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Novartis Research and Development

Clinical Trial Protocol Title:

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

Clinical Trial Protocol Number: CDFV890F12201 / NCT06031844

Version Number: v01 (Clean)

Compound: DFV890

Brief Title: A study to investigate the efficacy, safety, and tolerability of DFV890 for inflammatory marker reduction in adult participants with coronary heart disease and elevated High-sensitivity C-reactive protein (hsCRP)

Study Phase: IIa

Sponsor Name: Novartis

Regulatory Agency Identifier Number(s): IND 166,371

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Amendment 01 (June 2024)

Amendment Rationale

The main purpose of this amendment is to revise the inclusion/exclusion criteria to allow for facilitated recruitment in line with the study rationale and allow better representation of the study population to that of the contemporary post-myocardial infarction patient population. In summary, the key changes to the inclusion/exclusion criteria include: 1) maximum body mass index (BMI) increased to 45 kg/m^2 from 40 kg/m^2, 2) maximum age increased to 85 from 80 years of age, 3) exclusionary time post multi-vessel coronary artery bypass graft (CABG) procedures decreased from 3 years to 6 months, 4) recommended hemoglobin A1C threshold increased to 10% from 9% for the determination of uncontrolled diabetes, and 5) systemic autoimmune and systemic inflammatory disease exclusion was clarified. The updates are not expected to increase risk to patient safety or result in a meaningful decrease in study drug efficacy in the evaluations of dose and directly measured DFV890 exposure on cytokine reduction.

Second, the amendment includes additional expedited reporting instructions and serious adverse event (SAE) classification for a potential Hy's Law case with elevated liver enzymes. The amended reporting instructions are aligned to updated Novartis protocol language and not due to any safety concerns specific to DFV890. Potential Hy's law cases must be reported as a serious unexpected adverse event promptly, even before other possible causes of liver injury have been excluded or all supplementary data is obtained. Along with the expedited reporting of a treatment-related SAE due to potential Hy's law cases of elevated liver enzymes prior to ruling out other causes and obtaining supplemental data, study stopping rules are updated accordingly to increase from one to two non-life-threatening treatment-related SAEs. A study stopping rule is also now included if a death or one life threatening treatment-related SAE occurs. In addition, a study stopping rule remains that Novartis may put the study on hold if the number and/or severity of adverse events (AEs), abnormal safety monitoring tests, or abnormal laboratory findings justifies putting the study on hold even with one treatment-related SAE.

Third, additional minor edits to the protocol text are included to enhance clarity, accuracy, and understanding of the protocol.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline.

- Table 1-2: *Assessment Schedule* is updated to include the Optional Inflammation Marker Pre-Screening Informed Consent Form (ICF) in the assessment schedule and to clarify that if the Optional Inflammation Marker Pre-Screening ICF is used at Screening visit 1 to allow for the collection of the high-sensitivity C-reactive protein (hsCRP) sample, the main study ICF, optional genetics ICF, demography, and medical history can be obtained at Screening visit 2.
- Section 2.3.1.3: *Potential risk and recommended treatment of infection* is updated to reflect that the GLP toxicology study in cynomolgus monkeys has been completed as per IB edition v06.

- Section 5.1: *Inclusion Criteria* is updated to increase the maximum allowable BMI to 45 kg/m^2 and the maximum allowable age to 85 years old.
- Section 5.2: *Exclusion criteria* that limited the time window after multi-vessel CABG surgery, in which a subject may be enrolled, has been reduced to 6 months. The hemoglobin A1C threshold value used as guidance for investigators to assess uncontrolled diabetes has been increased to 10%. Systemic inflammatory disease was added as an exclusionary medical history.
- Section 6.2: *Preparation, handling, storage, and accountability* is updated to clarify that Drug Accountability and Returns Management (DARM) is not the only possible drug accountability log which can be used.
- Section 6.2.1: *Handling of study treatment* section is updated to clarify that Drug Accountability and Returns Management (DARM) is not the only possible drug accountability log which can be used.
- Table 6-2: *Dose and Treatment schedule* is updated to correct typographical error for the last day of the dosing periods.
- Section 6.4: *Study treatment compliance* reporting instructions are updated to clarify that IMP compliance is not reported in the case report form (CRF) completion and that clarify that Drug Accountability and Returns Management (DARM) is not the only possible drug accountability log which can be used.
- Table 6-4: *Drugs to be used with caution* is updated to remove indinavir from this list as it is a prohibited medication.
- Section 7.1: *Discontinuation of study treatment* is updated to provide additional clarity regarding when EOT and EOS visits are to occur in case of study treatment discontinuation.
- Section 7.5: *Study stopping rules* is updated to increase the number of treatment-related SAEs to meet stopping occur and to add a stopping rule for death or life-threatening event.
- Section 8.3.1: *IL-6 and IL-18 Cytokines* section is updated to reflect that enzyme-linked immunosorbent assay (ELISA) will be the analysis method used for IL-6 and IL-18.
- Section 8.6.2: *Serious adverse events* is updated to include reporting language relating to Hy's Law.
- Section 8.7: *Pharmacokinetics* section is updated to clarify when an unscheduled pharmacokinetic (PK) sample may be needed.
- Section 8.8: *Biomarkers* section is updated to clarify the handling of unscheduled samples.
- Section 9.3.2: *Treatments* section is updated to clarify that compliance is calculated and not reported.
- Section 10.1.2: *Informed consent process* is updated to include the Optional Inflammation Marker Pre-Screening ICF and describe how it is used with the main study ICF.
- Section 10.2.1: *List of abbreviation* is updated to include new abbreviations.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

1 Protocol summary

1.1 Summary

Protocol Title:

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.

Brief Title:

A study to investigate the efficacy, safety, and tolerability of DFV890 for inflammatory marker reduction in adult participants with coronary heart disease and elevated High-sensitivity C-reactive protein (hsCRP).

Purpose

The purpose of this study is to evaluate the efficacy, safety, and tolerability of intra-individual dose escalation of oral DFV890 in reducing circulating levels of inflammatory markers in adult participants with known coronary heart disease and elevated hsCRP.

Study Indication /Medical Condition:

Coronary Heart Disease

Treatment type

Drug

Study type

Interventional

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 (AE), and parameters from safety assessments, including vital signs, electrocardiograms, and laboratory assessments (urine and blood)

Objective(s)	Endpoint(s)
• To assess the pharmacokinetics (PK) of DFV890 in participants with coronary heart disease and elevated hsCRP	• Plasma trough concentrations (Ctrough) of DFV890 at steady state

Trial Design:

- Parallel-group, placebo-controlled, multi-center Phase 2a study
- Patients with coronary heart disease and elevated hsCRP
- Investigator- and participant-blinded; matching placebo
- Randomization

The trial will be comprised of:

- A total study duration of approximately 24 weeks
- A screening period of up to 60 days
- A treatment duration of approximately 12 weeks
- Intra-individual study drug uptitration at approximately 3-week intervals over 4 dosing periods
- The visit frequency will include at least 2 screening visits within the 60-day screening period followed by visits at approximately Day 1, 22, 43, 64, 85, 92 and a safety follow-up phone call at Day 114

Brief Summary: Cardiovascular diseases (CVD) remain the leading cause of disease burden in the world. Persistent inflammation is common in populations at increased risk of CVD events and medications that reduce inflammation have been linked to improved CVD outcomes. Inhibition of the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome may safely and effectively lower the risk of CVD among people with known heart disease and markers of elevated inflammation. This Phase 2a clinical trial will evaluate the effectiveness, safety, and tolerability of increasing dose strengths of an oral daily medication, DFV890, administered for 12 weeks, to reduce key markers of inflammation related to CVD risk, such as IL-6 and IL-18, in approximately 24 people with known heart disease and an elevated marker of inflammation, hsCRP.

Primary estimand/analysis:

The primary estimand will address potential intercurrent events that may influence the primary endpoints (IL-6 and IL-18) largely with a hypothetical strategy, which aims to estimate the effect of treatment under research-like conditions. The primary analysis for each endpoint is based on a dose-response modeling approach that integrates all cytokine measurements under increasing NLRP3 inflammasome inhibition resulting from uptitrated doses of DFV890.

Treatment of interest

The treatment of interest is oral daily DFV890 at various dose levels (10 milligram (mg), 25 mg, 50 mg and 100 mg daily) on top of clinically indicated standard-of-care CVD prevention medications (eg. statin treatment).

Number of Participants:

The study population is comprised of male and female adults. A total of approximately 24 participants will be enrolled to study intervention.

Key Inclusion criteria

- Male and female participants aged between 18 - 85 years (inclusive) at the start of screening will be included.
- Subjects must have a body mass index (BMI) within the range of 18 - 45 kg/m^2. BMI = Body weight (kg) / [Height (m)]^2
- Documented spontaneous myocardial infarction (MI) (diagnosed according to the universal MI criteria with or without evidence of ST segment elevation) at least 30 days before the start of screening (Thygesen et al 2007).
- Participants must have hsCRP levels ≥ 2 mg/L at two timepoints during screening. Screening values must be separated by a minimum of 8 days. The initial hsCRP value must be a minimum of 30 days after the qualifying MI or after any percutaneous coronary intervention (PCI) performed separately from the qualifying MI.
- For participants on statin therapy (HMG-CoA reductase inhibitor), as clinically indicated, participants must be on a stable regimen (at least 4 weeks before randomization), with no planned statin dose changes over the course of the trial treatment period. Unplanned statin dose changes during the trial treatment period may occur.

Key Exclusion criteria

- Patients receiving concomitant medications that are known to be strong or moderate inducers of cytochrome CYP2C9 enzyme and/or strong inducers of CYP3A, strong inhibitors of CYP2C9 and/or strong or moderate inhibitors of CYP3A and the treatment cannot be discontinued or switched to a different medication within 5 half-lives or 1 week (whichever is longer) prior to Day 1 and for the duration of the study.
- Patients with suspected or proven immunocompromised state at screening
- History of ongoing, chronic, or major recurrent infectious disease, at the discretion of the investigator, at the start of screening.
- Use of any biologic drugs targeting the immune system within 26 weeks of Day 1
- Multi-vessel Coronary Artery Bypass Graft (CABG) surgery within the past 6 months prior to the start of screening
- Symptomatic Class IV heart failure (New York Heart Association) at the start of screening.
- Planned coronary revascularization (PCI or CABG) or any other major surgical procedure during the study

Treatment Groups:

Active treatment: DFV890 administered orally once daily at various doses (0 mg [matching placebo], 10 mg, 25 mg, 50 mg, 100 mg) over four dosing periods of ~3 weeks each, for a total of ~12 weeks of treatment. Randomized to one of four treatment sequences comprised of various doses of DFV890 and/or placebo. Investigational study treatment dose adjustments and/or interruptions are not permitted.

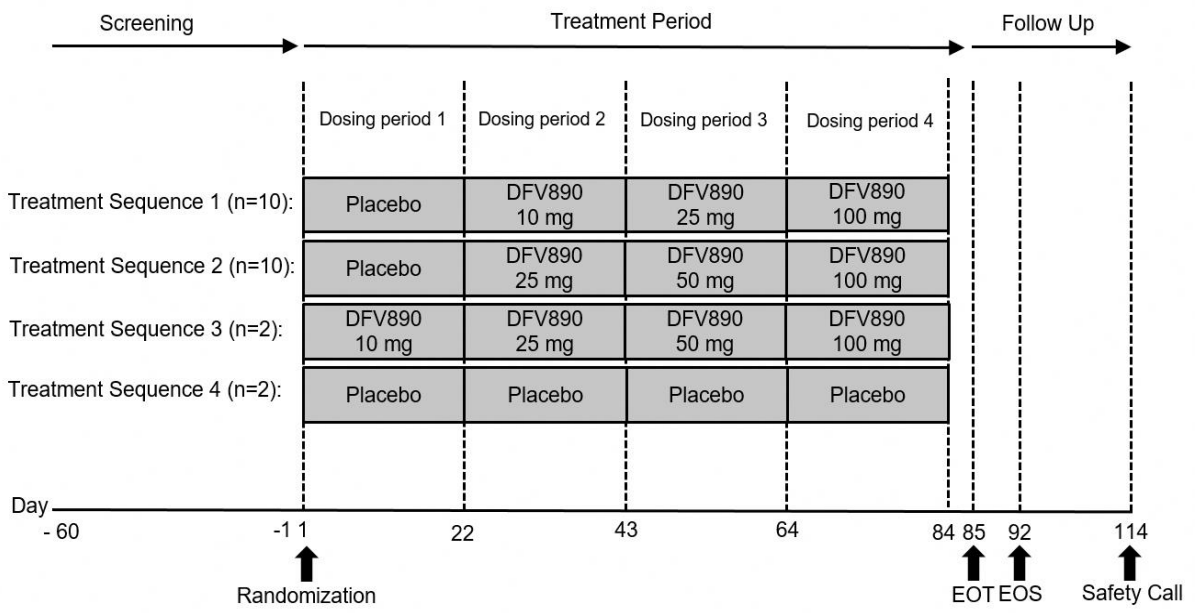
Data Monitoring/Other Committee: No

Key words

Coronary heart disease, elevated hsCRP, inflammatory marker reduction, NLRP3 inflammasome inhibitor

1.2 Schema

Figure 1-1 Study Design



1.3 Schedule of activities (SoA)

The SoA lists all the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation. The "X" in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The "S" in the table denotes the assessments that are only in the participant's source documentation and do not need to be recorded in the clinical database.

Participants should be seen for all visits/assessments as outlined in the SoA or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Participants who discontinue from study should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all of the assessments listed for the End Of Study (EOS) visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the AEs and concomitant medications not previously reported must be recorded on the Case Report/Record Form (CRF).

Every effort will be made to take PK samples at the protocol-specified time. The preferred sequence of assessments and data collection during study visits is: Electrocardiogram (ECG), vital signs, blood sampling, and any remaining assessments for that visit. For visits during which the participant is scheduled to take the study drug, all assessments will be conducted pre-dose administration.

