NOVARTIS

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 and MAS825 for inflammatory marker reduction in an adult population with coronary heart disease and Clonal Hematopoiesis of Indeterminate Potential (CHIP)

Clinical Trial Protocol Number: CADPT15A12201

Version Number: v00 (Original Protocol)

Compound: ADPT15

Brief Title: A study to investigate the efficacy, safety, and tolerability of DFV890 and MAS825 for inflammatory marker reduction in adult participants with coronary heart disease and Clonal Hematopoiesis of Indeterminate Potential (CHIP)

Study Phase: IIa

Sponsor Name: Novartis Pharma AG or its affiliates outside of the EEA (where applicable)

Sponsor Address in the EEA: Novartis Pharma AG, Lichtstrasse 35, 4056 Basel, Switzerland

Regulatory Agency Identifier Number(s): IND Number 167,653; EU CT Number 2023-506741-34

Approval Date: 28-Jul-2023 (content final)

Table of contents

List of tables

List of figures

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 and MAS825 for inflammatory marker reduction in an adult population with coronary heart disease and Clonal Hematopoiesis of Indeterminate Potential (CHIP)

Brief Title:

A study to investigate the efficacy, safety, and tolerability of DFV890 and MAS825 for inflammatory marker reduction in adult participants with coronary heart disease and Clonal Hematopoiesis of Indeterminate Potential (CHIP)

Purpose

The purpose of this study is to evaluate the efficacy, safety, and tolerability of intra-individual dose escalation of oral DFV890 or a single subcutaneous (s.c.) dose of MAS825 in reducing circulating levels of inflammatory markers in adult participants with known coronary heart disease and the presence of CHIP. The results of the study will be used to inform future development plans for DFV890 and MAS825 in cardiovascular disease (CVD) event risk reduction.

Study Indication /Medical Condition:

Coronary heart disease, CHIP

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 CHIP	Serum levels of Interleukin (IL)-6 and IL-18 at 3 weeks after the start of a DFV890 dosing period

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

Primary estimand/analysis:

The primary estimand will address potential intercurrent events that may influence the primary endpoints, IL-6 and IL-18 (DFV890 only), largely with a hypothetical strategy, which aims to estimate the effect of treatment under research-like conditions. The primary analysis for DFV890 will assess the effect on the change in IL-6 and IL-18 after 3 weeks of treatment at each dose level as compared to placebo in a dose-response model, separately for the two biomarkers. The primary analysis for MAS825 will assess the effect on the change in IL-6 compared to placebo after 3 weeks of treatment.

Trial Design:

- Parallel-group, placebo-controlled, multi-center Phase 2a study
- Patients with coronary heart disease and *TET2* or *DNMT3A* CHIP (variant allele frequency [VAF] ≥2%)
- Investigator- and participant-blinded; matching placebo
- Randomization on Day 1

The trial will be comprised of:

- A total study duration of approximately 21 weeks
- A screening period of up to 30 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 one Screening visit within the 30-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 IL-1β and IL-18, either by inhibition of the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome or direct neutralization with a bispecific monoclonal antibody (mAb), may safely and effectively lower the risk of CVD among people with known heart disease and *TET2* or *DNMT3A* CHIP (VAF ≥2%). 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, or a single s.c. dose of MAS825, to reduce key markers of inflammation related to CVD risk, such as IL-6 and IL-18, in approximately 28 people with known coronary heart disease and *TET2* or *DNMT3A* CHIP (VAF ≥2%).

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), or a single s.c. dose of MAS825 (CCI mg), or placebo.

Number of Participants:

The study population is comprised of male and female adults. A total of approximately 28 participants will be enrolled to study intervention.

Key Inclusion criteria

- Male and female participants aged between 18 - 80 years (inclusive) at the start of screening will be included.
- Participants must have a body mass index (BMI) within the range of 18 - 40 kg/m^2 at screening. 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).
- Known presence of CHIP, restricted to driver mutations in *TET2* or *DNMT3A* with a VAF ≥2%, as documented in the participant's medical history.
- 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.

- At screening, pre-malignant clonal cytopenias or clonal cytopenia of unknown significance (CCUS).
- History of ongoing, chronic, or major recurrent infectious disease, at the discretion of the Investigator, at the start of screening.
- Patients with suspected or proven immunocompromised state at screening.
- Use of any biologic drugs targeting the immune system within 26 weeks of Day 1.
- Major non-cardiac surgical or major endoscopic procedures within the past 6 months prior to the start of screening.
- Multi-vessel coronary artery bypass graft (CABG) surgery within the past 3 years prior to the start of screening.
- Planned coronary revascularization (percutaneous coronary intervention (PCI) or CABG) or any other major surgical procedure during the study (until End of Study (EOS)).
- Symptomatic Class IV heart failure (New York Heart Association [NYHA]) at the start of screening.
- Women of childbearing 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 drug administration (Day 1), during dosing and for 5 months after Day 1.

Treatment Groups:

Active treatment: DFV890 administered orally once daily (QD) at various doses (0 mg [matching placebo], 10 mg, 25 mg, 50 mg, 100 mg) over four dosing periods of approximately 3 weeks each, for a total of approximately 12 weeks of treatment or a single s.c.dose (CCI mg) of MAS825 or matching placebo. Randomized to one of five treatment sequences comprised of various doses of DFV890, or a single s.c. dose of MAS825, and/or placebo. Investigational study treatment dose adjustments and/or interruptions are not permitted.

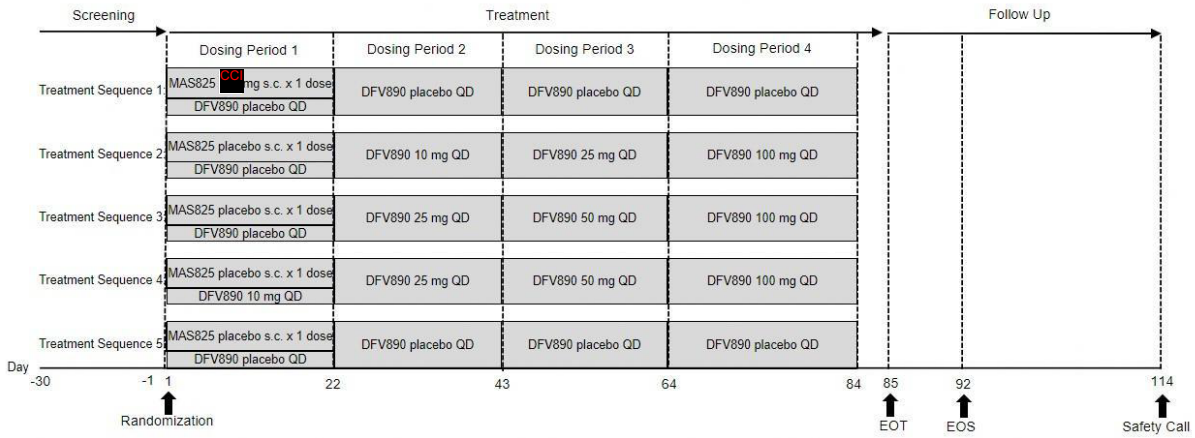
Data Monitoring/Other Committee: No

Key words

Coronary heart disease, CHIP, inflammatory marker reduction, NLRP3 inflammasome inhibitor

1.2 Schema

Figure 1-1 Study design



1.3 Schedule of activities (SoA)

The SoA lists all of 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 EOS visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse events (AEs) and concomitant medications not previously reported must be recorded on the Case Report Form (CRF).

Every effort will be made to take pharmacokinetic (PK) samples at the protocol-specified time.

The preferred sequence of assessments and data collection during study visits is shown below in Figure 1-2. For visits during which the participant is scheduled to take study treatment, all assessments will be conducted pre-dose administration.

