variability) on the placebo response E_0 and on ED_{50} (the dose that produces half the maximal effect), a covariate on E_0 for the baseline value of the biomarker, and a covariate on ED_{50} for baseline body weight. All biomarker measurements will be logarithm-transformed prior to the analysis. Baseline biomarker value and body weight will also be log transformed and centered using the median value over the patients included in the model.

Strategy in case of convergence issue.

If the above described model fails to converge other methods will be assessed such as:

Model 2= a model without the random effect on ED_{50} (2 covariates ,1 random effect).

Model 3 = a model removing the covariate on ED_{50} (1 covariate, 2 random effects)

Model 4 = a model removing both the covariate and the random effect on ED_{50} (1 covariate and 1 random effect).

Model 5 = a traditional linear model including treatment as a fixed categorical effect, a random intercept effect for participant, and the baseline value of the biomarker and baseline body weight as covariates. Only for IL6 this model will also include MAS825 sessions, managed as 4 different treatment groups (MAS 3w, MAS 6w, MAS 9w, MAS 12w).

An additional random effect reflecting between-participant variability on E_{max} may be incorporated if the data allows.

From each model, the predicted response at each treatment and associated 80% confidence interval (CI) will be extracted, along with the difference to placebo for each DFV890 dose level, the corresponding 2-sided 80% CI, and the p-value. The estimated response and the difference to placebo will be back-transformed and reported on the ratio scale.

From the model-based quantities, the following efficacy criteria will be evaluated at the log transformed median value of the biomarker and of body weight:

1. At least one of the following is observed in relation to placebo at the 100 mg dose:
   - IL-6 reduction ≥ 25%, or
   - IL-6 reduction ≥ 20% + IL-18 reduction ≥ 10%, or
   - IL-6 reduction ≥ 15% + IL-18 reduction ≥ 20%.
2. For any of the above criteria that are achieved, the one-sided p-value for the comparison of DFV890 vs. placebo for the associated biomarker(s) is less than 0.1.

A plot showing predicted responses at each treatment and associated 80% confidence interval (CI) as well as the observed mean response will be provided for the selected and the traditional model.

The evaluation of the MAS825 effect will be based on the model described as model 5. This will include a comparison of MAS825 effects vs placebo and comparisons of each DFV890 dose vs MAS825 3 week effect.

2.5.3 Handling of intercurrent events

As described in Section 1.2.1, the intercurrent events will be handled according to a hypothetical strategy, reflecting a scenario in which a given participant with an event had not actually experienced the event. To enable this strategy, depending on the type of event, either (1) the biomarker assessment at the visit immediately following the event will be set to missing for the primary analysis or (2) all subsequent biomarker assessments will be set to missing for the primary analysis, as described in that section. The exception to this is changes to standard of care cardiovascular disease prevention medication, which will be handled by a treatment policy strategy, in which any occurrence of the event is ignored and the subsequent data are included in the analysis.

The data from these assessments will be estimated in the primary analysis under the assumption that the outcome in the affected participant would be no different than in the population of participants assigned to the same treatment but that did not experience the event.

Although measurements collected after the events handled by this strategy are not used for the analysis, the planned assessments will take place for possible evaluation of supportive estimands.

A listing of all intercurrent events will be provided.

2.5.4 Handling of missing values not related to intercurrent event

If no measurements are collected after the intercurrent event is experienced, these missing measurements will not be imputed. Missing data not related to intercurrent events are expected to be intermittent and will be assumed to be missing at random. These data will not be explicitly imputed.

2.5.5 Sensitivity analyses

As a sensitivity analysis to the Emax model described in Section 2.5.2, a Hill coefficient other than 1 may be explored.

If the Emax model converges on either of the two primary endpoints, the traditional model previously described will be performed as a sensitivity analysis on that endpoint and/or to assess MAS825 effect.

2.5.6 Supplementary analyses

As a supplementary analysis, the primary analysis may be performed as described, except that some or all biomarker measurements collected after any change in standard of care cardiovascular disease prevention medication may be excluded from the analysis.

Further supplementary analyses will be performed: 1) excluding participants with BLQ value for the baseline primary outcome, and 2) by CHIP-mutation subtype.