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e., pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the Investigator as the situation dictates. If allowable by a local health authority, national and local regulations and depending on operational capabilities, phone calls, virtual contacts (e.g., tele consultation) or visits by site staff/ off-site healthcare professional(s) (OHP) staff to the participant´s home, can replace certain protocol assessments, for the duration of the disruption until it is safe for the participant to visit the site again. If the Investigator delegates tasks to an OHP, the Investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The Investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

Table 1-2 Assessment Schedule

Period	Screening		Treatment					Follow-Up	
Visit Name	**Screening 1**	**Screening 2[2]**	**Day 1[3]**	**Day 22[3]**	**Day 43[3]**	**Day 64[3]**	**EOT**	**EOS**	**Safety Follow Up Call**
Visit Numbers[1]	**1**	**10**	**100**	**110**	**120**	**130**	**199**	**1999**	
Days	**-60 to -9**	**-52 to -1**	**1**	**22 ±2**	**43 ±2**	**64 ±2**	**85 ±2**	**92 ±2**	**114 ±5**
Optional Inflammation Marker Pre-Screening Informed consent	X								
Main Study Informed consent	X								
Genetic consent	X								
Inclusion / Exclusion criteria	X	X							
Demography	X								
Medical history/current medical conditions	X								
Pregnancy and assessments of fertility[4]		X	X	X	X	X	X	X	
Physical Examination		S	S[5]	S[5]	S[5]	S[5]	S[5]	S	
Body Height		X							
Body Weight		X					X	X	
Body Temperature		X	X	X	X	X	X	X	
Pulse rate		X	X	X	X	X	X	X	
Blood Pressure		X	X	X	X	X	X	X	
Electrocardiogram (ECG)		X					X	X	
hsCRP	X	X	X	X	X	X	X	X	
Clinical Chemistry		X	X	X	X	X	X	X	
Hematology		X	X	X	X	X	X	X	

Period	**Screening**		**Treatment**					**Follow-Up**	
Visit Name	**Screening 1**	**Screening 2**[2]	**Day 1**[3]	**Day 22**[3]	**Day 43**[3]	**Day 64**[3]	**EOT**	**EOS**	**Safety Follow Up Call**
Visit Numbers[1]	**1**	**10**	**100**	**110**	**120**	**130**	**199**	**1999**	
Days	**-60 to -9**	**-52 to -1**	**1**	**22 ±2**	**43 ±2**	**64 ±2**	**85 ±2**	**92 ±2**	**114 ±5**
Coagulation Panel		X	X				X	X	
Urinalysis		X	X				X	X	
Randomization			S						
Dose administration			X[6]						
Dose uptitration				S	S	S			
Drug Accountability[7]				X	X	X	X		
PK blood collection				X[8]	X[8]	X[8]	X[8]	X	
IL-6 and IL-18 cytokines		X	X	X	X	X	X	X	
Blood collection for soluble biomarkers[9]			X	X	X	X	X	X	
Immunophenotyping[10]			X	X	X	X	X	X	
Lipid Parameters			X	X	X	X	X	X	
CHIP genotyping (optional)			X				X		
CYP genotyping			X						
Exploratory DNA Sampling (optional)			X						
Concomitant medications	X								
Adverse Events	X								
Serious Adverse Events	X								
Study completion information								X	
Safety Follow up Call									S

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Visit structure given for internal programming purpose only
[2] Screening 2 visit should take place at least 8 days after Screening 1 visit and after hsCRP results were reviewed against eligibility criteria. If Optional Inflammation Marker Pre-Screening ICF is used at Screening 1 visit, the main study Consent Form can be signed at Screening 2 visit. Refer to Section 10.1.2 for more information.
[3] All assessments should be done pre-dose
[4] Serum pregnancy test
[5] Brief physical exam, including rash assessment.
[6] Last dose administration is on Day 84 at home prior to EOT visit on Day 85
[7] IMP administration in the last 2 days before study visit as well as timing of the last dose before study visit should be confirmed with the patient.
[8] The sample taken on the study visit day must be taken approximately 24h (+/-2h) after the dose from previous day (ex: Day 22 pre-dose sample is 24 hours +/-2 hours after the timing of the Day 21 dose).
[9] May include but not limited to sASC, hsIL-1b, CXCL9, CXCL10, hsIFNg, vWF, protein profiling etc.
[10] May include but not limited to myeloid/lymphoid cell activation/enumeration, Whole Blood/PBMCs, etc.

2 Introduction

2.1 Study rationale

The purpose of this study is to evaluate the efficacy, safety, and tolerability of DFV890 in reducing circulating levels of inflammatory markers in adult participants with known coronary heart disease and elevated hsCRP. The results of the study will be used to inform future development plans for DFV890 in cardiovascular disease event risk reduction.

2.2 Background

Cardiovascular disease remains the leading cause of disease burden in the world. The estimated global prevalence of cardiovascular disease doubled from 271 million in 1990 to 523 million in 2019 (Roth et al 2020). A substantial residual risk for cardiovascular disease events related to chronic inflammation remains despite standard of care management of classic risk factors (diabetes, hypertension, lipids, etc.).

Atherosclerotic cardiovascular disease is a condition commonly characterized by an elevated inflammatory state. Arterial inflammation and endothelial dysfunction play key roles at all stages of the atherothrombotic process. Inflammatory mediators are intimately implicated with the cascade of events leading to atherosclerotic plaque initiation, progression, and rupture. Vascular endothelial cells express a variety of adhesion molecules that recruit monocytes when chronically exposed to noxious stimuli or pathological conditions. Adverse conditions such as hyperlipidemia are associated with enrichment of a pro-inflammatory subset of monocytes. These monocytes apparently enter the intima under the influence of chemotactic stimuli and engulf modified low-density lipoprotein (LDL) and cholesterol crystals (Duewell et al 2010). The material internalized by phagocytes induces phagolysosomal damage and subsequent leakage of contents into cytosol to activate inflammasomes and caspase 1, and consequently the generation of interleukin-1β (IL-1β) from pro-interleukin-1β.

Interleukins are key mediators in the chronic vascular inflammatory response in cardiovascular disease and have been demonstrated in animal models and in humans to be potent modulators of pro-inflammatory processes. The fact that these cytokines and their receptors are highly expressed and are functional in almost all cell types implicated in the pathogenesis of atherosclerosis including smooth muscle cells, certain subset of macrophages and T cells, as well as endothelium, support the role of interleukins in vascular disease. For example, IL-1β is a potent smooth muscle cell mitogen, an activator of endothelial cells and increases extra cellular matrix and collagen deposition, which plays a role in plaque burden and arterial thickening. Furthermore, lack of IL-1β or ablation of IL-1 receptor has been shown to decrease severity of atherosclerosis in apoE deficient mice.

Clinical evidence from the CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) clinical trial demonstrated that IL-1β neutralization with canakinumab can reduce cardiovascular risk in patients who have had a prior MI and elevated hsCRP. In CANTOS, increased IL-18 levels at baseline correlated with increased cardiovascular risk, corroborating other findings suggesting IL-18 plays a role in cardiovascular disease that is not attenuated by IL-1β neutralization (Ridker et al 2020).

Through the production of IL-1β and IL-18, the NLRP3 inflammasome has been implicated as a major driver of inflammation associated with chronic inflammatory diseases. Mechanistically, NLRP3 senses a diverse range of danger signals, and reacts by forming an inflammasome protein complex that drives an ensuing inflammatory response. Via genetic knockouts (Duewell et al 2010) or pharmacological inhibition (Hettwer et al 2022), abrogation of NLRP3 function is protective in mouse models of atherosclerosis, exerting a beneficial effect on both peripheral inflammatory leukocytes and cytokines, and local anti-inflammatory effects in the atherosclerotic plaque. DFV890 is a potent, small molecule inhibitor of the NLRP3 inflammasome pathway. DFV890 blocks IL-1β secretion, IL-18 secretion and pyroptotic cell death in response to a wide variety of NLRP3-dependent danger signals in vitro and in mechanistic mouse models in vivo, suggesting that NLRP3 inhibition could have improved efficacy over canakinumab in diseases where IL-1β and IL-18 both drive pathology. Through the inhibition of IL-1β and IL-18, DFV890 has the potential to significantly reduce cardiovascular risk in patients.

2.3 Benefit/Risk assessment

It is not known whether there will be a benefit for participants with known coronary heart disease and elevated hsCRP with DFV890 and NLRP3 inhibition. The CANTOS trial demonstrated reduction in cardiovascular risk in this population with canakinumab and IL-1β inhibition. NLRP3 inhibition could have improved efficacy over canakinumab by inhibiting both IL-1β and IL-18; however, this has not yet been demonstrated.

Based on the clinical experience with DFV890 in the CDFV890A02101 Phase 1 first in human (FIH) study, the CDFV890D12201 Phase 2 study in patients with COVID-19, relevant nonclinical findings, the biological understanding of the pathways and their relevance to CVD, the overall risk-benefit of DFV890 is, to date, considered favorable. The available clinical, safety and laboratory assessments from the FIH study and the COVID-19 study show that DFV890 is generally well tolerated and has a manageable safety profile. Potential compound risks are described in more detail in the following sections. In summary, based on the available non-clinical and clinical data the potential risks to be considered for DFV890 include: 1) self-limiting skin rash/pruritis, 2) changes in hematologic parameters, 3) management of concomitant infections, 4) co-administration of live vaccinations, 5) renal abnormalities in preclinical models, 6) changes in female reproductive tissues, which were observed in the rat, 7) considerations for women of child-bearing potential (WOCBP), 8) metabolism by CYP2C9 and CYP3A4 enzymes, and 9) general considerations related to hypersensitivity to any component of the drug product. In addition to the risks noted above, there may be risks to DFV890 that are unforeseen and serious.

The risk to participants in this trial may be minimized by adherence to the eligibility criteria, study procedures, stopping rules, and close clinical monitoring. Appropriate eligibility criteria, and specific dose-limiting toxicity definitions, as well as specific stopping rules, are included in this protocol. Please refer to the Investigator's Brochure (IB) for additional information.

2.3.1 Compound risks

2.3.1.1 Potential risk of skin rash and recommended monitoring

In the CDFV890A02101 FIH study, CCI [redacted]

In the completed CDFV890D12201 Phase 2 study in COVID-19, 70 participants in the active arm were administered DFV890 50 mg twice daily + SoC for 14 days. Maculopapular/pruritic skin rashes considered related to DFV890 were reported in 7 participants, of whom 2 participants discontinued the study treatment. These events were of mild and moderate severity, started 5 to 14 days after initiation of DFV890 treatment and resolved within 5 to 16 days after onset, with treatment administered to 6 out of the 7 participants.

In this trial with patients with known coronary heart disease and elevated hsCRP, up titration of DFV890 doses may reduce incidence of rash; however, that has yet to be demonstrated. Investigators should be vigilant for symptoms of pruritus and signs of rash (e.g., maculopapular on upper trunk, spreading centripetally and usually associated with pruritus) and should instruct participants to contact the investigator if they develop rash or pruritus to ensure a rapid clinical assessment.

See Section 6.4.1 for recommended management of maculopapular/pruritic rashes.

2.3.1.2 Potential risk and recommended monitoring of hematological parameters

Transient asymptomatic decreases in ANC and WBC (White Blood Cell) were observed in the CDFV890A02101 FIH and CDFV890D12201 COVID-19 studies. These transient self-limiting decreases in ANC and WBC were not associated with an increased risk of infection which could be consistent with a PD effect of DFV890 resulting from inhibition of IL-1β signaling downstream of NLRP3 (NLRP3 blockade, similar to known effects of canakinumab). To reduce the risk of developing neutropenia in participants treated with DFV890, all participants with evidence of an ANC count < 1000/mm^3 should be excluded from entry into this study (see Section 5.2).

2.3.1.3 Potential risk and recommended treatment of infection

As with any immune-modulating compound, there is a theoretical risk of immune system impairment, which might increase the risk of infection in treated participants. However, DFV890 is not expected to elicit broad immune suppression. Moreover, the target NLRP3 is not essential for health (NLRP3 deficient mice are generally healthy). CCI [redacted] The risk for patients in currently ongoing trials is considered low based on safety margins and/or short treatment duration. To mitigate potential risks of immune suppression and infection in this study, exclusion criteria include other immune suppressive treatments administered 28 days or 5 half-lives, whichever is longer, prior to screening. Participants with known or suspected immunodeficiency state or evidence of active or latent, serious bacterial, fungal, or viral infections will also be excluded. See Section 5.2.

In response to the COVID-19, pandemic site-specific procedures should be implemented to minimize COVID-19 infection risks for participants and site staff as per local guidance. These documents may cover, but are not limited to, local COVID-19 testing, infection prevention/control, hygiene and social distancing measures. Investigator must instruct participants to contact the investigator immediately if the participants develop any symptoms and/or signs of infection (e.g., fever, loss of smell, loss of taste, muscle aches, persistent or productive cough, abdominal pain, vomiting, nausea, shortness of breath, dysuria and/or diarrhea).

In the event of an infection, investigators should consider early treatment with specific antimicrobial therapy based on clinical diagnosis or suspicion there of (e.g., prompt antibiotic therapy for bacterial infections, anti-viral treatment for herpes simplex or zoster or SARS-CoV-2, etc.) in consultation with infectious disease experts, as appropriate.

2.3.1.4 Potential risk and guidance on vaccinations

To mitigate the risk from live vaccinations, participants who have received live vaccinations within one month prior to the first dose of the study will be excluded from entry in this study. Additionally, it is recommended that all participants should complete all immunizations in accordance with current immunization guidelines at least one month prior to administration of the first dose of DFV890.

Approved (including Health Authorities' conditional marketing authorization) killed, inactivated, peptide, DNA and RNA vaccines are permitted according to the investigator's discretion and per local guidance. Due to the mechanism of action of DFV890, specifically targeting the NLRP3 inflammasome, it is unlikely that treatment with this compound would interfere with vaccination responses. However, no specific preclinical nor clinical investigations of vaccine efficacy have been conducted to date with DFV890.

2.3.1.5 Potential risk of renal abnormalities and recommended monitoring

CCI [redacted]

Clinically, in the CDFV890A02101 FIH and CDFV890D12201 COVID-19 studies, based on available clinical safety data from both studies, there has been no evidence of adverse effects on kidneys or renal function related to DFV890 administration in COVID-19 participants and healthy participants.

Although it is not clear whether there are potential effects of DFV890 on kidney in humans, markers of renal function including electrolytes, creatinine and blood urea nitrogen (BUN)/Urea, and urinalysis will be monitored in this study (see Section 8.4.4 for further details and guidance).

2.3.1.6 Potential risks and guidance related to women of child-bearing potential (WOCBP)

At this stage of development, DFV890 has not yet been studied in developmental and reproductive toxicity studies, and WOCBP and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study, they must adhere to the contraception requirements outlined in the exclusion criteria. Oral hormonal contraception is allowed but must be supplemented with a barrier method, preferably a male condom, as DFV890, based on the in vitro data, may induce CYP3A4 enzyme in the intestine, where it is involved in the metabolism of some hormonal contraceptives. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

Thus, WOCBP can be included if they fulfill the following criteria:

- Practice highly effective contraception for at least 3 months prior to screening.
- Have a negative pregnancy test at the time of screening; pregnancy tests at each treatment visit, follow-up visit and at the end of the follow-up period.
- Practice highly effective contraception during the treatment period; (oral contraception to be supplemented by a barrier method, preferably a male condom).
- Practice highly effective contraception for 7 days following completion of treatment.