Figure 1-2 Recommended order of assessments

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**	**Day 1**[2]	**Day 22**[2]	**Day 43**[2]	**Day 64**[2]	**EOT**	**EOS**	**Safety Follow Up Call**
Visit Numbers[1]	**1**	**101**	**102**	**103**	**104**	**199**	**299**	
Days	**-30 to -1**	**1**	**22 ±2**	**43 ±2**	**64 ±2**	**85 ±2**	**92 ±2**	**114 ±5**
Informed consent	X							
Genetic consent	X							
Inclusion / Exclusion criteria	X							
Demography	X							
Medical history/current medical conditions	X							
Pregnancy and assessments of fertility[3]	S	S	S	S	S	S	S	
Physical Examination	S	S[4]	S[4]	S[4]	S[4]	S	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	
Clinical Chemistry	X	X	X	X	X	X	X	
Hematology	X	X	X	X	X	X	X	
Coagulation Panel	X	X				X	X	
Urinalysis	X	X				X	X	
Randomization		S						
Dose administration		X[5]						
Dose uptitration			S	S	S			
Drug accountability[6]			S	S	S	S		

Period	**Screening**	**Treatment**					**Follow-Up**	
Visit Name	**Screening**	**Day 1**[2]	**Day 22**[2]	**Day 43**[2]	**Day 64**[2]	**EOT**	**EOS**	**Safety Follow Up Call**
Visit Numbers[1]	**1**	**101**	**102**	**103**	**104**	**199**	**299**	
Days	**-30 to -1**	**1**	**22 ±2**	**43 ±2**	**64 ±2**	**85 ±2**	**92 ±2**	**114 ±5**
hsCRP	X	X	X	X	X	X	X	
IL-6 and IL-18 cytokines	X	X	X	X	X	X	X	
PK blood collection for DFV890			X[7]	X[7]	X[7]	X[7]	X	
PK blood collection for MAS825		X	X	X	X	X		
Immunogenicity		X		X		X		
Blood collection for soluble biomarkers[8]		X	X	X	X	X		
Immunophenotyping[9]		X	X	X	X	X	X	
Lipid Parameters		X	X	X	X	X	X	
Target capture biomarker for MAS825[10]		X	X	X	X	X		
CYP genotyping[11]		X						
CHIP genotyping[11]		X				X		
Skin microbiome collection[12]		X	X	X	X	X		
Exploratory DNA Sampling (optional)[13]		X						
Concomitant medications	X							
Adverse Events	X							
Serious Adverse Events	X							
Study completion information							X	

Period	**Screening**	**Treatment**					**Follow-Up**	
Visit Name	**Screening**	**Day 1**[2]	**Day 22**[2]	**Day 43**[2]	**Day 64**[2]	**EOT**	**EOS**	**Safety Follow Up Call**
Visit Numbers[1]	**1**	**101**	**102**	**103**	**104**	**199**	**299**	
Days	**-30 to -1**	**1**	**22 ±2**	**43 ±2**	**64 ±2**	**85 ±2**	**92 ±2**	**114 ±5**
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] All assessments should be done pre-dose
[3] Serum pregnancy test
[4] Brief physical exam, including rash assessment
[5] Last dose administration on Day 84 at home prior to EOT visit on Day 85
[6] IMP administration in the final 2 days before the next study visit as well as timing of the final dose before the next study visit should be confirmed with the participant
[7] 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). Sample to be taken pre-dose.
[8] May include but not limited to sASC, hsIL-1b, CXCL9, CXCL10, hsIFNg, vWF, protein profiling etc. in serum/plasma
[9] May include but not limited to myeloid/lymphoid cell activation/enumeration, Whole Blood/PBMCs, etc.
[10] Serum for total IL-18, IL-18 binding protein, and total IL-1b
[11] To be performed for exploratory assessment only at End of Study
[12] Assessment may or may not be performed based on participant's exposure to antimicrobial treatments
[13] Genetic ICF must be obtained before the optional DNA sampling

2 Introduction

2.1 Study rationale

The purpose of this study is to evaluate the efficacy, safety, and tolerability of intra-individual dose escalation of oral DFV890 or a single subcutaneous (s.c.) dose of MAS825 in reducing circulating levels of inflammatory markers in adult participants with known coronary heart disease and presence of Clonal Hematopoiesis of Indeterminate Potential (CHIP). The results of the study will be used to inform future development plans for DFV890 and MAS825 in cardiovascular disease (CVD) event risk reduction.

2.2 Background

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

Atherosclerotic CVD 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 CVD 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 by approximately 15% in patients who have had a prior myocardial infarction (MI) and elevated high-sensitivity C-reactive protein (hsCRP). Patients in the CANTOS trial that had lower on-treatment levels of IL-6 and hsCRP had even greater CVD

benefit (approximately 25-35%). IL-1β signalling promotes the release of IL-6 and hsCRP, and lower on-treatment levels may identify post-MI patients with the greatest potential CVD benefit. In *post-hoc* subgroup analyses in CANTOS, two populations demonstrated substantially increased residual risk of CVD that was not completely addressed by IL-1β neutralization. First, patients with increased IL-18 levels at baseline in CANTOS had an increased risk of major adverse cardiovascular event (MACE) (15% increase in risk [95% confidence interval (CI) 3-29%, p=0.02] for each tertile increase in baseline IL-18), corroborating other preclinical findings implicating IL-18 in CVD pathogenesis (Ridker et al 2020). Second, patients in CANTOS with evidence at baseline of CHIP were found to have higher risk of MACE during the trial follow-up as compared to patients without CHIP (Svensson et al 2022).

CHIP refers to the presence of clonal populations of hematopoietic stem cells that occur in absence of diagnostic criteria for hematologic malignancy, in absence of morphological variation in blood cells, and with candidate driver gene mutations at variant allele frequency (VAF) of at least 2% in peripheral blood (Steensma et al 2015). CHIP is a disorder of aging with about 15% of people affected by 75 years of age. The risk of coronary heart disease for individuals with CHIP is approximately 2-times greater than in non-carriers matched for CVD factors including age, sex, type 2 diabetes and smoking history, with higher cardiovascular risk among individuals with large clones (VAF >10%) (Jaiswal et al 2017). Small hematopoietic clones (eg. VAF >0.03%) can be found in almost all healthy 50 - 60 year old adults; however, the functional and clinical significance are unclear (Marnell et al 2021).

In murine models, there is data suggesting a causative role of CHIP in development of both atherosclerosis and cardiac dysfunction (Fuster et al 2017, Sano et al 2018). CHIP likely contributes to CVD risk through enhanced inflammation, including increased NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) activation. Analysis of the CANTOS data revealed that patients with CHIP, particularly CHIP due to somatic mutations in the *TET2* gene, were found to have over 60% higher risk of MACE during the trial follow-up as compared to patients without CHIP (Svensson et al 2022). Mutations in epigenetic regulators (*DNMT3A* and *TET2*) account for approximately 80% of CHIP and are linked to a pro-inflammatory state (Marnell et al 2021).

CVD is a heterogenous disorder, and the presence of CHIP may mark individuals with a greater inflammatory driven contribution to CVD pathogenesis and potentially greater response to targeted anti-inflammatory therapies. Therapeutic approaches that target additional inflammatory pathways (either upstream with NLRP3 inhibition via DFV890 or downstream with IL-1β and IL-18 cytokine capture with MAS825) and selecting populations with the potential for greater response to anti-inflammatory therapy (i.e., CHIP) may further attenuate the residual CVD risk seen in CANTOS.

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 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 was evaluated in a completed Phase 1 first-in-human (FIH) trial in healthy volunteers (CDFV890A02101), a Phase 2 SARS-CoV-2 (COVID-19) trial (CDFV890D12201) and is being assessed in ongoing Phase 2 clinical trials in familial cold auto-inflammatory syndrome (CDFV890A12201), osteoarthritis (CDFV890B12201), and myelodysplastic syndrome (CDFV890G12201).

MAS825 is a CCI bispecific monoclonal antibody (mAb) against human IL-1β and human IL-18 derived from CCI (anti-IL-1β or CCI) and CCI (anti-IL-18) antibodies. MAS825 was evaluated in a completed Phase 1 FIH trial in healthy volunteers (CMAS825A02101), a Phase 2 COVID-19 trial (CMAS825F12201) and is being assessed in ongoing Phase 2 clinical trials in patients with nucleotide-binding oligomerization domain-like receptor family caspase activation and recruitment domain-containing 4 protein (NLRC4) gain-of-function (NLRC4-GoF) mutations (CMAS825D12201) and hidradenitis suppurativa (HS) (platform study CCFZ533H12201BC).