Finally a supplementary analysis including all data available, without any exclusion due to Intercurrent Events (IEs), will also be provided.

2.6 Analysis supporting secondary objectives

The secondary objective is to evaluate the safety, tolerability, and pharmacokinetics of DFV890/MAS825 in participants with coronary heart disease and CHIP.

2.6.1 Secondary endpoint(s)

The secondary endpoints include safety endpoints (adverse events, vital signs, electrocardiograms, and laboratory assessments) and PK endpoints: plasma trough concentrations (Ctrough) of DFV890 at steady state, and MAS825 serum concentrations.

2.6.2 Statistical hypothesis, model, and method of analysis

Analysis of safety endpoints refers to Section 2.7.

PK set will be used for PK analysis. Summary statistics of Ctrough of DFV890 and plasma concentrations collected at day 92 will be provided by dose and time point including the frequency of concentrations below the LLOQ and reported as zero. Time will be defined at the

dosing period level. MAS825 serum concentrations will be summarized in the same way. Note that while DFV890 will be assessed over a 3-week period (4-week considering the EOS assessment), MAS825 PK will be assessed over a 12 week period.

Summary statistics will include mean (arithmetic and geometric), standard deviation (SD), and CV (arithmetic and geometric), median, minimum, and maximum concentration.

2.6.3 Handling of intercurrent events

Not applicable.

2.6.4 Handling of missing values not related to intercurrent event

Drug concentrations below LLOQ will be treated as missing for the calculation of the geometric means and geometric coefficient of variation (CV%), and as zero for all other calculations.

2.6.5 Sensitivity analyses

Not applicable.

2.6.6 Supplementary analyses

Not applicable.

2.7 Safety analyses

The safety set will be used for all safety analyses

2.7.1 Adverse events (AEs)

Treatment-emergent AEs (TEAEs) are those with an onset after the start of a specific dosing period, or which were present prior to the start of the dosing period but increased in severity, changed from being not suspected to being suspected of study treatment relationship, or developed into SAEs after the start of the dosing period.

AEs with an onset outside the on-treatment period (before first dosing or more than 30 days from last dosing) will be just listed. AEs with a day of onset coinciding with the start of a new treatment will be assigned to the new treatment. Therefore AEs occurred on Day 1 will be considered TEAEs.

AE summaries will include all TEAEs occurred in the on-treatment period. All AEs collected in the AE CRF page will be listed by treatment sequence and participant, along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome, etc.

AE summaries will be provided by treatment and by treatment sequence.

Summaries by treatment will be restricted to TEAEs occurred in the dosing periods (excluding TEAEs occurred in the follow-up) and percentages will be derived on the total number of dosing periods involved. This means that a participant treated with placebo for four 3-week treatment periods (as in treatment sequence 5) will be counted 4 times. Similarly, the same AE occurred in x separate dosing periods will be counted x times.

MAS825 dosing sessions will be defined as a 12-week interval from day 1 to Day 85 study visits.

Summaries by treatment sequence will consider all TEAEs occurred in the on-treatment period and will be referred to the number of participants assigned to each sequence.

An overview summary table will be provided reporting dosing sessions/participants with TEAEs (overall and by severity), treatment-related TEAEs (overall and by severity), serious TEAEs, and TEAEs/drug-related TEAEs leading to discontinuation of study treatment .

The number (and percentage) of dosing sessions/participants with TEAEs will be summarized by primary system organ class, and preferred term. An additional summary by primary system organ class, preferred term, and maximum severity will also be reported, as well as for serious (including fatal) TEAEs.

A participant with multiple AEs within a preferred term/primary system organ class is only counted once towards the total of the preferred term/primary system organ class. In the analyses based on dosing sessions this rule will be applied at each dosing session level.

2.7.1.1 Adverse events of special interest / grouping of AEs

Analyses focused on skin rash may be provided. Further details will be included in the TFL shells document.

2.7.2 Deaths

All deaths (if any) will be listed using the Safety set.

2.7.3 Laboratory data

Laboratory data collected sparsely (eg. for reflex testing for urine microscopy or safety follow-up testing for renal/hepatic events) will be listed but not included in summaries.