Women of child-bearing potential should avoid becoming pregnant while their male partners are using DFV890. Males treated with DFV890 must agree to abstain from donating sperm and from either any sexual activity with a female partner or to practice highly effective contraception, i.e., barrier protection (condom) with a female partner who is using an intrauterine device or hormonal contraception and for at least 7 days following completion of

study treatment and should not father a child in this period. A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner during DFV890 treatment and for at least 7 days following completion of study treatment.

Pregnant or lactating women are also excluded.

2.3.1.7 Potential risk due to CYP2C9 polymorphism and guidance on prior and concomitant medications and other substances

Clinical studies to investigate drug-drug interactions (DDI) using cytochrome P450 (CYP) substrates/modulators and DFV890 have not been performed yet, but based on in vitro data, DFV890 exposure may be affected by CYP2C9 and/or CYP3A4 interactions. Due to the polymorphic character of CYP2C9, the major enzyme involved in DFV890 metabolism, patients who are intermediate or poor CYP2C9 metabolizers can have up to [redacted]-fold higher exposure to DFV890 compared to patients with normal CYP2C9 function. An additional risk of increased DFV890 AUC exists when co-administered with CYP2C9 and CYP3A inhibitors due to DDI, which is most pronounced for poor CYP2C9 metabolizers. A risk of decreased DFV890 exposure to sub-therapeutic levels exists when co-administered with CYP2C9 and CYP3A inducers (for more details see IB and Section 6.8). Therefore, strong, and moderate inducers of CYP2C9 enzyme, strong inducers of CYP3A, strong inhibitors of CYP2C9, and/or strong or moderate inhibitors of CYP3A are prohibited in the study (Section 6.8.2).

Due to its in vitro weak-to-moderate CYP3A4 induction potential, DFV890 can potentially decrease systemic exposure of sensitive CYP3A4 substrates by approximately [redacted]-fold of some oral hormonal contraceptives which are CYP3A4 substates (e.g., ethinylestradiol), by [redacted]. Therefore, oral hormone-based contraceptives may not be considered as highly effective contraception method until the DDI risk is evaluated in dedicated clinical studies.

Considering clinical safety profile of DFV890, treatment duration and/or dose and sufficient safety margins, administration of DFV890 is considered safe.

2.3.1.8 Potential risk and recommended treatment of hypersensitivity

Treatment with DFV890 is contraindicated in people with hypersensitivity to any component of the drug product.

2.3.2 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected over a period of approximately 22 weeks from each participant as part of the study. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in Section 1.3 Schedule of Activities.

3 Objectives, endpoints, and estimands

Table 3-1 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)
• 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 (e.g., LDL, Lp(a), apolipoproteins)

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

3.1 Primary estimands

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 3-2.
5. Summary measure: the model-based difference in variable means between treatments.

Table 3-2 Intercurrent events for the primary estimand

Intercurrent event	Details (if necessary)	Handling of event
Permanent discontinuation of study treatment	N/A	Data collected after this intercurrent event will not be used for this estimand
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
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
	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
New-onset febrile infection	Febrile infection around time of assessment (details to be provided in the statistical analysis plan (SAP))	Only the assessment immediately following the event will be excluded for the purpose of this estimand

Intercurrent event	Details (if necessary)	Handling of event
Nonadherence to study treatment	Greater than 20% of missed daily doses within 3 weeks prior to an assessment	Only the assessment immediately following the event will be excluded for the purpose of this estimand
	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

The handling of each intercurrent event specified in Table 3-2, 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, 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 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.

Additional information on the handling of the intercurrent events in the primary analysis is described in Section 9.3.3.

3.2 Secondary estimands

Not applicable.

4 Study design

4.1 Overall 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). 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 (Schedule of Activities). Participants will then be provided with a sufficient amount of study medication for daily dosing until their next scheduled visit.

The dose of DFV890 will be up titrated (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.

All assessments specified in the SoA will be conducted at each visit.

4.2 Scientific rationale for study design

Table 4-1 Rationale for study design

Study Design Aspect	Rationale
Overall	In this study, participants will be randomized to one of four treatment sequences comprised of placebo and/or various up titrating doses of DFV890. The rationale behind the up titration of doses within sequences is the efficiency for evaluating cytokine reductions that result from intra-individual measurements. Up titration also may improve tolerability by decreasing the risk for rash; however, this has yet to be demonstrated. CCI [redacted] The up titration of doses and progressive further inhibition of the NLRP3 inflammasome is expected to result in a peak cytokine reduction similar to what would be seen regardless of prior dose exposures. This could be further evaluated in a subsequent Phase 2b dose-range finding study. A cross-over design or including placebo after active DFV890 was not implemented as this could potentially confound the interpretation of the primary endpoints, as it is not known precisely when cytokine levels return to baseline after DFV890 with the NLRP3 inflammasome activation profile in this population (which may differ from trial populations in prior or ongoing studies).
Primary Endpoints	Serum levels of IL-6 and IL-18 at 3 weeks after the start of a dosing period were chosen as the primary endpoints because both cytokines are linked to increased risk of CVD in numerous clinical populations. In addition, preclinical models implicated IL-6 and IL-18 in CVD pathogenesis. In the CANTOS trial of IL-1β inhibition, participants that had the lowest on-treatment IL-6 levels had the greatest CVD benefit. While IL-18 is associated with CVD risk in human populations and preclinical

Study Design Aspect	Rationale
	evidence supports a causal role, no pharmacologic intervention trials have yet demonstrated that IL-18 inhibition reduced CVD risk.
Analysis of primary endpoints	Each participant will contribute data on levels of IL-6 and IL-18 after 3 weeks of oral daily treatment with DFV890 at up to 3 different dose levels and/or placebo, depending on treatment sequence assignment. A dose-response modeling approach, which integrates the IL-6 or IL-18 levels across all dose levels to fit a dose-response relationship, will be utilized to quantify placebo-adjusted reductions at the highest tested dose level, 100 mg. The rationale for analyzing all of the IL-6 and IL-18 data from the end of each 3-week dosing period together in a dose-response model is to take advantage of the efficiencies introduced by the up titration design. The model treats each dosing period as independent of the prior period, which is justified because cytokine levels are expected to reach a maximum reduction within 7-14 days, and therefore the 3-week timepoint is expected to be at steady state reduction. The fact that dosing occurs in a monotonically increasing manner ensures that no washout between doses is required, as the effect is only expected to be greater with higher doses. It is possible that subsequent dose levels may reach steady state cytokine reduction sooner than if drug had not already been on board, but this will not impact the analysis as only the 3-week measurement is collected and used in the analysis.
Treatment Sequences	In Treatment Sequence 1 and Treatment Sequence 2, participants begin with placebo treatment and are followed with increasing doses of DFV890. Treatment Sequence 3 and Treatment Sequence 4 were primarily included to maintain the blind in each dosing period so that there is both active and placebo within each dosing period. Treatment Sequence 4, in addition, will generate more placebo data, which is useful for the primary analysis. More participants are allocated to Treatment Sequence 1 and Treatment Sequence 2 as they will contribute intra-individual placebo data, thereby making analyses more efficient.
Randomization	Participants will be randomized in a 5:5:1:1 ratio to the 4 treatment sequences. Randomization is used to limit selection bias and decrease the chance of an imbalance in participant characteristics between sequences, thereby facilitating an unbiased assessment of the effect of treatment. However, with a modest sample size and 4 treatment sequences, baseline clinical characteristic imbalances may occur across the sequences. This has limited consequence in this study design as most of the participants serve as their own placebo controls with intra-individual dose-response modeling rather than comparison between two equal active and placebo treatment arms.
Blinding	Blinding of participants and investigators during the study allows for an unbiased assessment of study endpoints.

Study Design Aspect	Rationale
Duration of study periods	The duration and frequency of screening was chosen to ensure hsCRP values obtained in this time period are representative of the participant's true sustained baseline value to capture a study population with sustained markers of chronic inflammation. The treatment period of approximately 12 weeks allows for a gradual up titration (up titration occurs approximately every 3 weeks) to the maximal dose of 100 mg of DFV890. From prior clinical trials with DFV890, the expected peak reduction of cytokines occurs within 7-14 days, and, therefore, approximately three weeks for each dosing period should allow adequate assessment of cytokine reduction efficacy and tolerability at each dose level. The follow-up period up to Day 114 allows for adequate safety monitoring over a period of approximately 5 half-lives.
Placebo comparator	The use of placebo provides a comparison group for an unbiased collection and assessment of safety, tolerability, efficacy, and PD parameters. The study design includes both inter- and intra-individual placebo comparators.

4.3 Justification for dose

In this study, film-coated tablets with 10 or 25 mg DFV890 will be administered orally to achieve doses of 10 mg, 25 mg, 50 mg, and 100 mg. Within each DFV890 treatment sequence, participants will start with either placebo or DFV890 10 mg dose given QD for approximately three weeks. Participants will then receive three up titrating DFV890 doses up to 100 mg, each for approximately three weeks as shown in the study design figure (Figure 1-1). The dose range 10-100 mg was selected based on data from the phase 1 FIH study in healthy volunteers (Study CDFV890A02101). In the FIH study, an ex vivo whole blood assay of lipopolysaccharide-stimulated IL-1β secretion was used as a PD readout to estimate pharmacological activity. CCI [redacted] the highest dose of 100 mg DFV890 given once daily is proposed in this study.

As indicated above, a positive food effect on PK (2.05-fold increase in Cmax and 1.49-fold increase in AUClast) was demonstrated with a 100 mg tablet after a high-fat / high-calorie meal in the FIH study. A less pronounced effect, especially on Cmax is expected for the 10 and 25 mg doses due to a better solubility; however, to maximize the effect and to limit variability, all tablets should be taken with a meal. The type of food should not have any impact on DFV890 exposure based on physiology-based PK simulation. The apparent terminal elimination half-life

of DFV890 tablet under fed conditions is approximately 10 hours (h) and the steady state is anticipated the next day after starting each dose treatment.

With the exception of maculopapular skin rash and/or pruritus, DFV890 was, in general, well tolerated in healthy participants and patients when dosed for up to 2 weeks in completed clinical studies (refer to the IB for further details). Skin reactions were reported when dosed with 30 mg, 100 mg, or 200 mg suspension QD, or with 50 mg tablet twice a day (BID). Skin reactions were not reported when dosed as 10 mg suspension QD or 25 mg tablet BID. All skin-related events were graded to be of mild or moderate intensity, started 5 to 17 days after treatment initiation and resolved following treatment discontinuation within 1 to 18 days after onset. Skin-related events were not reported in any animal toxicology studies and CCI [redacted] The response-exposure is not yet well understood, however skin reactions, especially for 50 and 100 mg QD doses cannot be ruled out.

Metabolism by cytochrome P450 2C9 (CYP2C9) and cytochrome P450 3A4 (CYP3A4) is considered to be the major clearance mechanism for DFV890 with fractional hepatic contributions of CCI [redacted]% and CCI [redacted]%, respectively. CYP2C9 is a polymorphic enzyme. Based on the physiology-based-PK prediction, the systemic DFV890 exposure in participants who are poor CYP2C9 metabolizers (e.g., *3*3) is likely to be approximately CCI [redacted]-fold higher compared to normal (extensive) metabolizers (*1*1) due to decreased or no CYP2C9 activity.

The safety for the DFV890 doses and treatment duration is supported by GLP toxicology studies in rat and cynomolgus monkey. Overall, on average for 100 mg QD of DFV890, the safety margins are CCI [redacted] and CCI [redacted] based on PK in healthy participants (majority were normal CYP2C9 metabolizers). Up to CCI [redacted]-fold lower safety margins are expected in patients who are intermediate or poor CYP2C9 metabolizers (for further details refer to the IB). Supported by sufficient safety margins, all eligible patients irrespective of CYP2C9 genotype are allowed to participate in the study.

4.4 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Placebo treatment will be used as a comparator to provide objective control for the evaluation of efficacy, safety, and tolerability during the 12-week treatment with DFV890. The oral tablet formulation will contain either active drug or placebo and will be indistinguishable in appearance and taste.

4.5 Rationale for public health emergency mitigation procedures

In the event of a public health emergency as declared by local or regional authorities (i.e., pandemic, epidemic or natural disaster), mitigation procedures may be required to ensure participant safety and trial integrity and are listed in relevant sections of the study protocol. Notification of the public health emergency should be discussed with Novartis prior to implementation of mitigation procedures and permitted/approved by local or regional health authorities and ethics committees as appropriate.

4.6 Purpose and timing of interim analyses/design adaptations

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.

4.7 End of study definition

The end of the study is defined as the date of the last visit of the last participant in the study.

Study completion is defined as when the last participant finishes their last study visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator.

All randomized and/or treated participants should have a safety follow-up phone call conducted at least 30 days after last administration of study treatment. The information collected is kept as source documentation. Serious Adverse Event (SAE) reporting continues during this time period as described in Section 8.6.3. Documentation of attempts to contact the participant are required to be recorded in the source documentation.

5 Study population

The study population is adults with known coronary heart disease and elevated hsCRP. In this study, approximately 24 participants will be enrolled.

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Able to communicate well with the investigator, to understand and comply with the requirements of the study.
3. Male and female participants aged between 18 - 85 years (inclusive) at the start of screening will be included.
4. Subjects must have a body mass index (BMI) within the range of 18 - 45 kg/m^2 at the start of screening. BMI = Body weight (kg) / [Height (m)]^2
5. Documented spontaneous myocardial infarction (MI) (diagnosed according to the universal MI criteria with or without evidence of ST segment elevation) at least 30 days before the start of screening (Thygesen et al 2007).

   Diagnosis of the qualifying MI should be based on medical history of clinical symptoms consistent with myocardial ischemia associated with elevation of cardiac biomarkers above the 99th percentile of the upper reference limit (preferably troponin) OR development of new pathological Q waves regardless of symptoms. For details, refer to the Universal Definition of MI (Thygesen et al 2007).

Documentation in the medical history to support evidence of prior MI may include:

- Evidence of an acute MI in hospitalization or medical records:
  - requires documentation of a rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit or above criteria diagnostic for MI

AND

- Evidence of myocardial ischemia as demonstrated by at least one of the following:
  - Symptoms of ischemia
  - ECG changes indicative of new ischemia (new ST-T changes or new LBBB)
  - Development of pathologic Q waves
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

If no documented evidence of an acute MI in the medical record, then evidence of a prior MI may include:

- Development of pathological Q waves with or without symptoms
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract in the absence of a non-ischemic cause
- Pathologic findings of a healed or healing MI

6. Participants must have hsCRP levels ≥ 2 mg/L at two timepoints during screening. Screening values must be separated by a minimum of 8 days. The initial hsCRP value must be a minimum of 30 days after the qualifying MI or after any percutaneous coronary intervention (PCI) performed separately from the qualifying MI.
7. For participants on statin therapy (HMG-CoA reductase inhibitor) as clinically indicated, participants must be on a stable regimen (at least 4 weeks before randomization), with no planned statin dose changes over the course of the trial treatment period. Unplanned statin dose changes during the trial treatment period may occur but must be documented as described in Section 6.2.2

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. Patients receiving concomitant medications (see list of prohibited drugs: Section 6.8.2) that are known to be:
   - strong or moderate inducers of cytochrome CYP2C9 enzyme, or
   - strong inducers of CYP3A, or
   - strong inhibitors of CYP2C9, or
   - strong or moderate inhibitors of CYP3A
   - and the treatment cannot be discontinued or switched to a different medication within 5 half-lives or 1 week (whichever is longer) prior to Day 1 and for the duration of the study.
2. Use of other investigational drugs within 5 half-lives of Day 1, or until the expected pharmacodynamic effect has returned to baseline, whichever is longer.