MAS825 can neutralize IL-1β and IL-18 driven effects regardless of the source of the cytokines, while DFV890 can reduce NLRP3 inflammasome driven production of IL-1β and IL-18. The relative contribution of the NLRP3 inflammasome to circulating cytokine levels in the CHIP population with known coronary heart disease is unknown. DFV890 tablets are taken orally (daily administration evaluated in this study) and MAS825 solution is injected subcutaneously (CCI , with only a single dose being evaluated in this study). A key marker of response, IL-6 levels, which robustly predicted CVD benefit in the CANTOS trial, will be used as a primary endpoint in this trial. In addition, for DFV890, IL-18 levels will be used a co-primary endpoint to capture the additional potential benefit above and beyond the IL-1β/IL-6/hsCRP pathway. IL-18 levels cannot be accurately used as an endpoint for MAS825 as the mAb binds to IL-18; although exploratory assays of total IL-18 and downstream markers of IL-18 activation, such as interferon-γ (IFN-γ), CXCL9, and CXCL10 will be incorporated.

Through the inhibition of IL-1β and IL-18, DFV890 and MAS825 have the potential to significantly reduce cardiovascular risk in patients. The safety profile, pharmacodynamic (PD) effects, and risk-benefit ratio support further studies of DFV890 and MAS825 to reduce inflammatory markers, and eventually MACE, in patients with known coronary heart disease and CHIP.

2.3 Benefit/Risk assessment

It is not known whether there will be a benefit for participants with known coronary heart disease and CHIP with DFV890 or MAS825 treatment. The CANTOS trial demonstrated reduction in cardiovascular risk in this population with canakinumab and IL-1β inhibition. Improved efficacy over canakinumab may be achieved by inhibiting both IL-1β and IL-18 with

either NLRP3 inhibition or direct neutralization with a bispecific mAb; however, this has not yet been demonstrated.

Based on the clinical experience with DFV890 and MAS825 from Phase 1 FIH studies (CDFV890A02101 and CMAS825A02101), the Phase 2 studies in patients with COVID-19 (CDFV890D12201 and CMAS825F12201), safety monitoring in ongoing clinical trials, relevant non-clinical findings, the biological understanding of the pathways and their relevance to CVD, the overall risk-benefit of both compounds is, to date, considered favorable. The available clinical, safety, and laboratory assessments from the FIH studies and the COVID-19 study show that DFV890 and MAS825 are generally well-tolerated and have manageable safety profiles. Potential compound risks are described in more detail in the following sections and the respective Investigator's Brochures (IBs).

In summary, based on the available non-clinical and clinical data, the potential risks to be considered shared by both DFV890 and MAS825 include potential risks related to: 1) infections, 2) vaccinations, 3) changes in hematologic parameters, 4) hypersensitivity to any component of the drug product, and 5) considerations for women of child-bearing potential (WOCBP). The potential risks to be considered for DFV890 include: 1) self-limiting skin rash/pruritis, 2) renal abnormalities in preclinical models, and 3) drug interactions linked to metabolism by CYP2C9 and CYP3A4 enzymes. The potential risks to be considered for MAS825 include: 1) immunogenicity (IG) and 2) metabolic abnormalities. In addition to the risks noted above, there may be risks for DFV890 or MAS825 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 IBs for additional information.

2.3.1 Risks shared by both DFV890 and MAS825

2.3.1.1 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 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 viable and fertile). CCI [redacted] These findings were not seen in a previous 13-week toxicology monkey study, which had higher systemic exposures.

Similarly, MAS825 is not expected to elicit broad immune suppression, rather selectively neutralize the pro-inflammatory IL-1β and free/bioactive IL-18.

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, immune suppressive treatments are prohibited to be administered 28 days or 5 half-lives, whichever is longer, prior to screening and concurrent use of these treatments is also prohibited. 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 thereof (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.

2.3.1.2 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 (Day 1).

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 and MAS825, specifically targeting the NLRP3 inflammasome or downstream cytokines IL-1β and IL-18, 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 or MAS825.

2.3.1.3 Potential risk and recommended monitoring of hematological parameters

For DFV890, transient asymptomatic decreases in absolute neutrophil count (ANC) and white blood cell (WBC) 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).

For MAS825, transient decreases in WBC and ANC may also occur with mAb inhibition of IL-1β as seen in the CANTOS study with canakinumab. In addition, transient decreases in platelet counts were observed following canakinumab treatment of inflammatory disorders, and dose-dependent decreases in platelet counts were observed in small numbers of patients in CANTOS. Based on the safety data available from the canakinumab clinical trials program, no correlation between reduced platelet counts and bleeding has been identified.

As a precaution, all patients with suspected or known immunodeficiencies will be excluded from this study. In addition, patients with cytopenias (such as persistent neutropenia (ANC < 1.8×10^9/L), and/or thrombocytopenia (platelets < 150×10^9/L)) will also be excluded from entry into this study (see Section 5.2). Complete blood counts will be monitored in this study. Subjects should be alert for the appearance of symptoms (bleeding from gums or nose) and signs of thrombocytopenia (purpura, petechiae, ecchymoses). Investigators should consider treatment of severe thrombocytopenia (<$50x10^9$/L) based on clinical assessment and/or evidence of bleeding in consultation with a hematologist, as appropriate.

2.3.1.4 Potential risk and recommended treatment of hypersensitivity reactions

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

As with most biologic compounds, administration of MAS825 carries the risk of anaphylaxis and/or hypersensitivity-type reactions. In the event of such a reaction, treatment with antihistamines and glucocorticoids may be considered, as clinically indicated. Depending on severity, patients may also require supplemental oxygen, volume expansion, catecholamines, and transfer to an intensive care setting. Plasmapheresis to decrease the systemic concentration of MAS825 may be considered dependent on the patient's condition. Patients should be observed for at least four hours after resolution of signs and symptoms, and those who have experience severe infusion reactions should be closely observed for 24 hours after resolution because of the risk of a biphasic episode. Based on the clinical experience to date with MAS825, CCI (CCI, anti-IL-1β mAb component), and CCI (anti-IL-18 mAb component), the risk of a hypersensitivity reaction is considered low.

2.3.1.5 Potential risks and guidance related to WOCBP

At this stage of development, DFV890 has not yet been studied in reproductive toxicology 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. Based on an *in vitro* induction of CYP3A4, there is a slight potential risk for a drug-drug interaction (DDI) of DFV890 with hormonal contraception at high exposures, therefore oral hormonal contraception is allowed, but must be supplemented with a barrier method, preferably a male condom. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

There is no available reproductive toxicity data for MAS825 nor clinical experience with the mAb in human pregnancies. CCI to other CCI antibodies, MAS825 may have CCI cross-placental transfer. The potential of placental transfer can be influenced by many factors (maternal level of the total CCI specific antibodies and their subclasses, gestational age and placental integrity) (Palmeira et al 2012).

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

- Practice highly effective contraception for at least CCI 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 (with oral hormonal contraception supplemented by a barrier method, preferably a male condom),
- Practice highly effective contraception for CCI months following the first drug administration on Day 1 (when participants may have received a single dose of MAS825 s.c., which is longer than the guidance for DFV890 for highly effective contraception until 7 days following completion of DFV890 treatment)

Pregnant and/or lactating women are also excluded.

Additionally, WOCBP should avoid becoming pregnant while their male partners are participating in this study. Male participants 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 (IUD) or hormonal contraception and for at least 90 days following completion of 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 study treatment and for at least 90 days following completion of treatment.

2.3.2 DFV890 compound risks

2.3.2.1 Potential risk of skin rash and recommended monitoring

In the CDFV890A02101 FIH study, 12 subjects out of 94 treated with DFV890 reported maculopapular rash and/or pruritus. The subjects had been administered DFV890, either after a single dose of 100 milligram(s) (mg) as crystalline tablet (n=1) or 600 mg as a spray-dried dispersion (SDD) suspension (n=1), or after 30 mg once daily (QD) as crystalline suspension (n=2), 100 mg QD (n=3) or 200 mg QD (n=2) as SDD suspension, or 50 mg twice daily (b.i.d.) as encapsulated crystalline tablet (n=3). For 10 of these subjects, these adverse events (AEs) led to treatment discontinuation. These AEs were transient, of mild to moderate intensity, and not associated with other symptoms, clinical findings, or changes in laboratory parameters. These AEs generally started within 1 to 17 days after initiation of treatment with DFV890 (within 1 to 9 days after a single dose, or within 7 to 17 days after initiation of multiple dose administration). They resolved within 1 to 18 days after onset (rashes within 3 to 18 days and pruritus within 1 to 5 days); in all cases without concomitant treatment. None of these were associated with other symptoms, clinical findings or changes in clinical laboratory parameters.

