NOVARTIS

Clinical Development

DFV890

CDFV890F12201 / NCT06031844

A randomized, placebo-controlled, parallel-group, investigator- and participant-blinded Phase 2a study to investigate the efficacy, safety, and tolerability of DFV890 for inflammatory marker reduction in adult participants with coronary heart disease and elevated hsCRP

Statistical Analysis Plan (SAP)

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18-Dec-2023	Start of the trial	Creation of final version	N/A - First version	NA
04-Oct-2024	Prior to Interim	Considering new information arising during the course of the trial	Added reference to Protocol Amendment 1	1
			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
			Removed the reporting of some variables which even if included in the study administration form are not part of the database	2.4.1
			Added a note to highlight that analyses by treatment sequence may be used to investigate potential period/carry-over effects	2.5.1
			Added a supplementary analysis without exclusions due to IEs	2.5.6
			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 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
06-Mar-2025	Post IA and prior to DBL	Considering new information arising from dry-run and from the completion of the protocol deviation process	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

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
			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
			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 details on management of LDL data	5.3.3
			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.

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AE	Adverse Event
ASC	Apoptosis-associated speck-like protein containing a caspase recruitment domain
CHIP	Clonal Hematopoeisis indeterminate potential
CI	Confidence Interval
CRF	Case Report Form
CSR	Clinical Study Report
CV	Coefficient of variation
CXCL9	C-X-C Motif Chemokine Ligand 9
CXCL10	C-X-C Motif Chemokine Ligand 10
EOT	End of Treatment (Visit)
EOS	End of Study (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 events
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
TEAE	Treatment Emergent Adverse Event
TET2	Tet methylcytosine dioxygenase 2 gene
TFLs	Tables, Figures, Listings
VAF	Variant allele frequency
vW	Von Willebrand Factor

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the Clinical Study Report (CSR) of study CDFV890F12201, a randomized, placebo-controlled, parallel-group, investigator- and participant-blinded Phase 2a study to investigate the efficacy, safety, and tolerability of DFV890 for inflammatory marker reduction in adult participants with coronary heart disease and elevated hsCRP.

The content of this SAP is based on Amendment 1 of study protocol dated 18-June-2024 and Case Report Form (CRF) version 1.0 dated 26-Sep-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.

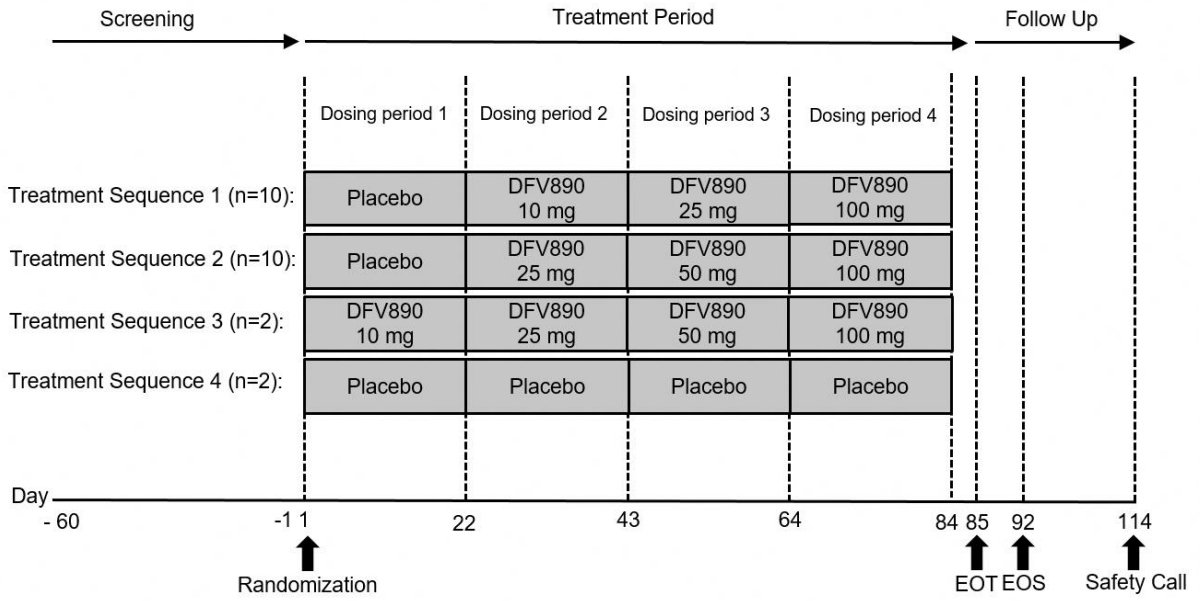
1.1 Study design

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 for inflammatory marker reduction in participants with coronary heart disease and elevated hsCRP. The study consists of a screening period of up to 60 days, a treatment period of approximately 12 weeks, an end of treatment (EOT) visit on Day 85, which is one day after the last dose on Day 84, 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 24 weeks and approximately 24 participants will be enrolled into the trial.