3. History of hypersensitivity to any of the study treatments or excipients or to drugs of similar chemical classes.
4. History of drug abuse or unhealthy alcohol use within the 12 months prior to the start of screening, per investigator judgement.

   Unhealthy alcohol use may be considered with a history of, or current, alcohol misuse/abuse or “Five or more drinks on the same occasion on each of 5 or more days in the past 30 days." However unhealthy alcohol use may be considered at lower level per investigator judgement based on the participant's history.
5. Pregnant or nursing (lactating) women.
6. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception for at least 3 months prior to first dose administration (Day 1), during dosing and for 7 days after stopping of investigational drug. Highly effective contraception methods include:
   - Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
   - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
   - Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.
   - Use of oral (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an intrauterine device or intrauterine system or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception. Based on an in vitro induction of CYP3A4, there is a slight potential risk for a DDI of DFV890 with hormonal contraception at high exposures, therefore oral hormonal contraception must be supplemented with a barrier method, preferable a male condom.

   In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment. Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential. Refer to (Section 8.4.5 Pregnancy Testing). If local regulations deviate from the contraception methods listed above and require more extensive measures to prevent pregnancy, local regulations apply and will be described in the Informed Consent Form (ICF).

7. Sexually active males unwilling to use a condom during intercourse while taking study treatment and for 7 days after stopping study treatment. A condom is required for **all** sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants must not donate sperm for the time period specified above.
8. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years of the start of screening (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, or carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed).
9. Any diagnosed psychiatric condition that includes, but is not limited to, a history of mania, bipolar disorder, psychotic disorder, schizophrenia, or schizoaffective disorder, depression or anxiety, which may jeopardize patient safety or compliance with study procedures, as judged by the investigator.
10. History of ongoing, chronic, or major recurrent infectious disease, at the discretion of the investigator, at the start of screening.
11. Live vaccinations within 1 month prior to Day 1 or live vaccinations planned during the trial.
12. Patients with suspected or proven immunocompromised state at screening, including:
    a. known clinical diagnosis of Human Immunodeficiency Virus (HIV) infection. Patients on systemic anti-retroviral therapy are also excluded from the trial;
    b. those with any other medical condition which in the opinion of the investigator places the patient at unacceptable risk for participation in immunomodulatory therapy;
    c. absolute neutrophil count ≤ 1000/mm3;
    d. those requiring systemic or local treatment with any immune modulating agent in doses with systemic effects e.g., high dose oral or intravenous (i.v.) steroids (> 20 mg prednisone orally daily for > 14 days, > 5 mg prednisone orally daily or equivalent dose of i.v. steroid) or high dose methotrexate (> 15 mg weekly).

    Topical, inhaled, local steroid use in doses that are not considered to cause systemic effects are permitted.
13. Use of any biologic drugs targeting the immune system (for example, but not limited to): TNF blockers, anakinra, rituximab, abatacept, tocilizumab, or canakinumab) within 26 weeks of Day 1. Refer to Section 6.8.2 of the protocol.
14. Known diagnosis of a systemic auto-immune or systemic inflammatory disease (eg. systemic lupus erythematosus, etc.).
15. Current use or within 5 half-lives of colchicine at the start of screening.
16. Participants with a MI resulting from PCI or CABG procedures.
17. Major non-cardiac surgical or major endoscopic procedure within the past 6 months prior to the start of screening.
18. Multi-vessel CABG surgery within the past 6 months prior to the start of screening.
19. Planned coronary revascularization (PCI or CABG) or any other major surgical procedure during the study (until EOS).

20. Symptomatic Class IV heart failure (New York Heart Association) at the start of screening.
21. History or current diagnosis of ECG abnormalities indicating significant risk of safety for participants participating in the study such as:
    - Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
    - History of familial long QT syndrome or known family history of Torsades de Pointe
22. Uncontrolled hypertension (defined as systolic blood pressure (SBP) >160 mmHg or diastolic blood pressure (DBP) >100 mmHg) at screening.
23. Uncontrolled diabetes, as defined by the investigator, at screening. The following should be considered by the investigator in guiding the determination as part of the overall assessment, but should not be considered in isolation:
    - Clinical and laboratory evidence of uncontrolled diabetes may include but are not limited to hemoglobin A1C >10%, recurrent fasting glucose >200mg/dL, frequent urination/thirst not explained by other causes, etc.
24. Known nephrotic syndrome diagnosis, or eGFR < 30 mL/min calculated using the CKD-EPI formula (https://www.kidney.org/professionals/KDOQI/gfr_calculator), or ≥ 2+ protein on urine dipstick testing at screening
25. History of clinically significant liver disease or liver injury at screening as indicated by abnormal liver enzymes or function tests (as defined below) including but not limited to Alanine Aminotransferase (ALT), Aspartate Transaminase (AST), Serum Glutamic Oxaloacetic Transaminase (SGOT), Serum Glutamic Pyruvic Transaminase (SGPT), alkaline phosphatase (ALP), serum bilirubin, albumin, and prothrombin time (PT). The Investigator should be guided by the following criteria:
    - Any single parameter may not exceed 2 x upper limit of normal (ULN).
26. Uncontrolled asthma at the start of screening, as defined by the investigator, with high likelihood of requiring systemic corticosteroids during treatment period.

5.3 Lifestyle considerations

For the duration of the study, participants should be informed and reminded of the restrictions outlined in this section.

5.3.1 Meals and dietary restrictions

Participants are to take DFV890 or placebo once daily at approximately the same time each day.

No grapefruit or grapefruit juice is to be consumed from first day of dosing until 7 days following the last dose.

No St. John's wort (*Hypericum perforatum*) is to be consumed 14 days before start of treatment until 7 days following the last dose.

5.4 Screen failures

Participants who sign an ICF and are subsequently found to be ineligible prior to randomization will be considered as screen failures. The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a SAE during the screening period (see Section 8.6.3 for reporting details). If the participant fails to be randomized, the Interactive Response Technology (IRT) must be notified within 2 days of the screen fail that the participant was not randomized. Data and samples collected from participants prior to screen failure may still be analyzed.

Participants who are randomized and fail to start treatment, e.g., participants randomized in error, will be considered an early terminator. The reason should be recorded on the appropriate Case Report Form.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Each case of re-screening must be discussed and agreed with Novartis on a case-by-case basis.

Participants who failed their initial screening due to elevated blood pressure (BP) may be re-screened if anti-hypertensive therapy has been started or increased as a result of initial screening BP above these limits.

Genotyping will not need to be repeated in case of re-screening.

Participants who are re-screened will be assigned a new participant number and will be reconsented.

5.4.1 Replacement policy

The proposed sample size accounts for dropouts at rates depending on the dose level of DFV890 or placebo (as described in Section 9.9.1), therefore discontinued patients will not be replaced.

5.4.2 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is rescreened. The Participant No. consists of the Site Number (Site No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the ICF, the participant is assigned to the next sequential Participant No. available.

A new ICF will need to be signed if the Investigator chooses to rescreen the participant after a participant has screen failed, and the participant will be assigned a new Participant No.

6 Study treatment(s) and concomitant therapy

6.1 Study treatment(s)

The investigational drug, DFV890, will be prepared by the sponsor as indicated in Table 6-1. DFV890 will be administered orally with food once a day (QD).

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Treatment Form or Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)
DFV890 10 mg	Tablet	Oral use	Blinded Supplies in HDPE Bottle of 35 tablets	Sponsor (global)
DFV890 25 mg	Tablet	Oral use	Blinded Supplies in HDPE Bottle of 35 tablets	Sponsor (global)
DFV890 10 mg Placebo	Tablet	Oral use	Blinded Supplies in HDPE Bottle of 35 tablets	Sponsor (global)
DFV890 25 mg Placebo	Tablet	Oral use	Blinded Supplies in HDPE Bottle of 35 tablets	Sponsor (global)

6.1.1 Additional study treatments

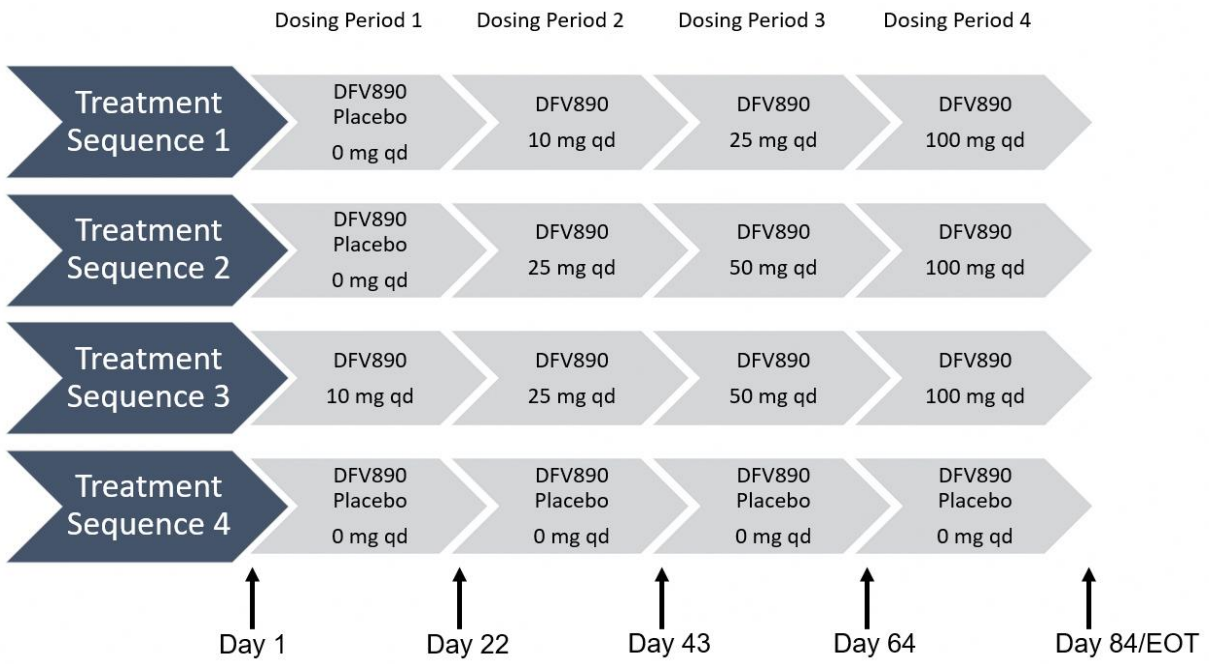
No other treatment beyond investigational drug and control drug are included in this trial.

As this is a population with known coronary heart disease, participants would be expected to be on standard of care therapies to reduce risk of recurrence of cardiovascular disease events (eg. lipid lowering therapy, anti-hypertensives, etc.), if clinically indicated.

6.1.2 Treatment arms/group

Participants will be assigned at Day 1 to one of the following 4 treatment arms/groups in a ratio of 5:5:1:1

Figure 6-1 Treatment arms



6.2 Preparation, handling, storage, and accountability

Each study site will be supplied with study treatment in packaging as described under Table 6-1 Investigational and control drugs.

A unique medication number is printed on the study medication label of each bottle. Investigator staff will identify the study medication bottle(s) to dispense to the participant by contacting the IRT system and obtaining the medication number(s). Drug accountability and reconciliation data is recorded in a drug accountability log (e.g. the Drug Accountability and Returns Management functionality in the IRT system)

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of Investigational Medicinal Product (IMP) directly to a participant's home may be permitted (if allowed by local or regional health authorities and ethics committees, as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 1-month supply. In this case, regular phone calls or virtual contacts (every 2 weeks or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, investigation of any AEs, ensuring participants continue to benefit from treatment, and discussion of the participant's health status until the participants can resume visits at the study site.

In order to reduce waste, the study medication will be sent to a site when the first patient enters Screening 2 visit. Sites should allow for approximately seven days between screening and

randomization visit/first study treatment dose (choose which is applicable for the study) of their first participant for the first study medication shipment. For the precise timeframe or to accommodate exceptional circumstances, sites should discuss with their Field Monitor.

6.2.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the Investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization (CO) Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The Investigator or designated site staff (blinded or unblinded, as applicable) must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log (e.g. the Drug Accountability and Returns Management functionality in the IRT system). All bottles of study treatment assigned by the IRT will be recorded in the IRT system. Monitoring of drug accountability will be performed by field monitors during site or remote monitoring visits, and at the completion of the trial.

As study treatment is administered at home, e.g., oral medication, participants will be asked to return all unused study treatment and packaging at each visit or at the time of discontinuation of study treatment.

The site may destroy and document destruction of unused study treatment, drug labels and packaging, as appropriate in compliance with site processes, monitoring processes, and per local regulation/guidelines. Otherwise, the Investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the Investigator folder at each site.

6.2.2 Handling of other treatment

The following non-study treatment must be monitored specifically:

- Statin (HMG-CoA reductase inhibitor) therapy. Any changes in statin dose should be recorded on the appropriate Case Report Forms.

6.2.3 Instruction for prescribing and taking study treatment

Participants will be randomized to one of four treatment sequences. Based on the treatment sequence assignment, patients will start on either placebo or DFV890 at Day 1 and then receive up titrating doses of DFV890 or further placebo at the corresponding study visits.

Participants will be dispensed with double-blind HDPE bottle packs for each 3-week dosing period to ensure the appropriate dosage is being taken while maintaining the blind.

Table 6-2 Dose and treatment schedule

Dosing Period	Dose/Strength	Investigational / Control Drug (Name and Strength) + Number of Tablets	Frequency and/or Regimen
Dosing Period 1 (Day 1 to 21)	10 mg	1 tablet of DFV890 10 mg	Once daily with food for 3 weeks
	0 mg	1 tablet of 10 mg matching placebo	
Dosing Period 2 (Day 22 to 42)	25 mg	1 tablet of DFV890 25 mg + 1 tablet of 10 mg matching placebo	Once daily with food for 3 weeks
	10 mg	1 tablet of DFV890 10 mg + 1 tablet of 25 mg matching placebo	
	0 mg	1 tablet of 25 mg matching placebo + 1 tablet of 10 mg matching placebo	
Dosing Period 3 (Day 43 to 63)	50 mg	2 tablets of DFV890 25 mg	Once daily with food for 3 weeks
	25 mg	1 tablet of DFV890 25 mg + 1 tablet of 25 mg matching placebo	
	0 mg	2 tablets of 25 mg matching placebo	
Dosing Period 4 (Day 64 to 84)	100 mg	4 tablets of DFV890 25 mg	Once daily with food for 3 weeks
	0 mg	4 tablets of 25 mg matching placebo	

Up titration will occur at the study visits during the Treatment Period as indicated in Section 1.3, Schedule of Activities.