In the completed CDFV890D12201 Phase 2 study in COVID-19, 70 participants in the active arm were administered DFV890 50 mg b.i.d. + 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 CHIP, 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.

2.3.2.2 Potential risk of renal abnormalities and recommended monitoring

In non-clinical studies of DFV890, analysis of the data from the 13-week GLP repeat-dose study in rats showed unexpected adverse effects in kidneys consistent with obstructive nephropathy at doses ≥100 mg/kg/day accompanied by changes in kidney-specific urinary and blood parameters. In the non-clinical monkey studies, up to 13 weeks (4- and 13-week GLP studies, at doses up to CCI mg/kg/day) no adverse effects on kidneys or renal function were observed. 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).

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

Clinical studies to investigate drug-drug interactions using cytochrome P450 (CYP) substrates/modulators and DFV890 have not been performed yet, but, based on *in vitro* data, DFV890 PK 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 plasma exposure 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 2-fold of some oral hormonal contraceptives which are CYP3A4 substates (e.g., ethinylestradiol), by 20-30%. Therefore, oral hormoned-based contraceptives may not be considered as highly effective contraception method (unless supplemented by a barrier method, preferably a male condom) 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.

2.3.3 MAS825 compound risks

2.3.3.1 Potential risk for immunogenicity

As with other therapeutic antibodies, there is a possibility of MAS825 inducing an immune response in human subjects. The consequence of IG may be altered pharmacokinetics (PK) and PD properties of the drug, leading to a potential loss in efficacy. There is also a theoretical possibility of immune-mediated reactions. It is important to note that the occurrence of anti-drug antibodies (ADA) and resulting ADA-mediated immune reactions in animals are generally not considered predictive of the same responses in humans and that severe responses to mAb in humans are rare (Bugelski, Treacy 2004, Rojko et al 2014). Regardless, ADA monitoring is included in this study.

In vitro evaluation of MAS825 has shown a low risk for immunogenicity. In the FIH study with MAS825 (CMAS825A02101), immunogenicity in response to MAS825 CCI [redacted] across different cohorts and time points CCI [redacted]. CCI [redacted] exhibited an unexpected PK/PD profile or experienced adverse effects suggestive for immunogenicity.

2.3.3.2 Potential risk for metabolic abnormalities

In preclinical studies of MAS825, two isoforms of LDL receptor (LDLR) were identified as CCI [redacted] off-targets; however, no effects on cholesterol nor LDL were observed in the 26-week toxicity study in non-human primates (marmosets). MAS825 was tested in a functional assay by monitoring uptake of LDL in CCI [redacted] (human cell line expressing LDLR). MAS825 inhibited LDL uptake from CCI [redacted] µg/mL, reaching CCI [redacted]% inhibition at [redacted] mg/mL, providing a further safety factor of CCI [redacted] to the predicted Cmax of CCI [redacted] µg/mL at CCI [redacted] mg/kg intravenous (i.v.) for human. Lipid parameters will be monitored in this study.

2.3.4 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, SoA.

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 CHIP	• Serum levels of IL-6 and IL-18 at 3 weeks after the start of a DFV890 dosing period
• To evaluate the effect of MAS825 versus placebo to reduce circulating levels of inflammatory markers in participants with coronary heart disease and CHIP	• Serum level of IL-6 at 3 weeks after a single s.c. dose of MAS825
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the safety and tolerability of DFV890 and MAS825 in participants with coronary heart disease and CHIP	• Adverse events, and parameters from safety assessments, including vital signs, electrocardiograms (ECGs), and laboratory assessments (urine and blood)
• To assess the PK of DFV890 in participants with coronary heart disease and CHIP	• Plasma trough concentrations (Ctrough) of DFV890 at steady-state
• To assess the PK of MAS825 in participants with coronary heart disease and CHIP	• Serum concentrations of MAS825 after a single s.c. dose of MAS825
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
• To assess the PK of IBW042 a metabolite of DFV890 in plasma	• Plasma Ctrough of IBW042 at various dose levels of DFV890
• To explore whether individual variation in the CYP2C9 gene related to drug metabolism confer differential PK response to DFV890	• Plasma Ctrough of DFV890 and its metabolite, IBW042, as well as CYP2C9 genotype
• To assess the effect of DFV890 and MAS825 on PD and inflammation-related, and CVD-related biomarkers (including PK/PD relationships)	• PD and inflammation-related markers may include but are not limited to hsCRP, soluble ASC, total IL-1β, CXCL9, CXCL10, hsIFN-γ, vWF, myeloid/lymphoid cell activation/enumeration by flow cytometry, and total IL-18 (MAS825 only) • CVD-related biomarkers may include but are not limited to lipid parameters (e.g., LDL, Lp(a), apolipoproteins) • DFV890 and MAS825 concentrations at or up to corresponding time point

Objective(s)	Endpoint(s)

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

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

3.1 Primary estimands

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

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

The estimand is defined by the following attributes:

1. Population: participants with known coronary heart disease and *TET2* or *DNMT3A* CHIP (VAF ≥2%) and potential SoC CVD prevention medication
2. Endpoints: Serum levels of IL-6 and IL-18 at 3 weeks after the start of a dosing period for DFV890 and serum level of IL-6 at Week 3 for MAS825
3. Treatment of interest: MAS825 or placebo single dose, DFV890 QD or DFV890 placebo QD
4. Handling of intercurrent events: see Table 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	-	Data collected after this intercurrent event will not be used for this estimand
Incidence of a new major CVD event (e.g., myocardial infarction, stroke, etc.)	-	Data collected after this intercurrent event will not be used for this estimand
Change in SoC CVD prevention medication	-	All data collected after this intercurrent event will be used for this estimand

Intercurrent event	Details (if necessary)	Handling of event
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)	Only the assessment immediately following the event will be excluded for the purpose of this estimand
Nonadherence to study treatment (DFV890 only)	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 SoC CVD prevention medication, reflects what is referred to as the hypothetical strategy, which aims to mimic a scenario in which the intercurrent event did not actually occur and all participants had adhered to the randomized treatment throughout the course of the study. To enable this strategy, data from various assessments taking place after the event will be excluded from the primary analysis, as described in the table. The exception to this is changes to SoC CVD prevention medication, which will be handled by a treatment policy strategy, in which any occurrence of the event is ignored and the subsequent data are included in the analysis.

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

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

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

On Day 1, participants will receive the first oral dose of DFV890 or placebo and the single s.c. dose of either MAS825 or placebo. None of the treatment sequences include a combination of both active DFV890 and active MAS825. After initial dosing, assessments will be conducted at site, as specified in Section 1.3, the SoA. Participants will then be provided with a sufficient amount of study medication for daily dosing until their next scheduled visit.

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

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

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 five treatment sequences comprised of various uptitrating doses of DFV890, or a single s.c. dose of MAS825, and/or placebo. The rationale behind the up-titration of DFV890 doses within sequences is the efficiency for evaluating cytokine reductions that result from intra-individual measurements. Uptitration also may improve tolerability by decreasing the risk for rash; however, this has yet to be demonstrated. Clinical experience from prior clinical trial data with DFV890 suggests that most AEs, especially the emergence of rash, should occur within the first 17 days of dosing and therefore limited carry-over of the initiation of AEs into subsequent dosing periods is expected to occur. The uptitration of DFV890 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 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 for DFV890 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 clinical 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 evidence supports a causal role, no pharmacologic intervention trials have yet demonstrated that IL-18 inhibition reduced CVD risk.

Study Design Aspect	Rationale
	For MAS825, the only primary endpoint is IL-6 levels measured 3 weeks after a single s.c. dose (IL-18 is not a primary endpoint for MAS825) as the bispecific mAb binds to IL-18 and IL-18 levels cannot be robustly measured in this context but downstream markers of IL-18 will be evaluated.
Analysis of primary endpoints	For participants randomized to receive active DFV890 treatment, 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 and IL-18 levels across all dose levels and fits a dose-response relationship, will be utilized to quantify placebo-adjusted reductions at the highest tested dose level, 100 mg daily DFV890. 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 for DFV890 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. For participants randomized to receive active MAS825 treatment, the uptitration and dose-response modeling is not applicable to a single dose in the MAS825 active treatment sequence. The IL-6 response to MAS825 will be measured at approximately 3 week intervals (corresponding to DFV890 uptitration intervals) during the approximately 12 week treatment period after only a single dose level. The level of IL-6 obtained 3 weeks after the single dose of CCI mg MAS825 s.c. will be used for the primary endpoint, as the peak observed reduction of IL-6 (when measured q3 weeks over the 12 week treatment period) is expected to occur at that point.