The screening period includes 2 visits. During Screening 1, hsCRP levels will be measured. If hsCRP levels at Screening 1 meet the eligibility criteria, participants will complete Screening 2 (at least 8 days after Screening 1), where other eligibility assessments will be performed. Participants who don't meet hsCRP levels at Screening 1 visit will be considered screen failures.

Participants meeting all eligibility criteria will be randomized in a 5:5:1:1 ratio to one of four treatment sequences (three DFV890 treatment sequences or a placebo-only sequence). No stratifications will be applied in randomization. Within each DFV890 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. After initial dosing, assessments will be conducted at site, as specified in Section 1.3 of protocol (Schedule of Activities). Participants will then be provided with a sufficient amount of study medication for daily dosing until their next scheduled visit.

Figure 1-1 Study Design



The dose of DFV890 will be uptitrated (according to the specific treatment sequence that the participant is assigned to) approximately every three weeks at the scheduled visits on Days 22, 43 and 64, as shown in the study design figure (Figure 1-1). At these visits, efficacy, safety, and tolerability assessments will be performed. Participants will take oral daily doses of DFV890 for a total of approximately 12 weeks. Participants will return for an end of treatment (EoT) period visit on Day 85.

After the EoT visit, participants will return approximately 1 week later (Day 92) for an EoS visit.

No interim analysis is planned for this study, but ad-hoc 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.

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 elevated hsCRP	• Serum levels of IL-6 and IL-18 at 3 weeks after the start of a dosing period
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the safety and tolerability of DFV890 in participants with coronary heart disease and elevated hsCRP	• Adverse events, and parameters from safety assessments, including vital signs, electrocardiograms, and laboratory assessments (urine and blood)

Objective(s)	Endpoint(s)
• To assess the pharmacokinetics of DFV890 in participants with coronary heart disease and elevated hsCRP	• Plasma trough concentrations (Ctrough) of DFV890 at steady state
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
• To explore whether individual variation in genes related to drug metabolism confer differential pharmacokinetic response to DFV890	• Plasma Ctrough of DFV890 and its metabolite, IBW042, by CYP2C9 genotype
• To assess pharmacokinetics of IBW042, metabolite of DFV890 in plasma	• Plasma Ctrough of IBW042 at various doses of DFV890
• To assess the effect of DFV890 on pharmacodynamic (PD), inflammation-related, and cardiovascular disease-related biomarkers (including pharmacokinetic/pharmacodynamic relationships)	• Pharmacodynamic and inflammation-related markers may include but are not limited to hsCRP, soluble ASC, IL-1β, CXCL9, CXCL10, hsIFNg, von-Willebrand-Factor (vWF), myeloid/lymphoid cell activation/enumeration by flow cytometry (whole blood/PBMC) • Cardiovascular disease-related biomarkers may include but are not limited to lipid parameters

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

1.2.1 Primary estimand(s)

The primary clinical question of interest is: What is the effect of DFV890 in addition to standard of care cardiovascular disease prevention medication in patients with known coronary heart disease and elevated hsCRP on the inflammatory markers IL-6 and IL-18, 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 standard of care cardiovascular disease prevention medication.

The justification for the estimand is that it will capture the effect of the investigational treatment 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 standard of care cardiovascular disease prevention medication).

The estimand is defined by the following attributes:

1. Population: patients with known coronary heart disease, elevated hsCRP, and background cardiovascular disease prevention medication.
2. Endpoints: Serum IL-6 and IL-18 levels at 3 weeks after the start of a dosing period.
3. Treatment of interest: DFV890 once daily (QD) or 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	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 (if any) will not be used for this estimand and set to missing.
Incidence of a new major cardiovascular disease event (e.g., MI, stroke, etc.)	N/A	Data collected after this intercurrent event will not be used for this estimand and set to missing
Change in standard of care CVD prevention medication	N/A	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	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 standard of care cardiovascular disease 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, 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 Table 1-2. 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.

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 concentrations 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 general 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 or placebo.