Biomarkers not included as part of trial safety monitoring (Table 8-1 of the study protocol) included among the laboratory data wil be analyzed as described in Section 2.11. Specifically the following parameters will be considered as exploratory outcome biomarkers:

Table 2-2 Laboratory parameters to be managed as biomarkers

Code (LBPARM)	Description (parameter)	Code (LBTEST)
TRIG	Triglycerides	TRIG
VLDL	VLDL cholesterol	VLDL
LDLDIRCT	LDL Cholesterol (Direct)	LDL
NHDL	Non HDL cholesterol	NONHDL
HDL	HDL cholesterol	HDL
HSCRP	High sensitivity C-reactive protein	CRP
LDLCALM	LDL Cholesterol (Calculated)	LDL
CHOL	Cholesterol	CHOL
APOA1	Apolipoprotein A1	APOA1
APOB	Apolipoprotein B	APOB
Not available yet	vWF	not available yet
Not available yet	Lp(a)	not available yet

Only Low Density Lipoprotein Cholesterol (LDL-C) will be reported as both safety laboratory data and an exploratory outcome biomarker. Data collected on local labs won't be reported.
In the summaries, laboratory results expressed as <x or > y will be considered as ½ x or y, respectively.
Other derivations related to laboratory parameters are described in Section 5.3

The following descriptive summaries will be produced for laboratory data for each laboratory parameter

- Actual value and change from baseline summaries by treatment and timepoint as well as by treatment sequence
- Shift tables using the low/normal/high /(low and high) classification to compare baseline to the worst on-treatment value will be presented for all the parameters with normal ranges available only by treatment sequence.

Estimated glomerular filtration rate (eGFR) data (mL/min/1.73 m**2) as calculated by the CKD-EPI equation will be categorized according to these rules:

G1 (Normal) = >=90

G2 (Mildly decreased) = 60-89

G3a (Mildly to moderately decreased) = 45-59

G3b (Moderately to severely decreased) = 30-44

G4 (Severely decreased) = 15-29

G5 (Kidney failure) = < 15

Shift table for this parameter will be based on the categories described above.

For categorical parameters, the frequency and percentage of participants falling in each category will be presented in the summary tables.

In the analyses by treatment and timepoint, the time will be referred to the start of each dosing period. Therefore for instance a day 43 assessment will be considered a 3-week assessment and assigned to the treatment received by the participant in the second dosing period (except in treatment sequence 1). Time will be managed differently for the participants randomized to treatment sequences 1 and 5. In this case time will be referred to the start of the first treatment (MAS825 in treatment sequence 1, Placebo for treatment sequence 5). Therefore for these participants assessments after 6, 9 and 12 weeks will also be derived.

Analyses by treatment won't be performed for the laboratory data collected just at the start and at the end of the trial (Coagulation panel and Urinalysis).

In the analyses by treatment sequence and timepoints the following time points will be reported:: screening, baseline, Days 22, 43, 64, 85 and 92.

Box-plots by treatment sequence and time, as well as by treatment will be provided. In the latter case the horizontal axis will include the baseline and the 3-week assessments. Weeks 6,9,12 distributions will be plotted just for the placebo and the MAS arm. Further details will be included in the TFL shells document.

Listing for participants with lab values outside the normal range (per normal ranges provided in the source dataset) will be provided. If there is any abnormal lab value for a participant, all measurements of this lab value for the participant will be presented in this listing with the abnormal values flagged.

2.7.4 Other safety data

2.7.4.1 12-lead ECG

All ECG parameters (absolute values and changes from baseline) will be descriptively summarized by treatment sequence and time. All ECG data will be listed by treatment sequence and participant. Box-plots by treatment sequence and time will be provided.

In the listings values will be flagged according to the following rules:

QT, QTcF

- New value of > 450 and ≤ 480 ms
- New value of > 480 and ≤ 500 ms
- New value of > 500 ms
- Increase from baseline of > 30 ms to ≤ 60 ms
- Increase from baseline of > 60 ms

- HR
  - Decrease from baseline >25% and a value < 50 beats per minute
  - Increase from baseline > 25% and a value > 100 beats per minute

- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms

- QRS
  - Increase from baseline >25% and to a value > 120 ms
  - New values of QRS > 120 ms

The definition of 'new value' is any case meeting the criteria during the on-treatment period not already present at baseline.