Study Design Aspect	**Rationale**
Treatment Sequences	In Treatment Sequence 2 and Treatment Sequence 3, participants begin with placebo treatment and are followed with increasing doses of DFV890. Treatment Sequence 4 and Treatment Sequence 5 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 5, in addition, will generate more placebo data, which is useful for the primary analysis. More participants are allocated to Treatment Sequence 2 and Treatment Sequence 3 as they will contribute intra-individual placebo data, thereby making analyses more efficient. Treatment Sequence 1 is the only sequence that contributes data for a single dose of active MAS825.
Randomization	Participants will be randomized in a 4:4:4:1:1 ratio to the 5 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 5 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.
Duration of study periods	DFV890 treatment sequences: 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 the first 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. MAS825 treatment: the single dose allows benchmarking of NLRP3 inhibition effects relative to direct biologic neutralization of IL-1β and IL-18. MAS825 will result in the CCI reduction of CCI IL-1β and IL-18 levels in serum and effective neutralization of IL-

Study Design Aspect	Rationale
	1β as well as IL-18 with reductions captured at each 3 week assessment in the 12 week treatment period. 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

DFV890

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. Depending on the randomization to one of five treatment sequences, 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 (or placebo), 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 FIH study in healthy volunteers (Study CDFV890A02101). In the FIH study, an *ex vivo* whole blood assay of lipopolysaccharides (LPS)-stimulated IL-1β secretion was used as a PD readout to estimate pharmacological activity. CCI [redacted] the highest dose of 100 mg DFV890 given QD 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 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 IB for further details). Skin reactions were reported when dosed with 30 mg, 100 mg, or 200 mg suspension QD, or 50 mg tablet b.i.d. Skin reactions were not reported when dosed as 10 mg suspension QD or 25 mg tablet b.i.d. 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 the mechanism causing rash is likely T-cell driven. 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 CYP2C9 and CYP3A4 is considered to be the major clearance mechanism for DFV890 with fractional hepatic contributions of CCI% and CCI% 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-fold higher compared to normal (extensive) metabolizers (e.g., *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 (CCI) and CCI (CCI CCI) based on PK in healthy participants (majority were normal CYP2C9 metabolizers). Up to CCI-fold lower safety margins are expected in patients who are intermediate or poor CYP2C9 metabolizers (for further details see IB). Supported by sufficient safety margins, all eligible participants irrespective of CYP2C9 genotype are allowed to participate in the study.

MAS825

Depending on the randomization to one of five treatment sequences, a single dose of CCI mg MAS825 or placebo will be injected subcutaneously on Day 1.

MAS825 has been evaluated in a FIH single ascending dose study up to CCI mg/kg i.v. and CCI mg s.c. in healthy volunteers, in COVID-19 patients (single dose with 10 mg/kg i.v.), in HS patients (CCI mg every CCI or every CCI) as well as in NLRC4-GoF patients (CCI mg/kg i.v. every CCI) without any drug-related Serious Adverse Events (SAEs); the PK of MAS825 in humans is CCI .

In a FIH single ascending dose study MAS825 peak serum concentrations were observed CCI the CCI i.v. infusion. The median Tmax was approximately 3 hours from the start of the infusion (120 minutes). The Cmax and AUCinf increased with increasing doses in a CCI manner. The mean terminal elimination half-life (T1/2) is ranging from approximately CCI days at CCI mg/kg to approximately CCI days at CCI mg/kg. Volume of distribution was CCI with the mean Vz between CCI L and CCI L. Additionally, MAS825 was administered subcutaneously at a dose of CCI mg, CCI mg and CCI mg. The mean Cmax of MAS825 ranged from CCI to CCI ug/mL at about CCI days post dose. Exposure in CCI at CCI mg/kg i.v. is approximately 1.16-fold higher as in CCI subjects while after CCI mg s.c. the exposure was 1.25-fold higher compared to

the CCI subjects based on AUCinf. For CCI cohorts CCI mg s.c. dose compared to the CCI mg/kg i.v. dose, bioavailability was approximately CCI %. For CCI cohorts CCI mg s.c., CCI mg s.c. and CCI mg s.c. dose compared to the CCI mg/kg i.v. dose, bioavailability were approximately CCI %, CCI % and CCI %.

The single s.c. dose of MAS825 CCI mg is justified by: the dose is predicted to lead to rapid and CCI neutralization of all systemic free IL-1β and IL-18. The exposure after CCI mg s.c. will exceed the in-vitro CCI for IL-1β and IL-18 for more than 150 days after a single dose. The dose and the Cmax is lower than the well tolerated MAS825 dose administered to healthy volunteers with no identified safety concerns (CCI mg/kg i.v.). CCI (anti-IL-18 mAb) has been administered to healthy subjects in doses up to CCI mg/kg i.v. and was well tolerated. Phase 2 studies with CCI in CCI and CCI patients with CCI mg/kg i.v. monthly are currently ongoing. In the CCI study, an arm with a roughly three fold lower dose of CCI mg s.c. monthly is included. In addition, CCI (anti-IL1b mAb) is approved in doses up to 300 mg every 4 weeks. In the MAS825 26-week toxicology study, in non-human primates (marmoset), the highest tested dose, CCI mg/kg i.v., CCI, did not result in any MAS825-related effects.

IG in response to MAS825 CCI across different cohorts and time points in the FIH study CCI. These results suggest that MAS825 can be safely used for further clinical trials for indications.

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 or MAS825.

For DFV890, the oral tablet formulation will contain either active drug or placebo, and will be indistinguishable in appearance and taste.

For MAS825, matching placebo in individual CCI mL glass vials each containing 0 mg/1 mL as a liquid solution will be provided, and will be indistinguishable in appearance.

4.5 Rationale for public health emergency mitigation procedures

During a public health emergency as declared by local or regional authorities e.g., pandemic, epidemic, or natural disaster, mitigation procedures to ensure participant safety and trial integrity may be implemented. Notification of the public health emergency as declared by local or regional authorities should be discussed among investigators and Novartis. All procedures adapted to the situation must be submitted, if required as per local regulations, through a protocol amendment for approval by local or regional Health Authorities and Ethics Committees prior to implementation of mitigation procedures.

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 EOS 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 treated participants should have a safety follow-up conducted at least 30 days after last administration of study treatment. This follow up may be a phone call or a study site visit. The information collected is kept as source documentation. 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 CHIP with somatic mutations in *TET2* or *DNMT3A* (VAF ≥2%). In this study, approximately 28 participants will be randomized.

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. Male and female participants aged between 18 - 80 years (inclusive) at the start of screening will be included.
3. Subjects must have a body mass index (BMI) within the range of 18 - 40 kg/m^2. BMI = Body weight (kg) / [Height (m)]^2 at screening.
4. Documented spontaneous 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 Left bundle branch block (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

5. Known presence of CHIP, restricted to driver mutations in *TET2* or *DNMT3A* with a VAF ≥2%, as documented in the participant's medical history.

   Participants may have a second or additional mutation in a different CHIP driver gene (e.g., *DNMT3A* + *JAK2*); however, the most common mutation (highest VAF) must be in either *TET2* or *DNMT3A*. Patients may have more than one different CHIP-driver mutation in the same gene (e.g., two unique known CHIP mutations in *TET2*) but at least one unique mutation must be present at VAF ≥2%.
6. 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.
7. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

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 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 PD 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 participant's history.
5. 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.
6. WOCBP, 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 drug administration (Day 1), during dosing and for 5 months after the single s.c.dose administration of MAS825 or placebo dose. Highly effective contraception methods include:
   - Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the participant). 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 participants on the study, the vasectomized male partner should be the sole partner for that participant.
   - Use of oral (estrogen and progesterone), injected, or implanted hormonal methods of contraception or placement of an IUD 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, thus hormonal contraceptives must be supplemented by a barrier method, preferably a male condom. In case of use of oral contraception, women should be stable on the same pill for a minimum of 3 months before taking study treatment.

   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).

   Women are considered post-menopausal and not of child bearing 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 prior to Day 1. 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).