Each 3-week dosing period (i.e., Day 1-21, Day 22-42, Day 43-63, and Day 64-84) is approximately 21 days in duration but must be at least 17 days in duration. The following/next visit should be scheduled the day after the last dose of that current dosing period. In the event that an up titration visit cannot be scheduled within the allowed visit windows, the participants should continue to take their dose up to a maximum of 35 days (maximum number of tablets dispensed for a given dosing period) and every effort should be made to schedule the visit before the participant's supply of tablets for the given period runs out.

If participants run out of tablets before the next up titration visit can be scheduled, a visit should be scheduled as soon as possible to only perform safety assessments described in Section 8.4 (Safety/Tolerability Assessments). Other non-safety assessments described in Section 8.3 (Efficacy assessments) must not be performed. Participants will then start the next dosing period as applicable.

The last dose will be taken on Day 84 prior to the EOT visit on Day 85. Allowable visit windows are listed in Section 1.3, Schedule of Activities. To achieve the target doses for each time period, please refer to Table 6-2. Participants are to take DFV890 or placebo once daily at approximately the same time each day. On days of study visits with dose administration, the participants should not take their daily dose until they are on-site and instructed to do so by the site staff. On days that pre-dose PK samples are obtained, the participant should take DFV890 or placebo after the pre-dose PK samples, as instructed by site staff. In the event that the participants have taken their daily dose on the visit day prior to arriving for their on-site visit, the visit and associated assessments should be rescheduled as soon as possible (e.g., next day or after the weekend). Participants should take DFV890 or placebo at home with food or no later than 5 minutes after completion of the meal with a glass of water or any non-alcoholic beverage (see Section 5.3.1 for dietary restrictions). Participants should be instructed to

swallow whole tablets and not to chew or break them. On days of study visits with dose administration, DFV890 or placebo does not need to be taken with food.

If vomiting occurs during the course of treatment, participants should not take the study treatment (DFV890 or placebo) again before the next scheduled dose. Participants should be instructed not to make up missed doses. A missed dose is defined as a case when the full dose is not taken within 12h after the approximate time of the usual daily dosing. That day's dose should be omitted, and the participant should continue treatment with the next scheduled dose.

6.3 Measures to minimize bias: randomization and blinding

6.3.1 Treatment assignment, randomization

At Day 1, all eligible participants will be randomized via IRT to one of the treatment arms. The Investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify a unique medication number for the first bottle of study treatment to be dispensed to the participant.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and Investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

The randomization scheme for participants will be reviewed and approved by a member of the Randomization Office.

6.3.2 Treatment blinding

This is a participant- and investigator-blinded study. Participants and investigators will remain blinded to study treatment throughout the study, except where indicated below.

The identity of treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Site staff

All site staff (including study investigator, study nurse) will be blinded to study treatment throughout the study.

Unblinding a single participant at site for safety reasons (necessary for participant management) will occur via an emergency system in place at the site.

Sponsor staff or delegate

Unblinded sample analysts are required for this study. The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office) to facilitate analysis

of the samples. The sample analysts will provide the sample data to the study team under blinded conditions unless otherwise allowed.

The study statistician will be able to access the randomization list at any time throughout the study and is allowed to share unblinded information with the rest of the clinical team as appropriate for internal decision purposes, as outlined in Table 6-3. For example, unblinded summaries and unblinded individual data can be shared with the team for interim analyses.

Study programmers and other personnel involved in study data analyses (e.g., biomarker expert, pharmacometrician, and potentially others) are also allowed to access treatment assignment information at any time throughout the study for the purpose of conducting data analyses.

The Clinical Trial Team (CTT) is allowed to share unblinded results with other sponsor staff (e.g., decision boards) as required for internal decision making on the study or the project at the time of interim analyses while the study is ongoing.

All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure except as described above.

Following final database lock, all roles may be considered unblinded.

Table 6-3 Blinding and unblinding plan

Role	**Time or Event**			
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)	Interim Analysis/ dose escalation/ safety review
Participants	B	B	UI	B
Site Staff	B	B	UI	B
Global Clinical Supply	UI	UI	UI	UI
Randomization Office	UI	UI	UI	UI
Statistician/statistical programmer/ data analysts (e.g. biomarker, PK)	B	UI	UI	UI
Unblinded Sponsor staff, e.g. for study treatment re-supply, unblinded monitor(s), sample analyst(s)	B	UI	UI	UI
Sponsor CTT	B	B	UI	UI
All other Sponsor staff not identified above (i.e. project team, management & decision boards, support functions)	B	B	UI	UI

B Complete blinded

UI Unblinded to individual participant treatment codes

6.3.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required in order to treat the participant safely.

Most often, discontinuation from study treatment and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the Investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The Investigator will then receive details of the investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the Investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The Investigator will provide:

- protocol number
- participant number

In addition, oral and written information to the participant must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

6.4 Study treatment compliance

The Investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the Investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the Investigator and/or site study personnel at each visit using pill counts and information provided by the participant. This information should be captured in the source document at each visit. CRF documented compliance measures, as reported by the participant, include: 1) any missed doses within the 2 days prior to the study visit, and 2) confirmation that the time the participant took the last dose on the day prior to the study visit was 24h ± 2h from the PK sample collection. Assessments of compliance at study visits are reflected in Section 1.3, Schedule of Activities.

All study treatment dispensed and returned must be recorded in a drug accountability log (e.g. the Drug Accountability and Returns Management functionality in the IRT system).

6.4.1 Recommended treatment of adverse events

The following recommendation for managing potential suspected DFV890-related skin rashes are provided.

- Depending on severity, investigators can consider, as per medical judgment, early treatment of mild rashes (maculopapular rash covering <10% body surface area with or without symptoms, e.g., pruritis, burning) with symptomatic treatment (e.g., topical steroids) and close monitoring of the participant's response.
- For skin rashes covering >10% body surface area (corresponding to a Common Terminology Criteria for Adverse Events (CTCAE) grade 2 or higher), investigators should discontinue DFV890 and closely monitor participants to ensure resolution of the rash. In the case of participants with systemic or cutaneous signs or symptoms suggesting a severe cutaneous reaction, a short course of systemic corticosteroids (e.g., prednisone 1 to 2 mg/kg per day for 5 to 7 days) may be considered.

At present, there is insufficient information to provide specific recommendations regarding treatment of other potential AEs in this participant population.

Medication used to treat AEs must be recorded on the appropriate CRF.

6.5 Dose modification

Investigational or other study treatment dose adjustments and/or interruptions are not permitted.

6.6 Continued access to study treatment after the end of the study

Investigational drug will not be provided to participants following the end of the study.

6.6.1 Post-trial access

Not applicable.

6.7 Treatment of overdose

In the event of an overdose, the investigator/treating physician should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study treatment should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until DFV890 can no longer be detected systemically (at least 7 days).
- Obtain a plasma sample for PK analysis within 7-10 days from the date of the last dose of study treatment if requested by the medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose.

6.7.1 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant, or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE. Study treatment errors and uses outside of what is foreseen in the protocol, misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24h of Investigator's awareness. For more information on AE and SAE definition and reporting requirements, please see the respective sections.

6.8 Concomitant and other therapy

6.8.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate Case Report Forms.

Each concomitant drug must be individually assessed against all exclusion criteria and prohibited medication. If in doubt, the Investigator should contact the Novartis medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

6.8.1.1 Permitted concomitant therapy requiring caution and/or action

Clinical studies to investigate DDIs between DFV890 and concomitant medications have not been performed. Evaluation and recommendations are based on in vitro / preclinical data and physiology-based PK simulations.

DDI with DFV890 as victim (exposure of DFV890 may increase)

DFV890 is expected to be eliminated mainly via hepatic CYP-mediated metabolism with CYP2C9 (CCI %) and CYP3A4 (CCI %) as the main contributing enzymes. DFV890 may therefore be affected by CYP2C9 and/or CYP3A4 interactions. In particular,

- Chronic dosing with drugs, which are dual CYP2C9/CYP3A4 inducers (e.g., rifampicin) is expected to induce both enzymes, thereby may reduce DFV890 exposure by approximately CCI -fold in participants with normal CYP2C9 activity to sub-therapeutic levels. Lower impact is foreseen for intermediate and poor CYP2C9 metabolizers.

- Co-administration of DFV890 with strong inhibitors of CYP2C9 is expected to reduce enzymatic metabolic capacity, thereby may increase DFV890 drug exposure by approximately [redacted]-fold.
- When dosing DFV890 together with strong or moderate CYP3A inhibitors or moderate dual CYP3A/CYP2C9 inhibitor, [redacted] effect is expected for participants with normal CYP2C9 activity and intermediate metabolizers (AUC-fold increase [redacted]), while [redacted] effect is very likely for poor CYP2C9 metabolizers (AUC-fold change [redacted]).

DDI with DFV890 as perpetrator (exposure of concomitant medication may decrease)

Due to its in vitro weak-to-moderate CYP3A4 induction potential, DFV890 can potentially decrease systemic exposure of sensitive CYP3A4 substrates by approximately [redacted]-fold or some oral hormonal contraceptives (e.g., ethinylestradiol) by [redacted]. As a consequence, decreased efficacy of those concomitant medications cannot be excluded.

Considering DDI risk, certain concomitant medications when dosed with DFV890 are required to be used with caution or they are prohibited. List of concomitant medications to be used with caution is presented in Table 6-4 and prohibited drugs are listed in Table 6-5.

Table 6-4 Drugs to be used with caution

Narrow therapeutic index substrates of CYP3A	abemaciclib, acalabrutinib, alectinib amiodarone, amitriptyline, astemizole, axitinib, baricitinib, bosutinib, brigatinib, cabazitaxel, cabozantinib, clomipramine, cobimetinib, copanlisib, cyclosporine, dabrafenib, dasatinib, dihydroergotamine, docetaxel, entrectinib, erdafitinib, ergotamine, everolimus, imipramine, ixazomib, lomitapide, midostaurin, neratinib, panobinostat, pexidartinib, pimozide, ponatinib, quinidine, regorafenib, romidepsin, sirolimus, sonidegib, sorafenib, sunitinib, tacrolimus, tamoxifen, temsirolimus, tolvaptan, trabectedin, venetoclax, vinblastine, zanubrutinib
Sensitive substrates of CYP3A	abemaciclib, acalabrutinib, alisporivir, almorexant, alfentanil, alpha-dihydroergocryptine, aplaviroc, asunaprevir, atorvastatin, avanafil, avapritinib, blonanserin, bosutinib, brecanavir, brigatinib, brotizolam, budesonide, buspirone, cabazitaxel, capravirine, cobimetinib, cyclosporine, danoprevir, darifenacin, dasatinib, ebastine, eletriptan, eliglustat, elvitegravir, entrectinib, eplerenone, everolimus, felodipine, fluticasone, grazoprevir, ibrutinib, itacitinib, ivabradine, ivacaftor, levomethadyl (LAAM), lomitapide, lopinavir, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, morphothiadin, naloxegol, neratinib, nisoldipine, paritaprevir, perospirone, quetiapine, ridaforolimus, sildenafil, simeprevir, simvastatin, sirolimus, tacrolimus, ticagrelor, tilidine, tipranavir, tolvaptan, triazolam, ubrogepant,

	ulipristal, vardenafil, venetoclax, vicriviroc, vilaprisan, voclosporin, zanubrutinib
Moderate inhibitor of CYP2C9	amiodarone, ataciguat, azapropazone, benzbromarone, bucolome, milk thistle (silymarin, silibinin)[1], nitisinone, oxandrolone, phenylbutazone, piperine[2], tienilic acid

[1] Herbal product

[2] Food product

Investigators at their discretion may administer concomitant medications known to be metabolized by CYP3A. All participants receiving such medications may however require higher doses of the concomitant drug as efficacy might be compromised by DFV890. Particularly, caution is advised when DFV890 is co-administered with drugs that are sensitive substrates of CYP3A and/or have a narrow therapeutic index.

If it cannot be replaced by other medications, investigators may, at their discretion, co-administer known moderate inhibitors of CYP2C9. Their duration, however, should be kept as short as possible, and participants must be closely monitored.

The participant and the investigator should be aware of potential signs of DDIs of the concomitant medication and in the event of suspected toxicity; administration of concomitant medication should be discontinued according to investigator judgment and an unscheduled PK sample should be taken to evaluate systemic exposure to DFV890.

6.8.2 Prohibited medication

Strong or moderate inhibitors of CYP3A and/or strong inhibitors of CYP2C9 are prohibited. Strong or moderate inducers of CYP2C9 and/or strong inducers of CYP3A or strong or moderate dual inhibitors of CYP2C9 / CYP3A are also prohibited (for detailed list see Table 6-5 below (please note that this list may not be comprehensive)).

Considering the DDI potential for DFV890, should a participant have an incidental and limited need for a prohibited medication to be taken within the restricted timeframe, investigators should discuss the case with the sponsor. The administration of any prohibited concomitant medication may require the participant to be withdrawn or DFV890 treatment to be put on hold.

Use of the treatments displayed in the below table is prohibited approximately 5 half-lives or 1 week (whichever is longer) prior to Day 1 until end of study as described in Table 6-6.

Table 6-5 Prohibited drugs due to DDI (CYP3A and CYP2C9 modulators)

Category of interaction	Drug Names
Strong inhibitors of CYP3A	boceprevir, ceritinib, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir[3], elvitegravir/ritonavir[3], grapefruit juice[2], idelalisib, indinavir, indinavir/ritonavir[3], itraconazole, josamycin, ketoconazole, lopinavir/ritonavir[3], mibefradil, mifepristone, nefazodone, nelfinavir, ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak)[3], posaconazole, ribociclib, ritonavir, saquinavir, saquinavir/ritonavir[3], telaprevir, telithromycin, tipranavir/ritonavir[3], troleandomycin, tucatinib, voriconazole
Moderate inhibitors of CYP3A	aprepitant, amprenavir, atazanavir, atazanavir/ritonavir[3], casopitant, cimetidine, ciprofloxacin, crizotinib, darunavir, darunavir/ritonavir[3], diltiazem, dronedarone, duvelisib, erythromycin, faldaprevir, fedratinib, fluconazole, grapefruit juice, imatinib, isavuconazole, istradefylline, lefamulin, letermovir, Magnolia vine (*Schisandra sphenanthera*)[1], netupitant, nilotinib, ravuconazole, tofisopam, verapamil, voxelotor
Strong inhibitors of CYP2C9	miconazole, sulfaphenazole, tasisulam
Strong inducers of CYP2C9	None reported to date
Moderate inducers of CYP2C9	enzalutamide, rifampicin
Strong inducers of CYP3A	apalutamide, avasimibe, carbamazepine, enzalutamide, ivosidenib, lumacaftor, mitotane, phenobarbital, phenytoin, rifampicin, rifapentine, St. John's wort (*Hypericum perforatum*)[1]

[1] Herbal product

[2] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).