Baseline definition is provided in Section 2.1.1.9

2.7.4.2 Vital signs

All vital signs data (absolute values and changes from baseline) will be summarized by treatment/treatment sequence and time. Time will be managed as previously described for labs data. All vital signs data will be listed by treatment sequence and time. Box-plots by treatment sequence and time as well as by treatment will be provided.

A listing for complete vital signs data for all partecipants will be presented with the abnormalities flagged according to the following rules:

Notable criteria (High/Low):

- Systolic blood pressure [mmHg]: >140/<90 mmHg
- Diastolic blood pressure [mmHg]: >90/<50 mmHg
- Pulse rate [bpm]: >90/<40 bpm
- Weight [kg]: >110/<35 Kg
- Temperature [°C]: >37.5/<35.0°C.

2.8 Pharmacokinetic endpoints

Plasma Ctrough of DFV890 and its metabolite, IBW042, will be descriptively summarized by CYP2C9 genotype, dose, and time point, including the frequency of concentrations below the LLOQ and reported as zero. Serum MAS825 concentrations will be summarized similarly without a breakdown by CYP2C9 genotype and considering a wider time interval.

Plasma Ctrough/concentrationsof DFV890 and its metabolite, IBW042, will be descriptively summarized by dose, and by CYP2C9 genotype and dose, including the frequency of concentrations below the LLOQ reported as zero. Serum MAS825 concentrations will be summarized by time point.

Time will be defined at the dosing period level except in MAS825 analysis.

Individual plots and mean plots by CYP2C9 (for DFV9890 and IBW02) and dose will also be provided.

2.9 PD and PK/PD analyses

Correlation analyses between plasma Ctrough of DFV890 and selected biomarkers and between concentrations of MAS825 and selected biomarkers may be performed by a scatterplot together with a regression line respectively. Correlation statistics such as Pearson correlation coefficient and its p-value may be presented on the graph as well.

2.9.1 Immunogenicity

2.9.1.1 Sample ADA Status

Immunogenicity analysis will be restricted to the MAS825 arm.

Each anti-drug anti-body (ADA) sample is assessed in a three-tiered ADA testing approach. All ADA samples are analyzed in the initial screening assay (first tier). Samples testing negative in the screening assay are not subject to a confirmatory assay. Samples testing positive in the screening assay are then subjected to the confirmatory assay to demonstrate that ADA are specific for the therapeutic protein product (second tier). The titer of confirmatory positive samples will be subsequently determined in the titration assay (third tier).

Samples can test negative in either the screening or confirmatory assay but for statistical analysis purposes they are not differentiated. The following properties of each sample will be provided in the source data (i.e. the third party data output (e.g. WLIMS) processed by PreAdvance):

- Result of assay according to pre-specified confirmatory cut point: ‘POSITIVE’, ‘NEGATIVE’, or ‘NOT REPORTABLE’
- Titer: numerical representation of the magnitude of ADA response

Sample ADA status will be listed in the safety set and summarized by treatment and time point in the MAS arm. Overall prevalence will also be summarized including/excluding the baseline assessment.

2.10 Patient-reported outcomes

Not applicable.

2.11 Biomarkers

All participants in the PD analysis set will be included in the biomarker analysis. The following exploratory biomarkers may be analyzed in this trial and reported in the CSR.

- Pharmacodynamic, inflammation-related biomarkers:
  - Inflammatory biomarkers: hsCRP
  - Soluble Biomarkers: soluble ASC, hsIFN-γ, and vWF
- Immunophenotyping: A whole blood monocyte / neutrophil panel will evaluate the total cell count and percentage of monocyte and neutrophil subsets in peripheral blood of patients.
- Target capture biomarkers for MAS825: total IL-1β, total IL-18 and IL-18bp.
- CVD-related biomarkers
  - Lipid parameters: total cholesterol, HDL-C, triglycerides (TGs), LDL-C, Lp(a), apolipoproteins

For each of the biomarker endpoints, the actual value, the change from baseline, and the percent change from baseline will be listed by treatment sequence, participant, and visit/timepoint. Summary statistics will be provided by treatment/treatment sequence and visit/timepoint for the actual value, the change from baseline and percent change from baseline. The frequency (n, %) of values outside of the limits of quantification will be reported in each table.