7. Pregnant or nursing (lactating) women.
8. Sexually active males unwilling to use a condom during intercourse while taking study treatment and for 90 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.
9. 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).
10. At screening, pre-malignant clonal cytopenias or clonal cytopenia of unknown significance (CCUS). Cytopenia in the context of clonal abnormalities is defined as an acquired and persistent anemia (hemoglobin < 12 g/dL in females and < 13 g/dL in males), neutropenia (ANC < 1.8×10^9/L), and/or thrombocytopenia (platelets < 150×10^9/L) that is not explained by another known or identifiable condition.
11. History of ongoing, chronic, or major recurrent infectious disease, at the discretion of the Investigator, at the start of screening.
12. Live vaccinations within 1 month prior to Day 1 or live vaccinations planned during the trial.
13. 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

    or (c) those requiring systemic or local treatment with any immune modulating agent in doses with systemic effects, e.g., high dose oral or 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.
14. Use of any biologic drugs targeting the immune system (for example, but not limited to: tumour necrosis factor (TNF) blockers, anakinra, rituximab, abatacept, tocilizumab, or canakinumab) within 26 weeks of Day 1. Refer to Section 6.8.2.
15. Known diagnosis of a systemic auto-immune disease (e.g., systemic lupus erythematosus, etc.).
16. Current use or within 5 half-lives of use of colchicine at start of screening.
17. Participants with a MI resulting from percutaneous coronary interventions (PCI) or coronary artery bypass graft (CABG) procedures.
18. Major non-cardiac surgical or major endoscopic procedure within the past 6 months prior to the start of screening.
19. Multi-vessel CABG surgery within the past 3 years prior to the start of screening.

20. Planned coronary revascularization (PCI or CABG) or any other major surgical procedure during the study (until EOS).
21. Symptomatic Class IV heart failure (New York Heart Association [NYHA]) at the start of screening.
22. 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
23. Uncontrolled hypertension (defined as systolic blood pressure (SBP) >160 mmHg or diastolic blood pressure (DBP) >100 mmHg) at screening.
24. Uncontrolled diabetes, as defined by the Investigator, at screening. Clinical and laboratory evidence of uncontrolled diabetes may include but are not limited to: hemoglobin A1C >9%, recurrent fasting glucose >200 mg/dL, frequent urination/thirst not explained by other causes, etc.
25. 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.
26. 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. The Investigator should be guided by the following criteria:
    - Any single parameter may not exceed 2x upper limit of normal (ULN)
27. Uncontrolled asthma at the start of screening, as defined by the Investigator, with high likelihood of requiring systemic corticosteroids during the 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 QD 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 (CRF). 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 CRF.

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.

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

Details on the requirements for storage and management of MAS825 and instructions to be followed for prescribing/dispensing and administering MAS825 are outlined in the Pharmacy Manual.

Refer to the Section 5.3.1 for details of dosing and food intake related to DFV890.

6.1 Study treatment(s)

The investigational drugs, DFV890, MAS825, or placebo, will be prepared by the Sponsor as indicated in Table 6-1. DFV890 or placebo will be administered orally with food QD. MAS825 or placebo will be administered subcutaneously once on Day 1.

Table 6-1 Investigational and control drug

Treatment Title	DFV890 10 mg	DFV890 25 mg	DFV890 10 mg Placebo	DFV890 25mg Placebo	MAS825	MAS825 Placebo
Treatment Description	10 mg tablet QD	25 mg tablet QD	0 mg tablet QD	0 mg tablet QD	CCI mg single injection	0 mg single injection
Type	Drug	Drug	Drug	Drug	Biologic	Biologic
Dose Formulation	Tablet	Tablet	Tablet	Tablet	Solution for injection	Solution for injection
Unit Dose Strength(s)	10 mg	25 mg	0 mg	0 mg	CCI mg/mL	0 mg/mL
Dosage Level(s)	10 mg QD	25 mg QD	0 mg QD	0 mg QD	CCI mg single dose	0 mg single dose
Route of Administration	Oral	Oral	Oral	Oral	Injection	Injection
Use	Experimental	Experimental	Placebo	Placebo	Experimental	Placebo
IMP	Yes	Yes	Yes	Yes	Yes	Yes
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	Study treatment will be provided in blinded HDPE bottles of 35 tablets. Each bottle will be labeled as required per country requirement	Study treatment will be provided in blinded HDPE bottles of 35 tablets. Each bottle will be labeled as required per country requirement	Study treatment will be provided in blinded HDPE bottles of 35 tablets. Each bottle will be labeled as required per country requirement	Study treatment will be provided in blinded HDPE bottles of 35 tablets. Each bottle will be labeled as required per country requirement	Study treatment will be provided in vials via open label supply. Each vial will be labeled as required per country requirement	Study treatment will be provided in vials via open label supply. Each vial will be labeled as required per country requirement

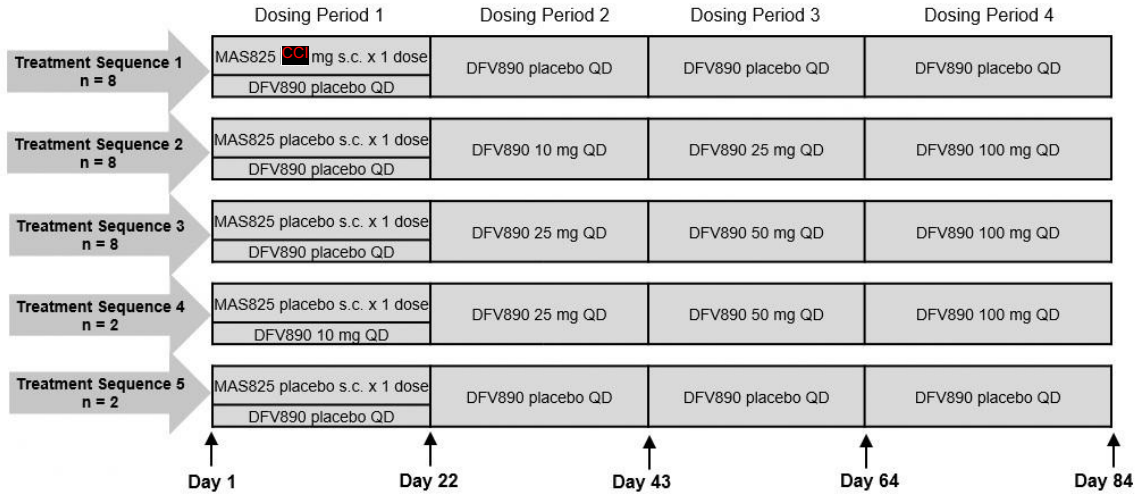
6.1.1 Additional study treatments

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

6.1.2 Treatment arms/group

Participants will be assigned at Day 1 to one of the following 5 treatment sequences in a ratio of 4:4:4:1:1, as shown in Figure 6-1 below.

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.

Unblinded Investigator staff will identify the treatment to administer to the participant by contacting the IRT and obtaining the treatment assignment.

MAS825

Unblinded Investigator staff will select the study treatment to administer to the participant and record the batch number on the accountability logs accordingly.

DFV890

A unique medication number is printed on the study medication label of each bottle. Investigator staff will identify the study medication kits to dispense to the participant contacting the IRT and obtaining the medication number(s). DFV890 drug accountability and reconciliation data is recorded 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.

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 Quality Assurance.

MAS825 and placebo will be provided as open-label bulk supply. All study treatment must be prepared by an unblinded pharmacist to ensure treatment masking. Please refer to the Pharmacy Manual for complete preparation instructions.

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. All bottles of DFV890 or placebo 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. The Investigator must provide accountability also for locally sourced materials used for administration of MAS825 or placebo (e.g., syringes).

As DFV890 or placebo study treatment is administered at home, e.g., oral medication, participants will be asked to return all unused study treatment and packaging at the end of the study 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

Not applicable.

6.2.3 Instruction for prescribing and taking study treatment

Participants will be randomized to one of five treatment sequences. Based on the treatment sequence assignments, participants will start on either a combination of MAS825 and placebo, DFV890 and placebo, or placebo and placebo on Day 1, and then, within each DFV890 treatment sequence, participants will receive up-titrating doses of DFV890 or placebo at the corresponding study visits.

Participants will be dispensed with DFV890 double-blind high density polyethylene (HDPE) bottle packs for each 3-week dosing period to ensure the appropriate dosage is being taken while maintaining the blind.