[3] combination therapy

Table 6-6 Prohibited medication

Medication	Prohibition period	Action taken
Inhibitors and inducers of CYP3A or CYP2C9 according to Table 6-5	5 half-lives or 1 week (whichever is longer) prior to Day 1 through EOS	Discontinue study treatment
Other investigational drugs	Within 5 half-lives of Day 1 through EOS	Discontinue study treatment
Systemic or local treatment with any immune modulating agent in doses with systemic effects	4 weeks prior to Day 1 through EOS	Discontinue study treatment
Biologic drugs targeting the immune system	26 weeks prior to Day 1 until EOS	Discontinue study treatment
Colchicine	Within 5 half-lives of the time of screening through EOS	Discontinue study treatment
Live vaccinations	4 weeks prior to Day 1 through EOS	Discontinue study treatment

7 Discontinuation of study treatment and participant discontinuation/withdrawal

7.1 Discontinuation of study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study treatment administration, if any) and can be initiated by either the participant or the Investigator.

The Investigator must discontinue study treatment for a given participant if he/she believes that continuation would negatively impact the participant's well-being.

Discontinuation from study treatment is required under the following circumstances:

- Participant decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which continued study participation might result in a safety risk to the participant
- Following emergency unblinding
- Emergence of at least one of the following AEs:
  - An AE of severe intensity (corresponding to CTCAE Grade 3 or higher) or life-threatening SAE, considered to be related to DFV890 treatment
  - Skin rashes greater than mild (covering >10% of the body surface area, corresponding to CTCAE Grade 2 or higher) and considered to be related to DFV890 treatment
  - Any laboratory abnormalities, that in the judgment of the investigator, taking into consideration of the participant's overall status, prevents the participant from continuing participation in the study.
  - Any situation, in the judgment of the investigator, in which study participation might result in a safety risk to the patient
  - Severe hypersensitivity reaction occurs, including any of the following: anaphylaxis, fever, chills, urticaria, dyspnea, headache, myalgia, hypotension.

If a liver or renal event occurs, follow guidelines outlined in Section 10.5 and Section 10.6 regarding discontinuation of study treatment.

If discontinuation from study treatment occurs, the Investigator should make a reasonable effort to understand the primary reason for the participant’s discontinuation from study treatment and record this information.

Participants who discontinue from study treatment agree to return for the end of treatment (EOT visit) and follow-up visits (EOS and Safety Follow-Up Call) indicated in Section 1.3 Schedule of Activities. If EOT visit cannot be performed the day after the last dose is taken, only EOS visit should be performed.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the

participant. This telephone contact should preferably be done according to the study visit schedule.

After discontinuation from study treatment, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- AEs / SAEs

The Investigator must also contact the IRT to register the participant's discontinuation from study treatment.

7.2 Participant discontinuation from the study

Discontinuation from study is when the participant permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in Section 1.3 Schedule of Activities.

7.3 Withdrawal of informed consent and exercise of participants' data privacy rights

Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a participant:

- Explicitly requests to stop use of their data

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be as per local regulations (e.g. in writing) and recorded in the source documentation.

Withdrawal of consent impacts the ability to further contact the participant, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

In this situation, the Investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/exercise data privacy rights and record this information. The Investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

Study treatment must be discontinued, and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/exercise data privacy rights should be made as detailed in Section 1.3 Schedule of Activities.

Further details on withdrawal of consent or the exercise of participants' data privacy rights are included in the corresponding ICF.

7.4 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent (or exercise other participants' data privacy rights), the Investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until the planned end of the study would have occurred.

7.5 Study stopping rules

The study will be stopped, and no further dosing will occur pending a full safety review, if any/all of the following criteria are met:

- Any death or life-threatening event occur that is considered to be related to DFV890 treatment;
- Two or more SAEs of a similar type (other than death or life-threatening) occur that are considered to be related to DFV890 treatment;
- Two or more participants experience hypersensitivity reactions of moderate to severe intensity that are considered to be related to DFV890 treatment;
- Two or more participants experience a similar AE which was assessed as severe in intensity and are considered to be related to DFV890 treatment;
- Novartis considers that the number and/or severity of AEs, abnormal safety monitoring tests, or abnormal laboratory findings justifies putting the study on hold.

Dependent on regional guidance, any restart following a temporary hold due to stopping rules being met will require prior submission and approval of a substantial CTA amendment to the competent authorities.

7.6 Early study termination by the Sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination (but not limited to):

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study treatment development for cardiovascular disease event risk reduction.

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, instructions will be communicated at the time of notification. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The Investigator or Novartis depending on local regulation will be responsible for informing Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

8 Study Assessments and Procedures

Study procedures and their timing are summarized in Section 1.3 Schedule of Activities.

Adherence to the study design requirements, including those specified in Section 1.3 Schedule of Activities, is essential and required for study conduct. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with Novartis upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Screening

The screening assessments should be completed as per Section 1.3, Schedule of Activities, starting with informed consents. The assessments should be performed in order from the least invasive/burdensome to the more invasive/burdensome for the participant. Screening assessments (including safety laboratory assessments and hsCRP) may be repeated once (twice for vitals – see Section 8.4.2) at the discretion of the Investigator if there are questionable results or if abnormalities are felt to be due to inherent variability of the test procedure. If the repeat value remains outside the specified range, the participant will be considered a screen failure (See Section 5.4 for more details about screen failures). During screening, the investigator should detect any active infections that would disqualify the participant from this study (exclusion criterion).

The decision to locally test the participant for active SARS-CoV-2 infection in order to evaluate the exclusion criterion is at the investigator's discretion and should be in adherence to local policies or regulations. However, it is highly recommended that PCR or antigen testing for COVID-19 be completed within 1 week prior to first dosing. If testing is performed, negative test results are required prior to enrollment into the study. PCR or antigen test against COVID-19 is mandatory where required by the local Health Authority and/or by local regulations. COVID-19 testing should be completed via nasal or throat swabs. If testing is not performed, the investigator must document their discussion with the participant regarding testing, and the rationale for not testing, in the source documentation. This requirement may be ignored if the pandemic is declared ended by the country where the site is located and resumed if the pandemic recurs.

8.2 Participant demographics/other baseline characteristics

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with eCRF.

Participant demographics: age, sex, race/predominant ethnicity (if permitted) and relevant medical history/current medical conditions (until date of signature of informed consent), and date of prior MI will be recorded in the eCRF. Participant race/ethnicity data are collected and analyzed to identify any differences in the safety and/or efficacy profile of the treatment due to these characteristics. In addition, these data are necessary to assess the diversity of the study population as required by health authorities.

All prescription medications, over-the-counter drugs, and significant non-drug therapies prior to the start of the study must be documented. See the protocol Section 6.8.1 Concomitant Therapy for further details on what information must be recorded on the appropriate page of the eCRF.

8.3 Efficacy assessments

The efficacy assessments described in this section will be evaluated in all participants. Samples will be collected as defined in Section 1.3, Schedule of Activities.

8.3.1 IL-6 and IL-18 Cytokines

The circulating serum levels of the cytokines IL-6 and IL-18 will be measured by an enzyme-linked immunosorbent assay (ELISA) at a qualified vendor. Detailed descriptions of the assays will be included in the bioanalytical data reports and assay validation reports.

Planned time points for all assessments are provided in Section 1.3 Schedule of Activities.

8.3.2 Appropriateness of efficacy assessments

The result of the NLRP3 inflammasome formation is the production of IL-1β from pro-IL-1β. Similarly, pro-IL-18 is cleaved into its active form, IL-18. These cytokines are released to activate a variety of inflammatory cells and produce IL-6, which stimulates the production of CRP from the liver and amplifies the inflammatory cascade within the vessel wall.

Abrogation of NLRP3 inflammasome function is protective in mouse models of atherosclerosis, exerting a beneficial effect on both peripheral inflammatory leukocytes and cytokines, and local anti-inflammatory effects in the atherosclerotic plaque. Measures of local anti-inflammatory effects in the atherosclerotic plaque are not well-established surrogate outcomes of cardiovascular disease risk reduction and are challenging to measure in clinical trials (usually done with non-invasive imaging with or without specific tracers), especially in relatively small samples sizes over short treatment periods. Therefore, the reduction in circulating cytokines will be examined as primary efficacy markers in this early exploratory Phase 2a trial. For example, reductions in IL-6 with IL-1β neutralization with canakinumab in Phase 2 trials preceded the demonstration of cardiovascular disease risk benefit in the CANTOS trial. Through the production of IL-1β and IL-18, the NLRP3 inflammasome has been implicated as a major driver of inflammation associated with chronic inflammatory diseases. As the magnitude of IL-1β reduction is not clearly benchmarked to cardiovascular disease reduction

in the CANTOS trial (due to canakinumab binding), IL-6 is one of the key downstream cytokines of focus in this trial (NLRP3 activation -> IL-1β -> IL-6 -> CRP). In the CANTOS trial, participants had mean IL-6 reductions from baseline of ~35% and ~45% after ~3 months of 150 mg and 300 mg of canakinumab treatment administered q3 months. This corresponded to an ~15% reduced risk of major adverse cardiovascular events (MACE) in the 150 mg/300 mg treatment arms (Ridker et al 2017).

Increased levels of IL-18 are also the result of NLRP3 inflammasome activation. IL-18 levels were not reduced in the CANTOS trial with IL-1β neutralization and were markers of residual cardiovascular disease risk. Patients with increased IL-18 levels at baseline in CANTOS had a 15% increased risk of MACE [95% confidence interval (CI) 3-29%, p=0.02] for each tertile increase in baseline IL-18 (Ridker et al 2020). The CANTOS findings corroborated population studies associating IL-18 levels with cardiovascular disease risk and preclinical studies linking IL-18 with cardiovascular disease pathogenesis. However, interventional studies evaluating the reduction of IL-18 on risk of MACE have not yet been conducted.

DFV890 is an inhibitor of the NLRP3 inflammasome pathway. Therefore, IL-6 and IL-18 are being measured as PD biomarkers (primary endpoints) to determine pathway inhibition.

NLRP3 inhibition could have improved efficacy over canakinumab in diseases where IL-1β and IL-18 both drive pathology. Through the inhibition of IL-1β and IL-18, DFV890 has the potential to significantly reduce cardiovascular risk in patients. In this Phase 2a study, reduction of IL-6 and IL-18 are the primary efficacy endpoints but change in a range of cytokines and immunophenotyping will also be evaluated.

Each participant will contribute data on levels of IL-6 and IL-18 after 3 weeks of oral daily treatment with DFV890 at up to 3 different dose levels and/or placebo, depending on treatment sequence assignment. A dose-response modeling approach will be utilized that integrates IL-6 or IL-18 levels at each dose level and fitting a dose-response relationship to extrapolate reductions at the highest tested dose, 100mg QD, which is expected to achieve Ctrough exposures >CCI for inhibition of the NLRP3 inflammasome. See Section 9.3 for additional details on the analysis of the primary endpoint.

8.4 Safety/tolerability assessments

Safety assessments are specified below with Section 1.3 Schedule of Activities detailing when each assessment is to be performed. Safety assessments include:

- Physical examination
- Vital signs (BP, pulse rate, body temperature)
- ECG
- Clinical safety laboratory assessments
- Height and weight

For details on AE collection and reporting, refer to Section 8.6.

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 3 weeks or more frequently if needed) for safety

monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

8.4.1 Physical examinations

A complete physical examination will include the examination of general appearance, skin (including rash assessment), neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent, which meet the definition of an AE must be recorded as an AE.

A brief physical exam will include the examination of general appearance, a skin assessment for rash, a brief cardiorespiratory assessment, and vital signs (oral body temperature, BP [SBP and DBP] and pulse rate).

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured at the time points specified in Section 1.3, Schedule of Activities. Body weight will be measured on a calibrated scale and under similar conditions (e.g., in similar indoor clothing and at a similar time of day).

8.4.2 Vital signs

Vital signs will include the collection of oral body temperature (recorded in °C), BP and pulse rate measurements.

After the participant has been sitting for 3 minutes, with back supported and both feet placed on the floor, systolic and diastolic BP will be measured using an automated validated device, e.g., OMRON with an appropriately sized arm cuff. In case the arm cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

If vital signs are out-of-range at screening (see Exclusion Criteria Section 5.2 of the protocol for details), two additional readings can be obtained, so that up to three consecutive assessments are made, with the participant seated quietly for approximately five minutes preceding each repeat assessment. The last reading must be within the ranges provided in the eligibility criteria in order for the participant to qualify.

In case of repeated vital assessments, the eCRF should contain the qualifying results.

8.4.3 Electrocardiograms

ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. In the case of a series of assessments, ECG should be the first assessment obtained while the participant is at rest.

Figure 8-1 Recommended order of assessments

The Fridericia QT interval corrected by Fridericia's formula (QTcF) must be used for clinical decisions. The Investigator must calculate QTcF if it is not auto-calculated by the ECG machine.

Single local 12 lead ECGs are collected. ECGs will be locally collected and evaluated. Interpretation of the tracing must be made by a qualified physician and documented on the appropriate CRF. Each ECG tracing should be labeled with the study number, participant initials (where regulations permit), participant number, date, and kept in the source documents at the study site. Clinically significant abnormalities present at screening should be reported on the appropriate CRF. Clinically significant findings must be discussed with Novartis prior to enrolling the participant in the study. New or worsened clinically significant findings occurring after informed consent must be recorded as AEs.

The original ECGs on non-heat-sensitive paper, appropriately signed, must be archived at the study site.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the Investigator at any time during the study as clinically indicated. For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. ECG safety monitoring, or a review process, should be in place for clinically significant ECG findings at baseline before administration of study treatment and during the study.

Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or AEs as appropriate.

8.4.4 Clinical safety laboratory tests

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or AEs as appropriate.

In the case where a laboratory range is not specified by the protocol, but a value is outside the reference range for the laboratory at screening and/or initial baseline, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator (in consultation with Novartis, as needed) and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once prior to randomization.

In all cases, the Investigator must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the participant to continue in the study.

A central laboratory will be used for analysis of all safety specimens collected. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to Investigators in the central laboratory manual.

As per Section 4.5, during a public health emergency as declared by local or regional authorities' i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study

visits, if participants cannot visit the site for protocol-specified safety lab assessments, an alternative lab (local) collection site may be used.