Study treatment refers to oral daily dose of placebo or DFV890 at various dose levels: 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 four treatment sequences, each contains four dosing periods. The study treatment planned for each dosing period within each treatment sequence is shown below:

Treatment sequence 1: Placebo – DFV890 10 mg – DFV890 25 mg – DFV890 100 mg

Treatment sequence 2: Placebo – DFV890 25 mg – DFV890 50 mg – DFV890 100 mg

Treatment sequence 3: DFV890 10 mg – DFV890 25 mg – DFV890 50 mg – DFV890 100 mg

Treatment sequence 4: 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 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 nonzero 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.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative. Study day will also be defined at the dosing period level.

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 may 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 three planned assessments before dosing, collected at screening visits 1 and 2 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.

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
Within1 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	Data not included in the statistical Emax/traditional model

2.2 Analysis sets

Participants will be analyzed according to either the study 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 with 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

At the discretion of the pharmacokineticist:

- 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

Not applicable.

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 sets

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: 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/reported term.

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-eight 3-week dosing sessions with placebo. 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.

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 elevated hsCRP.

2.5.1 Primary endpoint(s)

The primary endpoints are the 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 will include all the assessments taken at the end of each dosing period and the baseline as a covariate. Individual 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.

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 IL-6 and IL-18 compared to placebo in a dose-response model, separately for the two biomarkers.

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 previously 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.

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. Individual plot by treatment sequence, mean plots on raw means by treatment and a plot of the predicted response at each treatment and associated 80% confidence interval (CI) will be produced.

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.

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 implicitly imputed 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 events

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.

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 excluding participants with BLQ values for the baseline primary outcome.

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 in participants with coronary heart disease and elevated hsCRP.

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.

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 will be provided by dose time point, including the frequency of concentrations below the LLOQ and reported as zero. Time will be defined at the dosing period level.

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 will be counted 4 times. Similarly, the same AE occurred in x separate dosing periods will be counted x times.

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, moderate/severe TEAEs, treatment-related fatal TEAEs, TEAEs leading to discontinuation, TEAEs requiring additional therapy.

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 may be reported if deemed necessary.

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 will be listed using 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 will 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 by 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 will be presented in the summary table.

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. Time will be managed differently for the participants randomized to treatment sequence 4, expected to be treated 4 times with placebo. In this case time will be referred to the start of the treatment sequence (dosing period 1). 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 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 (actual 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 (actual 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 participants 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 IBW042 will be descriptively summarized by dose and time point, including the frequency of concentrations below the LLOQ and reported as zero.

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.

Time will be defined at the dosing period level.

Individual plots and mean plots by CYP2C9 and dose will also be provided.

2.9 PD and PK/PD analyses

Correlation analyses between plasma Ctrough of DFV890 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.

2.10 Patient-reported outcomes

Not applicable.

2.11 Biomarkers

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

- PD and inflammation-related markers:
  - Soluble Biomarkers: hsCRP, soluble ASC, hsIFNg and vWF.
- Immunophenotyping: A whole blood monocyte / neutrophil panel will evaluate the total cell count and percentage of monocytes and neutrophil subsets in peripheral blood of patients.
- Cardiovascular disease-related biomarkers:
  - Lipid parameters: total cholesterol, HDL-C, LDL-C, triglycerides, 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 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.

PD and inflammation-related exploratory biomarkers, immunophenotyping endpoints and disease-related biomarkers will be analyzed using a linear mixed effects model of the same form as the traditional model previously specified for the primary endpoint.

As for the analysis on primary endpoints, 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 response per treatment dose with associated 80% CIs will also be produced, together with individual plots by treatment.

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 two treatment groups (combined DFV890 arms, and placebo-only arm).

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 decided, 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-four (24) randomized participants in a 5:5:1:1 allocation to the treatment sequences will provide high probability (88%) of achieving the efficacy criteria if the true, maximum effect of DFV890 on IL-6 and IL-18 within the dose range studied is a 30% reduction, there is no effect on placebo (i.e., $E_0 = 0$), and the ED_{50} is 20 mg. Under these assumptions, the true E_{max} is approximately -0.5, or log(0.6), representing a 40% reduction. If DFV890 is not different from placebo, there will be a 5% chance of erroneously achieving the efficacy criteria.

The stated probabilities of achieving the efficacy criteria were derived by performing 5,000 simulations of an analysis similar to the primary analysis but performed on the ratio to baseline in IL-6 and IL-18, and with no covariates for the baseline value or for baseline body weight.

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 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, when the day is missing it will be considered the mid of the month (15), while 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 activities
- 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)
Safety	Not receiving any study drug dose or protocol deviation INCL01.
PK	Not member of the Safety or without any valid PK concentration measurement or protocol deviations: WITH01, TRT01, TRT03, OTH01, OTH03.
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:

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.