Table 6-2 DFV890 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 Day 21)*	DFV890 10 mg	1 tablet of DFV890 10 mg	QD with food for 3 weeks
	DFV890 0 mg	1 tablet of 10 mg matching placebo	
Dosing Period 2 (Day 22 to 42)	DFV890 25 mg	1 tablet of DFV890 25 mg +1 tablet of 10 mg matching placebo	QD with food for 3 weeks
	DFV890 10 mg	1 tablet of DFV890 10 mg + 1 tablet of 25 mg matching placebo	
	DFV890 0 mg	1 tablet of 10 mg matching placebo + 1 tablet of 25 mg matching placebo	
Dosing Period 3 (Day 43 to 62)	DFV890 50 mg	2 tablets of DFV890 25 mg	QD with food for 3 weeks
	DFV890 25 mg	1 tablet of DFV890 25 mg + 1 tablet of 25 mg matching placebo	
	DFV890 0 mg	2 tablets of 25 mg matching placebo	
Dosing Period 4 (Day 63 to 84)	DFV890 100 mg	4 tablets of DFV890 25 mg	QD with food for 3 weeks
	DFV890 0 mg	4 tablets of 25 mg matching placebo	

*Participants assigned to Treatment Sequence 1 will receive a single s.c. dose of MAS825 CCI mg on Day 1 and then receive DFV890 0 mg matching placebo the remainder of the treatment period; participants assigned to Treatment Sequences 2-5 will receive a single s.c. dose of MAS825 0 mg matching placebo on Day 1 and then receive DFV890 active or placebo according to their assigned treatment sequence.

DFV890 up-titration will occur at the study visits during the Treatment Period as indicated in Section 1.3, SoA.

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 (i.e., the 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 tables for the given period runs out.

If a participant runs out of tablets before the next visit can be scheduled, a visit should be scheduled as soon as possible to only perform safety assessments described in Section 8.4. Other non-safety assessments described in Section 8.3 must not be performed. Participants will then start the next dosing period as applicable.

The last DFV890 dose will be taken on Day 84 prior to the EOT visit on Day 85. Allowable visit windows are listed in Section 1.3, SoA. To achieve the target doses for each time period, please refer to Table 6-3 below.

Table 6-3 Dose and treatment schedule

Investigational / Control Drug (Name and Strength)	Dose	Number of tablets	Frequency and/or Regimen
MAS825 CCI mg/mL	CCI mg	N/A	Once on Day 1 by s.c. injection
MAS825 0 mg/mL	0 mg	N/A	Once on Day 1 by s.c. injection
DFV890 10 mg or matching placebo	10 mg	1	QD with food for 3 weeks
DFV890 25 mg or matching placebo	25 mg	1	QD with food for 3 weeks
DFV890 25 mg or matching placebo	50 mg	2	QD with food for 3 weeks
DFV890 25 mg or matching placebo	100 mg	4	QD with food for 3 weeks

Participants are to take DFV890 or placebo QD 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 collection of 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 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 12 hours 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.

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

6.3 Measures to minimize bias: randomization and blinding

6.3.1 Treatment assignment, randomization

On Day 1, all eligible participants will be randomized via IRT to one of the treatment arms. The unblinded pharmacist or his/her unblinded 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 and assignment to either MAS825 or placebo.

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 or by a designated member following Contract Research Organization (CRO) procedures.

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

With the exception of any unblinded site staff identified below, all site staff (including study Investigator and 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.

MAS825 and matching placebo will be supplied as open-label bulk supply, thus an unblinded pharmacist who is independent of the study team will be required in order to maintain the blind. The unblinded pharmacist or delegate will receive randomization assignments via the IRT system. Appropriate measures must be taken by the unblinded pharmacist or delegate to ensure that the treatment assignments are concealed from the rest of the site staff.

Sponsor staff or delegate

The following unblinded sponsor roles are required for this study:

- Unblinded field monitor(s): The unblinded field monitors are required to review drug accountability and allocation at site. The unblinded monitors are not provided with a randomization list directly but will be unblinded through review of source documentation compiled by the unblinded pharmacist, which details treatment allocation to individual participants.
- Unblinded clinical staff managing drug re-supply to site: The unblinded clinical staff managing drug re-supply will be notified directly by the unblinded field monitors or unblinded site staff that additional drug supply is needed for drug administration at the site. The unblinded clinical staff will have no other study responsibilities.
- Unblinded sample analyst(s) (PK, IG): The unblinded sample analysts will receive a copy of the randomization schedule (via a 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 making purposes, as outlined in Table 6-4. 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 6-4 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 site staff, e.g. pharmacy staff	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 to 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 reasons to take the study treatment as prescribed. Compliance will be assessed by the Investigator and/or 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. Compliance measures documented in the CRF, as reported by the participant, include: 1) dosing period percent compliance, assess by pill count; 2) any missed doses within the 2 days prior to the study visit; and 3) time the participant took the last dose on the day prior to the study visit. Assessments of compliance at study visits are reflected in Section 1.3, SoA.

All study treatment dispensed and returned must be recorded in the Drug Accountability and Returns Management functionality in the IRT system.

6.4.1 Recommended treatment of adverse events

The following recommendations 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 (CTC) AE 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 an assessment for a rash AE, a skin swab may be obtained for exploratory skin microbiome assessments (as described in Section 8.5.1). Therapies to manage the rash should not be delayed in order to obtain a skin swab of the rash. However, if practical, skin swabs of the rash prior to initiating topical therapy are preferable.

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

Medications 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 24 hours 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 CRFs.

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, MAS825, 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 a 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 CCI -fold.When dosing DFV890 together with strong or moderate CYP3A inhibitors or moderate dual CYP3A/CYP2C9 inhibitor, CCI effect is expected for participants with normal CYP2C9 activity and intermediate metabolizers (AUC-fold increase CCI), while CCI effect is very likely for poor CYP2C9 metabolizers (AUC-fold change CCI).

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 2-fold or some oral hormonal contraceptives (e.g., ethinylestradiol) by 20-30%. 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 6-5 and prohibited drugs are listed in Table 6-6.

Table 6-5 Drugs to be used with caution with DFV890

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, indinavir, 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 reduced 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. For example, blood concentrations of statins, such as atorvastatin, may be decreased with concomitant therapy with DFV890. Low density lipoprotein (LDL) cholesterol levels will be monitored at study visits approximately every 3 weeks and statin doses may be changed, if clinically indicated, during the course of the study to achieve appropriate LDL goal levels specific to a patient's cardiovascular risk profile. Statin dose changes during the trial should be recorded, as described in Section 6.2.2.

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.

MAS825

No formal DDI studies have been conducted with MAS825. Elimination pathways of mAb are distinct from metabolic pathways of small molecules. These molecules are cleared from the body by a combination of non-enzymatic metabolism processes whereas small molecular weight drugs are typically eliminated through CYP450-mediated oxidation pathways. Therefore, small molecular weight drugs are not expected to affect the PK of MAS825.

The expression of hepatic CYP450 enzymes may be suppressed by the cytokines that stimulate chronic inflammation, such as IL-1β and IL-18. Thus, CYP450 expression may be normalized when potent cytokine inhibitory therapy, such as MAS825, is introduced. This is clinically relevant for CYP450 substrates with a narrow therapeutic index where the dose is individually adjusted. On initiation of MAS825 in patients being treated with this type of medicinal product, therapeutic monitoring of the effect or of the active substance concentration should be performed and the individual dose of the medicinal product adjusted as necessary.

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 prohibited. For a detailed list, please see Table 6-6 below (please note that the 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 the EOS as described in Table 6-7.