All abnormal lab results must be evaluated for criteria defining an AE and reported as such if the criteria are met. For those lab AEs, repeated evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant.

Table 8-1 Safety laboratory evaluations

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells (RBC), White blood cells (WBC) and Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands)
Clinical Chemistry	Albumin, Alkaline phosphatase (ALP), Alanine transferase (ALT), Aspartate aminotransferase (AST), Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Chloride, Magnesium, Phosphate, Potassium, Sodium, Creatine kinase, Creatinine, Total Bilirubin, Direct Bilirubin, Indirect Bilirubin, LDL Cholesterol (non-fasting), Urea Nitrogen or Urea, Urate, Amylase, Lipase, Glucose (non-fasting), eGFR
Urinalysis	Macroscopic Panel (Dipstick) (Color, Bilirubin, Occult Blood, Macroscopic Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, If macroscopic panel comes back with abnormal values: Microscopic Panel (Erythrocytes, Leukocytes, Casts, Crystals, Bacteria and yeast cells, Epithelial cells)
Coagulation Panel	Prothrombin time (PT)*, International normalized ratio [INR]), Partial Thromboplastin Time (PTT)*, Activated partial thromboplastin time (APTT) *(PT and PTT only at screening)
Liver Event Testing and Liver Follow-Up Testing	Alanine transferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), total bilirubin (TBIL), international normalized ratio (INR), albumin, creatinine kinase (CK), glutamate dehydrogenase (if available), prothrombin time (PT) To evaluate for hemolysis: reticulocytes, haptoglobin, unconjugated (indirect) bilirubin These tests are in addition to routine testing, to be performed only in follow-up to safety events when indicated in Section 10.5 Liver safety monitoring
Renal follow-up Testing	Serum: albumin, total protein, creatinine, cystatin C, blood urea nitrogen (BUN), electrolytes (sodium, potassium, phosphate,

Test Category	Test Name
	calcium), bicarbonate and uric acid Urine: protein, creatinine, albumin, dipstick (specific gravity, pH, heme, protein, glucose, leukocyte esterase and nitrite) and sediment microscopy (crystals, casts, RBCs, WBCs, epithelial cells) Calculate urine albumin-to-creatinine ratio (may be done on a spot urine), urine protein-to-creatinine ratio (may be done on a spot urine) These tests are in addition to routine testing, to be performed only in follow-up to safety events when indicated in Section 10.6, Renal safety monitoring
Pregnancy Test	Serum pregnancy test
Inclusion/Exclusion	For inclusion or exclusion criteria testing not already included above, please refer to Section 5.1 and Section 5.2.

Urinalysis: A midstream urine sample (approx. 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments and allow proper assessments.

8.4.5 Pregnancy testing

A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner during study treatment and for at least 7 days following completion of treatment. In addition, male participants should not donate sperm while taking study treatment, and for 7 days after stopping study treatment.

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

Serum pregnancy testing is required at all time points as indicated in Section 1.3, Schedule of Activities.

As per Section 4.5, during a public health emergency as declared by local or regional authorities' i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if participants cannot visit the site to have serum pregnancy tests, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the site is informed and can verify the pregnancy test results (e.g., following country specific measures).

Assessments of fertility

A woman is considered of childbearing potential from menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy,

bilateral salpingectomy, and bilateral oophorectomy. Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause and an appropriate clinical profile.

In absence of the medical documentation confirming permanent sterilization, or if the post-menopausal status is not clear, the investigator should use his medical judgment to appropriately evaluate the fertility state of the woman and document it in the source document.

8.4.6 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/participant population.

8.5 Additional assessments

No additional tests will be performed on participants entered into this study.

8.6 Adverse events (AEs), serious adverse events (SAEs), and other safety reporting

The definitions of AEs and serious AEs can be found in Section 8.6.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up of all AEs.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 8.6.3.

8.6.1 Adverse events

An AE is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The Investigator has the responsibility for managing the safety of individual participants and identifying AEs.

Novartis qualified medical personnel will be readily available to advise on trial-related medical questions or problems.

The occurrence of AEs must be sought by non-directive questioning of the participant at each visit during the study. AEs also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

AEs must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 8.6.2):

1. The severity grade.
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates or ongoing) and the outcome must be reported
4. Whether it constitutes a SAE (see Section 8.6.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding study treatment.
   All AEs must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed
   - Dose Reduced/increased
   - Drug interrupted/permanently discontinued
6. Its outcome
   - not recovered/not resolved;
   - recovered/resolved
   - recovered/resolved with sequelae
   - fatal; or unknown

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

AEs (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

AE monitoring should be continued for at least 30 days following the last dose of study treatment.

Once an AE is detected, it must be followed until its resolution or until it is judged to be not recovered/not resolved (e.g., continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the IB.

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges or significant changes from baseline or the previous visit.

8.6.2 Serious adverse events

An SAE is defined as any AE [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening
  Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect, fetal death or a congenital abnormality or birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the participant's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g., defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

All reports of intentional misuse and abuse of the product are also considered serious AEs irrespective of whether a clinical event has occurred.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Treatment-emergent elevations in AST or ALT (>2x baseline AND 3x ULN) in combination with total bilirubin >2x ULN or jaundice in the absence of cholestasis (defined as ALP < 2 ULN) or other causes of hyperbilirubinemia can be an indicator of severe drug induced liver injury (Hy's Law). For this reason, a potential Hy's Law case requires expedited reporting, and will be handled as a serious unexpected adverse event (assessing it as medically significant in the absence of any other seriousness criteria). It must be reported as an SAE to the sponsor promptly (i.e., even before all other possible causes of liver injury have been excluded). Reporting should include all available information, especially that needed for evaluating the diagnosis, severity and likelihood that the study treatment caused the reaction. For patient monitoring and to better understand potential etiologies, the investigator must initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

8.6.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24h of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site. Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

Screen Failures

SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.

Randomized OR Treated Participants:

SAEs collected between time participant signs ICF until 30 days after the participant has discontinued from study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24h of the Investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or

otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the Investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with national regulatory requirements in participating countries.

Any SAEs experienced after the 30-day period following the last administration of study treatment should only be reported to Novartis Safety if the Investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

8.6.4 Pregnancy

If a female trial participant becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial participant. The participant must be given adequate time to read, review and sign the pregnancy consent form. This consent form is necessary to allow the Investigator to collect and report information regarding the pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24h of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the Investigator to the Novartis Chief Medical Office and Patient Safety. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

If a female partner of a male trial participant who took study treatment in this study becomes pregnant, pregnancy outcomes should be collected. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

8.6.5 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not applicable. All AEs and SAEs will be reviewed.

8.7 Pharmacokinetics

PK plasma samples will be collected at the visits defined in Section 1.3 Schedule of Activities. Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing, and shipment. See the potential use of residual samples for more information

(Section 8.8). In case needed (e.g., due to suspected toxicity-related AEs), an unscheduled sample should be collected as near as possible to the event in order to assess a potential PK relationship.

PK samples will be obtained from all participants, but samples will be analyzed in participants at all DFV890 dose levels except the placebo group.

DFV890 and IBW042 will be determined by a validated LC-MS/MS method; the anticipated Lower Limit of Quantification (LLOQ) is 1 ng/mL.

Concentrations will be expressed in mass per volume units. Concentrations below the LLOQ will be reported as "zero" and missing data will be labeled as such in the Bioanalytical Data Report.

Due to sparse sampling only plasma trough concentrations (Ctrough) will be available.

8.7.1 PK blood collection

For details on PK blood collection and processing, labeling, and shipment instructions, see laboratory manual.

The exact clock time of dosing, as well as actual sample collection date and time will be entered on the PK blood collection summary page of the CRF. Sampling problems will be noted in the relevant field of the CRF.

8.8 Biomarkers

The primary endpoint cytokines, IL-6 and IL-18, are addressed in Section 8.3. The current section describes the exploratory biomarker strategy.

The exploratory biomarker analyses will be used to further investigate the effect of DFV890 at the molecular and cellular level, for example the composition of various immune cells that can be affected by NLRP3 inhibition. Additional biomarkers will be utilized to investigate changes that may relate to pathway inhibition or mechanism of action. In addition, cardiovascular markers, for example lipid parameters, will be measured to understand disease-related effect. Further potential predictive biomarkers of efficacy will be explored, including but not limited to markers present in known downstream process of the inhibited pathway or other inflammatory mechanisms (e.g., hsCRP).

While the goal of the biomarker assessments is to provide supportive data for the clinical study, there may be circumstances when a decision is made to stop a collection, or not perform or discontinue an analysis due to either practical or strategic reasons (e.g., inadequate sample number, issues related to the quality of the sample or issues related to the assay that preclude analysis, impossibility to perform correlative analyses, etc.). Therefore, depending on the results obtained during the study, sample analysis may be omitted at the discretion of Novartis. In an event of unscheduled biomarker sampling, Novartis may analyze samples or discard them.

Samples will be collected from all participants in this study as specified in Section 1.3 Schedule of Activities. The exploratory biomarker strategy may include, but is not limited to, biomarkers that will inform on:

- PD and inflammation-related markers:

  - Soluble Biomarkers: hsCRP, sASC, hsIL-1b, CXCL9, CXCL10, hsIFNg, vWF
  - Immunophenotyping: myeloid / lymphoid cell activation/enumeration by flow cytometry (whole blood/PBMC)
- Cardiovascular disease-related biomarkers:
  - Lipid parameters: Total cholesterol, HDL, LDL, triglycerides, Lp(a), apolipoproteins
    - Further exploratory biomarkers may be investigated based on study outcomes. These markers may include but are not limited to MPO and free elastase, MMPs, fibrinogen, fibrosis (Biomarker plasma/serum)
- Stratification markers (i.e., hsCRP)
- Genetic markers that may impact primary and exploratory readouts or PK (to be done as part of the end of study analysis and will not be used for eligibility purposes):
  - CHIP mutations
  - CYP2C9 polymorphism assessment

Profiling in serum and plasma

Samples collected in serum and plasma may be investigated in multiplex hypotheses-free platforms where relevant to better understand the disease profile, or for markers that may be associated with treatment response or predict response to treatment.

Residual Samples

Samples and data may be used for another protocol specified endpoint or may be used for exploratory analyses related to the NLRP3 pathway, inflammation, cardiovascular disease, and/or PK. This may include, but is not limited to, additional analysis for bioanalytical purposes, protein binding, metabolite profiling or quantification, indicators of enzymatic activity, assessment of impact on clinical outcome, and the identification of potential biomarkers that may be predictive of benefit from treatment with DFV890. Given the exploratory nature of the work, the method used for the analyses may not be validated, and as such, the results from this exploratory analysis may not be included in the Clinical study report (CSR).

Optional Biomarker Samples

Optional Genetics

The study includes an optional genetic research component which requires a separate informed consent signature if the participant agrees to participate. As permitted by local governing regulations and by IRB/EC, it is required as part of this protocol that the Investigator present these options to the participant.

The purpose of genetic research may be to better understand the safety and efficacy of DFV890, or to learn more about human diseases, or to help develop ways to detect, monitor and treat diseases.

As technology changes over time, the most appropriate technology will be used at the time the exploratory genetic research is performed. This may include the study of the entire genome.

Laboratory manuals will be provided with detailed information on sample collection, handling, and shipment.

DNA samples

The use of DNA to search for biomarkers of disease and drug action is exploratory. Any results from this DNA study will not be placed in the participant's medical records. As an additional confidentiality measure, sample information is stored in one secured database while genetic data is stored in an independent secured database.

Optional Additional Research

If the participant agrees, by signing the optional consent for Additional Research, biological samples and data that remain after analysis is completed may be used for additional research to help better understand how the study treatment works, learn more about the disease, improve the way clinical studies are conducted, or to help develop ways to detect, monitor or treat human diseases. A decision to perform such exploratory research studies would be based on outcome data from this study or from new scientific findings related to the drug class or disease, as well as assay availability.

8.9 Immunogenicity assessments

Immunogenicity is not evaluated in this study.

8.10 Medical resource utilization and health economics

Medical resource utilization (RU) and health economics parameters are not evaluated in this study.

9 Statistical considerations

9.1 Analysis sets

For all analyses, unless specified otherwise, treatment will be defined as a dose level of DFV890 or placebo (placebo, DFV890 10 mg, DFV890 25 mg, DFV890 50 mg, or DFV890 100 mg).

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

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 that 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.

9.2 Statistical analyses

9.2.1 General considerations

Unless stated otherwise, baseline for all calculations will be the last measurement recorded prior to dosing on Day 1.

9.2.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed by treatment sequence for the safety analysis set. Relevant medical histories and current medical conditions at baseline will be listed by system organ class and preferred term by treatment sequence.

9.2.3 Treatments

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.

Compliance will be calculated as the percentage of participants who took a predefined percentage of the number of prescribed doses of study treatment.

9.3 Primary endpoint(s)/estimand(s) analysis

9.3.1 Definition of 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.

The definition of the primary estimand is provided is Section 3.1.

9.3.2 Statistical model, hypothesis, and method of analysis

The primary analysis will assess the effect of DFV890 on the change in IL-6 and IL-18 compared to placebo in a dose-response model, separately for the two biomarkers.

An E_{max} model will be fit to the post-baseline values of each biomarker, 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.

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

Additional details of the model will be specified in the SAP.

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.

In case of convergence issues, a linear mixed effects model will be fit in place of the E_{max} model (to be referred to as 'traditional model'). The model will include treatment as a fixed effect, a random intercept effect for participant, and the baseline value of the biomarker and baseline body weight as covariates. All biomarker measurements will be logarithm-transformed prior to the analysis. The least-square mean and associated 80% CI for each treatment, and the estimated mean difference to placebo for each DFV890 dose level, the p-value, and 2-sided 80% CI will be extracted from the model and back-transformed to the ratio scale for reporting.

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 ≥ 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.

9.3.3 Handling of intercurrent events of primary estimand (if applicable)

As described in Section 3.1, 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, with the exception of a change to standard of care cardiovascular disease prevention medication. 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 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. If no measurements are collected after the intercurrent event is experienced, these missing measurements will not be imputed.

9.3.4 Handling of missing values not related to intercurrent event

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.

9.3.5 Sensitivity analyses

As a sensitivity analysis to the Emax model described in Section 9.3.2, a Hill coefficient other than 1 may be explored.

If the Emax model converges on either of the two primary endpoints, the traditional model described in Section 9.3.2 will be performed as a sensitivity analysis on that endpoint.

9.3.6 Supplementary analysis

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.

9.4 Secondary endpoint(s)/estimand(s) analysis

Not applicable.

9.4.1 Safety endpoints

The safety set will be used for all safety analyses.

Adverse events

The number (and percentage) of participants with treatment emergent AEs will be summarized by treatment, primary system organ class, and preferred term. An additional summary by treatment, primary system organ class, preferred term, and maximum severity may be reported if deemed necessary.