The following inflammation-related exploratory biomarkers: hsCRP, soluble ASC, hsIFNg, vWF, Interleukin-1b (IL-1b), IL-18, IL-18bp and monocyte/neutrophil panel (whole blood) and disease-related biomarkers (LDL, Lp(a), and apolipoproteins) will be analyzed using a linear mixed effects model of the same form as the traditional model previously specified for the primary endpoint. When appropriate, the analysis will be restricted to DFV890 or MAS825 sessions with the corresponding control sessions.

As for the analysis on primary endpoint log transformations will be applied. Immunophenotyping endpoints considering percentages vs total monocytes/neutrophils will be summarized and listed while they won't be analyzed using any statistical model.

Corresponding plots showing the predicted response at each treatment dose (or time for MAS825) with associated 80% CIs will also be produced, together with individual plots by treatment (by time for MAS825 arm).

Handling of LLOQ and ULOQ

Biomarker data are reported as concentration results, measured using a specific assay with a working range defined by the two limits: Lower limit of quantification (LLOQ) and Upper limit

of quantification (ULOQ). Values which fall below the LLOQ or above the ULOQ are reported as < LLOQ * dilution factor (dilution factor: if sample diluted and concentration measured still below LLOQ) and > ULOQ * dilution factor, respectively.

To ensure that biomarkers only have numerical values, censored values will be imputed as follows:

- Values below the LLOQ are replaced by LLOQ/2.
- Values above the ULOQ are replaced by ULOQ.

Imputed values are used for summary statistics, inferential analyses and plots (with a special symbol). Values below LLOQ and values above ULOQ are shown as such in the listings.

If the proportion of imputed data is more than 20% for any treatment group at any time point, a footnote is added to the summary statistics table stating that the proportion of values outside the limits of quantification is more than 20% for some treatment groups at some time points and that in such cases summary statistics may be heavily biased.

If the proportion of imputed data for a given biomarker, across all treatment groups and time points, is more than 50%, no summary statistics are provided and the data are only listed.

2.12 Other Exploratory analyses

Exploratory targeted genetic and proteomic analyses, reported in CSR or separated documents, may include but are not limited to:

- Presence of somatic mutations (Clonal Hematopoiesis of Indeterminate Potential (CHIP)) at baseline and EOT.
- Presence of specific gene SNPs (not included in the CSR)
- Longitudinal treatment-induced changes in the circulating proteome (serum or plasma, not included in the CSR)

The presence of CHIP (as assayed by the central laboratory) will be reported in the CSR. More than one somatic mutation may be detected for each participant at each timepoint assayed (Day 1 [baseline] and Day 85 [EOT]) among the mutations assayed on the TSO500 platform. Mutations will be characterized in terms of gene location/allele change, protein location/amino acid change (if any), and cDNA change. VAF values will be multiplied by 100 to be expressed in terms of a percentage.Data will be listed by treatment sequence and participant.

The listing will also include the VAF change from baseline and data collected during the visits not included in the PD analysis set (if any) appropriately flagged. If a mutation is detected at baseline but not at EOT, then no value will be imputed and no change for that participant's mutation VAF will be reported.

Summary statistics of VAF change from baseline by treatment sequence will be provided for TET2 or DNMT3A both at the single mutation and at the gene level. Changes from baseline at the gene level will be summarized firstly deriving an average per participant over the different mutations within the same gene, followed by an average by treatment sequence. This procedure assigns the same weight to all the participants.

In this analysis, only cases with VAF>=2% at baseline will be considered and change will be reported across three treatment groups (MAS825 arm [Sequence 1], combined DFV890 arms [Sequence 2-4], and placebo-only arm [Sequence 5]).