A separate summary by treatment sequence, primary system organ class, and preferred term will also be provided.

Treatment-emergent AEs 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.

For the purposes of these summaries, 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, the first dosing period will begin at Day 1 (randomization) and end on the Day 22 visit, at which point the next treatment will be administered according to the specific treatment sequence.

A participant with multiple AEs within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be summarized by treatment and visit/time.

12-lead ECG

All ECG data will be summarized by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be summarized by treatment and visit/time.

9.4.2 Pharmacokinetics

Summary statistics of DFV890 plasma concentration data will be provided by treatment and visit/sampling time point, including the frequency of concentrations below the LLOQ and reported as zero.

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.

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

9.4.3 PK/PD relationships

Refer to Section 9.7.

9.5 Exploratory endpoint(s)/estimand(s) analysis

9.5.1 Biomarkers

The following inflammation-related exploratory biomarkers (hsCRP, soluble ASC, CXCL9, CXCL10**,** hsIFNg, Interleukin-1b (IL-1b), and neutrophil activation/frequency in whole blood) and disease-related biomarkers (LDL and Lp(a)) will be analyzed using a linear mixed effects model of the same form as the traditional model specified for the primary endpoints in Section 9.3.2.

Biomarker values above the Upper Limit of Quantification (ULOQ) will be imputed as ULOQ and values below the LLOQ will be imputed as LLOQ/2 for these analyses.

9.5.2 DNA

Exploratory DNA analyses might include presence of genetic polymorphisms in the inflammasome pathway, presence and change from baseline of somatic mutations (clonal hematopoieisis). Other exploratory DNA studies are designed to investigate the association between genetic factors (genotypes) and clinical assessments (phenotypes) which are collected during the clinical trial. Without prior evidence of a strong association, a number of possible associations are evaluated with exploratory analyses. A range of statistical tests are used for the analyses. Additional data, from other clinical trials, are often needed to confirm associations. Alternatively, if the number of participants enrolled in the study is too small to complete proper statistical analyses, the data may be combined, as appropriate, with those from other studies to enlarge the dataset for analysis.

Data generated on hypothesis-free platforms will be reported separately (e.g. CSR addendum).

9.6 (Other) Safety analyses

Not applicable.

9.7 Other analyses

To address the exploratory objective of assessing the effect of the CYP2C9 polymorphism on the PK of DFV890 and its metabolite IBW042, the trough concentrations of DFV890 and its metabolite will be summarized by CYP2C9 genotype and treatment, as feasible.

In addition, the relationship between trough concentrations of DFV890 and selected biomarkers may be evaluated in a graphical manner. Details will be provided in the SAP.

9.8 Interim analysis

No interim analysis is planned for this study. 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.

9.9 Sample size determination

9.9.1 Primary endpoint(s)

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.

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10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, [IDFU], and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments/modifications to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

Signing a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required

Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC

Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures

Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR (Code of Federal Regulations), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

Inform Novartis immediately if an inspection of the clinical site is requested by a regulatory authority

10.1.2 Informed consent process

The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

A copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional additional research. The Investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for additional research. Participants who decline to participate in this optional additional research will document this.

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

Information about common side effects already known about the investigational treatment can be found in the IB. This information will be included in the participant informed consent and should be discussed with the participant upon obtaining consent and during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an IN or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Optional Inflammation Marker Pre-Screening ICF, which can only be used for Screening Visit 1.
- Main study ICF, which can be used at Screening 1 visit if the optional Inflammation Marker Pre-Screening ICF is not used. The main study ICF can be used at Screening 2 visit if the optional Inflammation Marker Pre-Screening ICF was used at Screening 1 visit. The main study ICF includes:
    - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study

  - Optional consent for activities that may be done outside of the study site
- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the female partners of any male participants who took study treatment
- Patient information sheet for female partners of any male participants who took study treatment
- Optional Genetics Consent to provide a sample for exploratory DNA studies

The study includes an optional DNA component which requires a separate signature if the participant agrees to participate. It is required as part of this protocol that the Investigator presents this option to the participants, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in these optional assessments (DNA) will in no way affect the participant's ability to join the main research study.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

As per Section 4.5, during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local health authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g., the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

10.1.3 Data protection

Participants will be assigned a unique identifier by Novartis. Any participant records or datasets that are transferred to Novartis will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

10.1.4 Committees structure

Not applicable.

10.1.5 Data quality assurance

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novartis. No records may be transferred to another location or party without written notification to Novartis.

10.1.5.1 Data collection

All data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

Designated Investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the Electronic Data Capture (EDC) system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the Investigator staff.

The Investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the Investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

10.1.5.2 Database management and quality control

Novartis personnel (or designated Contract Research Organization (CRO)) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated Investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of screenings, randomizations, screen failures and treatment completion, as well as randomization codes and data about all study treatment (s) dispensed to the participant and all dosage changes will be tracked using an IRT. The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked, **and the treatment codes will be unblinded** and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

10.1.6 Source documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. The Investigator must also keep the original ICF signed by the participant (a signed copy is given to the participant).

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis /Clinical Research Associate organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters and provide reports to Novartis clinical teams to assist with trial oversight.

10.1.7 Publication policy

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov. In addition, after study completion (defined as last participant last visit (LPLV)) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required health authority websites (e.g., Clinicaltrials.gov, etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial Investigator meetings.

Any data analysis carried out independently by the Investigator should be submitted to Novartis before publication or presentation.

Summary results of primary and secondary endpoints will be disclosed based upon the global LPLV date, since multinational studies are locked and reported based upon the global LPLV.

10.1.8 Protocol adherence and protocol amendments

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure the safety of participants should be administered as deemed necessary on a case-by-case basis. Under no circumstances including incidental collection is an Investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the Investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

10.1.8.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

10.2 Appendix 2: Abbreviations and definitions

10.2.1 List of abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
BID	bis in die/twice a day
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CABG	Coronary Artery Bypass Graft
CANTOS	Canakinumab Anti-Inflammatory Thrombosis Outcome Study
CFR	Code of Federal Regulations
CHIP	Clonal Hematopoeisis of Indeterminate Potential
CK	Creatine Kinase
CO	Country Organization
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	Through concentration
CTT	Clinical Trial Team
CV	Coefficient of Variation
CVD	Cardiovascular Disease Prevention
DARM	Drug Accountability and Returns Management
DBP	Diastolic Blood Pressure
DDI	Drug-Drug Interaction
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EOS	End Of Study
eSource	Electronic Source
FIH	First in Human
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-Glutamyl Transferase
h	Hour
HIV	Human Immunodeficiency Virus
hsCRP	High-sensitivity C-Reactive Protein
i.v.	intravenous
IB	Investigator’s Brochure
ICF	Informed Consent Form

ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IL-1b	Interleukin-1b
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
LDH	Lactate Dehydrogenase
LDL	Low density lipoprotein
LFT	Liver function test
LLOQ	Lower Limit of Quantification
LPLV	Last Participant Last Visit
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
MI	Myocardial Infarction
mL	milliliter(s)
NLRP3	NOD-, LRR- and pyrin domain-containing protein 3
OHP	Off-site Healthcare Professional
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PoC	Proof of Concept
PT	Prothrombin Time
QD	Once a day
QTcF	QT interval corrected by Fridericia’s formula
RBC	Red Blood Cell(s)
RU	Resource Utilization
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SoA	Schedule of Activities
ULN	Upper Limit of Normal
ULOQ	Upper Limit of Quantification
vWF	von-Willebrand-Faktor
WBC	White Blood Cell(s)
WHO	World Health Organization

10.2.2 Definitions

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an IMP (e.g., any background therapy)
Assessment	A procedure used to generate data required by the study
Auxiliary medicinal product	Medicinal product used for the needs of a clinical trial as described in the protocol, but not as an IMP (e.g., rescue medication, challenge agents, background treatment or medicinal products used to assess endpoints in the clinical trial). Concomitant therapy is not considered as AMP.
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
CE marking	A marking by which a manufacturer indicates that a device is in conformity with the applicable requirements set out in European Union legislation providing for its affixing. CE marking of medical devices is required prior to lawfully placing them on the European Union market.
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
Control drug	A study intervention (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study intervention administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g., 100 mg QD, 75 mg BID)
Electronic Data Capture (EDC)	EDC is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant.
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants

eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to Novartis and other oversight authorities, as appropriate
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Investigational Medical Device	Medical Device being assessed for safety or performance in a clinical investigation. This includes devices already on the market and being evaluated for new intended uses, new populations, new materials, or design changes
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study or the participant allocated to an invalid stratification factor
Off-site	Describes trial activities that are performed at remote location by an OHP professional, such as procedures performed at the participant's home.
Off-site healthcare Professional (OHP)	A qualified healthcare professional, who performs certain protocol procedures for the participant in an off-site location such as a participant's home.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e., concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the participant about the status of a participant's health condition without amendment or interpretation of the participant's report by a clinician or anyone else

Period	The subdivisions of the trial design (e.g., Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Perpetrator drug	A drug which affects the pharmacokinetics of the other drug
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant
Remote	Describes any trial activities performed at a location that is not the investigative site.
Rescreening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Run-in Failure	A participant who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to participant's intervention or other treatment)
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study device	Study device is a medical device (marketed or investigational) that is used in a circumstance that makes it part of the investigation.
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Tele-visit	Procedures or communications conducted using technology such as telephone or videoconference, whereby the participant is not at the investigative site where the Investigator will conduct the trial.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g., as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.

Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of consent	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and/or biological samples AND no longer wishes to receive study treatment AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. This request should be distinguished from a request to discontinue the study. Other study participant's privacy rights are described in the corresponding ICF.

10.3 Appendix 3: Clinical laboratory tests

Not applicable

10.4 Appendix 4: Participant Engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants at the time points indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Thank You letter
- Plain language trial summary - after CSR publication

10.5 Appendix 5: Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Table 10-1 in Section 10.5 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 10-1 should be followed up by the Investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 10-2. Repeat liver chemistry tests (i.e., ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.

- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
    - These investigations can include based on Investigator's discretion: serology tests, imaging, and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information and procedures performed must be recorded as appropriate in the CRF.

10.5.1 Liver event and laboratory trigger definitions & follow-up requirements

Table 10-1 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	• ALT or AST > 5 × ULN • Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity
If ALT or AST abnormal at baseline:	• ALT or AST > 3x baseline or > 300 U/L (whichever occurs first)

Table 10-2 Follow up requirements for liver laboratory triggers - ALT, AST, TBL -

ALT	TBL	Liver Symptoms	Action
ALT increase without bilirubin increase:			
If normal at baseline: ALT > 3 x ULN	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	• **No Action**
If elevated at baseline: ALT > 2 x baseline or > 300 U/L (whichever occurs first)			
If normal at baseline: ALT > 5 x ULN for more than two weeks	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	• **Interrupt study treatment** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, and CKin 48-72h. • Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies. • Study treatment can be restarted if liver enzymes return to baseline.
If elevated at baseline: ALT > 3 x baseline AND >5x ULN for more than two weeks or ALT ≥ 5x baseline AND ≥ 8x ULN			
If normal at baseline: ALT > 8 x ULN	Normal	None	
ALT increase with bilirubin increase:			
If normal at baseline: ALT > 3 x ULN	TBL > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
If elevated at baseline: ALT > 2 x baseline AND >3x ULN			
If normal at baseline: ALT > 3 x ULN	Normal or elevated*	Severe fatigue, nausea, vomiting, right upper quadrant pain*	
If elevated at baseline: ALT > 2 x baseline AND >3x ULN			

* This situation suggests liver injury based on (i) elevation of ALT, and (ii) the presence of symptoms of liver injury. Even if bilirubin is normal, the presence of liver symptoms indicates potentially severe liver injury.

Table 10-3 Follow up requirements for liver laboratory triggers - Isolated Hyperbilirubinemia

Criteria	Actions required	Follow-up monitoring
Total Biliruin (isolated)		
>1.5 – 3.0 ULN	• Maintain treatment • Repeat Liver function test (LFTs) within 48-72h	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	• Interrupt treatment • Repeat LFT within 48-72h • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	• Discontinue the study treatment immediately • Hospitalize the participant • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion)
Any AE potentially indicative of a liver toxicity	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	Investigator discretion

Based on Investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

10.6 Appendix 6: Renal safety monitoring

Once a participant is exposed to study treatment, the following two categories of abnormal renal laboratory alert values should be assessed during the study period:

- Serum creatinine increase ≥ 25% compared to baseline during normal hydration status
- Any one of the following:
  - Urine protein-creatinine ratio (PCR) ≥1g/g or ≥100 mg/mmol, OR
  - New onset dipstick proteinuria ≥ 3+, OR
  - New onset dipstick hematuria ≥ 3+ (after excluding menstruation, UTI, extreme exercise, or trauma)

Abnormal renal event findings must be confirmed within 24-48h after the first assessment.

Once a participant is exposed to study treatment, renal laboratory alerts or renal safety events should be monitored and followed up by the Investigator or designated trial staff as summarized in Table 10-5.

10.6.1 Specific Renal Alert Criteria and Actions and Event Follow-up

Table 10-4 Specific renal alert criteria and actions

Renal Event	Actions
eGFR decrease 25 – 49%	• Consider causes and possible interventions • Repeat laboratory values within 48 hrs of receipt of abnormal test results. Assess patient for signs and symptoms of illness, AKI, etc.
eGFR decrease ≥ 50 % * OR if <18 years old, eGFR < 35 mL/min/1.73 m^2	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Repeat laboratory values within 48 hrs of receipt of abnormal test results. Assess patient for signs and symptoms of illness, AKI, etc. • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider referral to nephrologist for diagnosis and management • Consider patient hospitalization and specialized treatment
New onset dipstick proteinuria ≥ 3+ OR Protein-creatinine ratio (PCR) ≥ 1g/g Cr	• Confirm presence of true proteinuria by quantification: protein-creatinine on first morning void • Consider causes and possible interventions • Assess serum albumin & serum total protein • Repeat assessment to confirm

Renal Event	Actions
	• Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider referral to a nephrologist
New onset hematuria ≥ 3+ on urine dipstick	• Obtain urine microscopy to distinguish hemoglobinuria or myoglobinuria from hematuria • Assess sCr • Exclude infection, trauma, calculi, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

* Corresponds to KDIGO criteria for Acute Kidney Injury

Table 10-5 Renal Event Follow Up

FOLLOW-UP OF RENAL EVENTS
Monitor patient regularly (frequency dependent on clinical course and consultant advisement) until - • Event resolution: sCr within 10% of baseline or PCR < 1 g/g Cr, or ACR <300 mg/g Cr, or • Event stabilization: sCr level with ±10% variability over last 6 months or PCR stabilization at a new level with ±50% variability over last 6 months. • Analysis of urine renal markers in samples collected over the course of the DIN event

11 References

References are available upon request

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