2.13 Interim analysis

No interim analysis was originally planned for this study but ad-hoc interim analyses may be conducted to support decision making concerning the current clinical study, Novartis clinical development projects in general or in case of any safety concerns. The clinical team may communicate interim results (e.g., evaluation of Proof of Concept (PoC) criteria or information needed for planning/modifying another study) to relevant Novartis teams for information, consulting and/or decision purposes.

An unblinded ad-hoc interim assessment will be eventually performed considering the results of the first batch of IL6 and IL18 samples. The objectives of this interim assessment are:

- To investigate if the profile of the response is compatible with an Emax model/ the presence of convergence issues related to this model
- An assessment of within and between subjects variability
- An assessment of the power of the study, taking into account the results seen so far

On the basis of the interim results the study team may propose an increase of the sample size in case of results promising but not fully consistent with the original assumption. No reduction of the sample size can be applied, also because the interim will be completed after the completion of the enrollment phase (relative to the planned target). In absence of safety concerns the on-going participants will complete the study as planned.

3 Sample size calculation

Twenty-eight (28) randomized participants in a 4:4:4:1:1 allocation to the treatment sequences will result in, approximately, 8 participants randomized to each of the MAS825-only sequence and the first two ascending dose sequences of DFV890, and 2 participants to the third ascending dose sequence of DFV890 and to the placebo-only sequence.

This allocation of participants will provide at least 80% power of a statistically significant difference from pooled placebo and meeting criteria 1 below if the true, maximum effect of DFV890 on IL-6 and IL-18 within the dose range studied is a 30% reduction (i.e., log(0.7)=-0.36, there is no effect on placebo (i.e., $E_0 = 0$), and the ED_{50} is 20 mg and the within subject SD is 0.4. The variability was assessed from CANTOS trial of canakinumab using placebo-only data through 24 months. The assumed within subject variability of IL-18 is smaller than IL-6 so the sample size is driven by IL-6. This calculation assumes no correlation between the two markers.

The assumed true E_{max} is approximately -0.5, or log(0.6), representing a 40% reduction.

From the model-based quantities, the following efficacy criteria will be evaluated at the median baseline value of the biomarker and the median baseline body weight:

1. At least one of the following is observed in relation to placebo at the 100 mg dose:
    - IL-6 reduction $\geq$ 25%, or

- IL-6 reduction ≥ 20% + IL-18 reduction ≥ 10%, or
- IL-6 reduction ≥ 15% + IL-18 reduction ≥ 20%.

2. For any of the above criteria that are achieved, the one-sided p-value for the comparison of DFV890 vs. placebo for the associated biomarker(s) is less than 0.1.

Simulations have shown that there is at least 80% power in achieving statistical significance at the 10% level and the mean effect as shown above (with type 1 error of <=10%)

This allocation of participants will also provide at least 80% power of showing a statistically significant difference between MAS825 and pooled placebo, if the true effect of MAS825 on IL-6 is a 45% reduction (i.e., log(0.55)=0.60, there is no effect on placebo, and the between subject SD of IL-6 is <= 0.5 using a 1 sided alpha of 10%.)

If MAS825 is not different from placebo, there will be a 10% chance of achieving the efficacy criteria (Type 1 error).

4 Change to protocol specified analyses

This SAP is based on the analyses described in the study protocol. Additional details and clarifications have been introduced to provide a more accurate description of the statistical plan.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Not applicable.

5.1.2 AE date imputation

Table 5-1 Imputation of start dates (AE)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates. AEs without a date won't be assigned to any treatment.

day, month	• If available year = year of study treatment start date then
	  • If stop date contains a full date and stop date is earlier than study treatment start date then set start date = 01JanYYYY
	  • Else set start date = study treatment start date.
	• If available year > year of study treatment start date then 01JanYYYY
	• If available year < year of study treatment start date then 01JulYYYY

Day	• If available month and year = month and year of study treatment start date then
	  • If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 01MONYYYY.
	  • Else set start date = study treatment start date.
	• If available month and year > month and year of study treatment start date then 01MONYYYY

Missing Element	Rule
	• If available month and year < month year of study treatment start date then 15MONYYYY

Table 5-2 Imputation of end dates (AE)

Missing Element	Rule (*=last treatment date plus 30 days not > (death date, cut-off date, withdrawal of consent date))
day, month, and year	• Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	• If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
Day	• If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Imputed dates may be used to classify an event as AEs/TEAEs within a treatment sequence, while they won't be used to assign any treatment in analyses by dosing session.

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

5.1.3 Concomitant medication date imputation

Refer to Table 5-1 and Table 5-2.

5.1.3.1 Prior therapies date imputation

Not applicable.

5.1.3.2 Post therapies date imputation

Not applicable.

5.1.3.3 Other imputations

Partial dates in MH form, related to MI events, will be imputed considering the midpoint, that is to say that when the day is missing it will be considered the mid of the month (15), when when both the month and the day are missing it will be considered the mid of the year (30-June). Imputed dates will be used to derive the time from last MI events and study Day 1.

5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

AEs will be graded as:

- mild: usually transient in nature and generally not interfering with normal activitiessess
- moderate: sufficiently discomforting to interfere with normal activities

- severe: prevents normal activities

5.3 Laboratory parameters derivations

Two LDL-C measurements may be reported in the laboratory data file: measured directly by enzymatic assay (direct) or calculated by Friedewald equation (calculated). Directly-measured LDL-C was obtained in situations meeting standard pre-specified reflex testing criteria where calculated LDL-C is less accurate (triglycerides >= 400mg/dL [4.52 mmol/L] or calculated LDL-C <= 70 mg/dL [1.81 mmol/L]). These two parameters will be merged in a single derived parameter using the calculated value unless a direct value has been collected for any reason. For the derived LDL-C value, a 'high' flag of >=130mg/dL (3.36 mmol/L) and no 'low' flag will be utilized in safety laboratory outputs.

The rule is summarized in the table below.

Table 5-3 Management of LDL-C values

Case	Direct	Calculated	Final assessment
1	Not available	Not available	Missing
2	Not available	Available	Calculated
3	Available	Not Available	Direct
4	Available	Available	Direct

5.4 Statistical models

5.4.1 Analysis supporting primary objective(s)

Refer to Section 2.5.2

5.4.2 Analysis supporting secondary objective(s)

Refer to Section 2.6.2

5.5 Rule of exclusion criteria of analysis sets

Criteria leading to exclusion are summarized in the table below. Several exclusions are applied at the epoch level (dosing sessions plus follow-up). More details on protocol deviations are available in the Edit check Document.

Table 5-4 Criteria leading to exclusion

Analysis Set	Criteria that cause subjects to be excluded
Enrolled	Not having informed consent (INCL01) or OTH05 (only screening ECG)
Safety	Not receiving any study drug dose or protocol deviation INCL01 or OTH05 (only screening ECG)
PK	Not member of the Safety or without any valid PK concentration measurement or protocol deviations: WITH01, TRT01, TRT03, OTH01, OTH03

Analysis Set	Criteria that cause subjects to be excluded
PD	Not member of the safety or presenting protocol deviations with a relevant impact on PD (protocol deviations: TRT01, TRT02, TRT05, TRT06, TRT07, TRT08, OTH01, OTH02,)

Where:

OTH05= Screening ECG before ICF Signature. The exclusion is restricted to ECG at screening

WITH01 = sample analyzed after withdrawal of consent

TRT01= treatment deviation with impact on PD and PK analysis for the corresponding treatment period

TRT02= treatment deviation with impact on PD analysis for the corresponding treatment period

TRT03= treatment deviation with impact on PK analysis for the corresponding treatment period

TRT05= Treatment compliance >=60 and <80% within 3 weeks prior to an assessment

TRT06= Treatment compliance >=40 and <60% within 3 weeks prior to an assessment

TRT07= Treatment compliance >=20 and <40% within 3 weeks prior to an assessment

TRT08= Treatment compliance >=0 and <20% within 3 weeks prior to an assessment

OTH01= Other deviation with impact on PD and PK analysis for the corresponding treatment period

OTH02= Other deviation with impact on PD analysis for the corresponding treatment period

OTH03= Other deviation with impact on PK analysis for the corresponding treatment period

6 Reference

ICH E9(R1) Harmonized Guideline: addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Final version on 20 November 2019.