Table 6-6 Prohibited drugs due to DDI with DFV890 (CYP3A and CYP2C9 modulators)

Category of interaction	Drug Names
Strong inhibitors of CYP3A	boceprevir, ceritinib, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir[1], elvitegravir/ritonavir[1], grapefruit juice[2], idelalisib, indinavir, indinavir/ritonavir[1], itraconazole, josamycin, ketoconazole, lopinavir/ritonavir[1], mibefradil, mifepristone, nefazodone, nelfinavir, ombitasvir/paritaprevir/dasabuvir/ritonavir (Viekira Pak)[1], posaconazole, ribociclib, ritonavir, saquinavir, saquinavir/ritonavir[1], telaprevir, telithromycin, tipranavir/ritonavir[1], troleandomycin, tucatinib, voriconazole
Moderate inhibitors of CYP3A	aprepitant, amprenavir, atazanavir, atazanavir/ritonavir[1], casopitant, cimetidine, ciprofloxacin, crizotinib, darunavir, darunavir/ritonavir[1], diltiazem, dronedarone, duvelisib, erythromycin, faldaprevir, fedratinib, fluconazole, grapefruit juice, imatinib, isavuconazole, istradefylline, lefamulin, letermovir, Magnolia vine (*Schisandra sphenanthera*)[3], 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*)[3]

[1] Combination therapy

[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] Herbal product

Table 6-7 Prohibited medication

Medication	Prohibition period	Action taken
Inhibitors and inducers of CYP3A or CYP2C9 according to Table 6-6	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

Medication	Prohibition period	Action taken
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 of repeat dosing of MAS825 study treatment is not applicable as only a single s.c. dose of MAS825 on Day 1 is evaluated in this study.

Discontinuation from study treatment is required under the following circumstances:

- Participant/guardian 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 the following adverse events:
  - 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 and follow-up visits indicated in Section 1.3 SoA.

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, SoA.

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 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, SoA.

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 due diligence has been completed or until the end of the study.

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:

- One or more SAEs occur that are considered to be related to DFV890 or MAS825 study treatment;
- Two or more participants experience hypersensitivity reactions of moderate to severe intensity that are considered to be related to DFV890 or MAS825 study treatment;
- Two or more participants experience a similar AE which was assessed as severe in intensity and are considered to be related to DFV890 or MAS825 study 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 modification 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 CVD 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, SoA. Adherence to the study design requirements, including those specified in Section 1.3, SoA, 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, SoA, starting with informed consents. The assessments should be performed as outlined in Figure 1-2. Screening assessments (including safety laboratory assessments) 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.

The decision to locally test the participant for COVID-19 infection in order to evaluate eligibility is at the Investigator's discretion and should be in adherence to local policies or regulations. However, it is highly recommended that polymerase chain reaction 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 testing for 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 CRF.

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 electronic CRF (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. Please see Section 6.8.1 Concomitant therapy for further details on the information that must be recorded on the appropriate page of the eCRF.

8.3 Efficacy assessments

The efficacy assessments (reduction of IL-6 and IL-18 cytokines) described in this section will be evaluated in all participants. Samples will be collected as defined in Section 1.3, SoA.

8.3.1 IL-6 and IL-18 cytokines

The circulating serum levels of the cytokines IL-6 and IL-18 (IL-18 applicable for DFV890 only) will be measured by 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, SoA.

Participants 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, or levels of IL-6 after a single s.c. dose of MAS825, and/or placebo, depending on the treatment sequence assignment.

For DFV890, a dose-response modeling approach will be utilized that integrates each of the primary endpoints, IL-6 and IL-18 levels, at each dose level and fits a dose-response relationship to extrapolate reductions at the highest tested dose, 100 mg daily DFV890, which is expected to achieve Ctrough exposures > CCI for inhibition of the NLRP3 inflammasome.

For MAS825, the effect of a single s.c. dose on the change in IL-6 compared to placebo after 3 weeks of treatment (primary) and persistence of effect over 12 weeks will be assessed. See Section 9.3 for additional details on the analysis.

8.3.2 Exploratory efficacy assessments

Not applicable.

8.3.3 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 CVD 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 CVD 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 CVD 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 approximately 35% and approximately 45% after approximately 3 months of 150 mg and 300 mg of canakinumab treatment administered every 3 months. This corresponded to an approximately 15% reduced risk of 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 CVD risk. Patients with increased IL-18 levels at baseline in CANTOS had a 15% increased risk of MACE [95% 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 CVD risk and preclinical studies linking IL-18 with CVD 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.

Participants 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.

For MAS825, an alternate approach to inhibiting the production of IL-1β and IL-18 (via inhibition of the NLRP3 inflammasome) is to directly neutralize the circulating cytokines with a bispecific mAb. Therefore the same rationale for the appropriateness of downstream reduction of IL-6 applies. IL-6 is the only primary endpoint for MAS825 (measured at Week 3 after a single s.c. dose of MAS825) as MAS825 directly binds to IL-18 and therefore cannot be robustly measured in this context. Exploratory biomarkers for IL-18 in the context of MAS825 binding (e.g., target capture assays for total IL-18 and IL-18 binding protein) and cytokines downstream of IL-18 (e.g., IFN-γ, CXCL9, CXCL10, etc.) will be assessed.

8.4 Safety/tolerability assessments

Safety assessments are specified below with Section 1.3, SoA, detailing the timing of each assessment. 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 examination will include the examination of general appearance, a skin assessment for rash, a brief cardiorespiratory assessment, and vital signs (oral body temperature, blood pressure [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, SoA. 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, SBP and DBP 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 correction 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 randomizing 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 Day 1 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, WBCs and Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands)
Chemistry	Albumin, ALP, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Chloride, Magnesium, Phosphate, Potassium, Sodium, Creatine kinase (CK), 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, Urobilinogen) If macroscopic panel results in 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	ALT, ALP, AST, GGT, total bilirubin (TBIL), INR, albumin, CK, glutamate dehydrogenase (if available, [GLDH]), 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, BUN, electrolytes (sodium, potassium, phosphate, 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, red blood cells, 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 (approximately 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 90 days after stopping study treatment. In addition, male participants should not donate sperm while taking study treatment, and for 90 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 indicated in Section 1.3, SoA.

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

8.5.1 Skin microbiome collection

The skin swab samples collected will be used for microbiome DNA extraction and sequencing with the goal of characterizing the skin microbiome composition at 2 different skin sites where rash has been previously reported with DFV890 (i.e., chest and upper arms). Skin swab samples will be collected from all participants from two different skin sites: chest and upper arm. Microbiome DNA sequencing will be performed only if the extracted DNA is of sufficient quantity and quality.

These samples will be collected at times specified in Section 1.3. Depending on participant's exposure to antimicrobial treatments for adverse events, collection of skin swab samples may or may not be performed. Refer to the sample collection and processing instructions as outlined in the central laboratory manual.

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

The definitions of AEs and SAEs 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 all AEs (see Section 7).

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 participant 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 with 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, significant changes from baseline or the previous visit.

8.6.2 Serious adverse events

A 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 SAEs 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.

8.6.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until approximately 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 24 hours 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 eSAE with paper backup SAE 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 are collected between the time the participant signs the ICF until approximately 30 days after the participant 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 24 hours 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 Novartis Chief Medical Office & Patient Safety (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 (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Clinical Trial Regulation 536/2014 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30-day period after the last study visit 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

- Details of all pregnancies in female participants will be collected after the start of study treatment and until 5 months after the single dose administration of MAS825 or placebo on Day 1. If indicated, details of all pregnancies in female partners of male participants will be collected after the start of study treatment and until 90 days after the end of study drug administration.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- Any post study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to Novartis as described in Section 8.6.3. While the Investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study treatment or be withdrawn from the study.

Pregnancies

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 24 hours 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 Novartis CMO&PS. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment 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 SoA. Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing and shipment. See the potential use of residual samples for more information. In case needed (e.g., due to suspected toxicity, 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. The analysis of MAS825 concentration in serum will be done only from MAS825-treated patients and the DFV890/IBW042 concentration analysis in plasma will be done only from DFV890-treated patients.

DFV890

DFV890 and its metabolite IBW042 will be determined in plasma by a validated LC-MS/MS combo method; the anticipated lower limit of quantification (LLOQ) is 1 ng/mL.

Due to sparse sampling only plasma Ctrough will be available.

MAS825

MAS825 serum concentrations will be determined using a validated target-based sandwich ELISA. The LLOQ is 25.0 ng/mL in human serum.

8.7.1 PK blood/serum 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 (IL-18 applicable for DFV890 only) 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 or MAS825 at the molecular level 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 which are present in the 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.

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

- Pharmacodynamic, inflammation-related biomarkers:
  - Inflammatory biomarkers: hsCRP
  - Soluble Biomarkers: sASC (for DFV890), hsIL-1β (for DFV890), CXCL9, CXCL10, hsIFN-γ, vWF
  - Immunophenotyping: myeloid / lymphoid cell activation/enumeration by flow cytometry (whole blood/PBMC)
- Target capture biomarkers for MAS825, i.e., total IL-1β, total IL-18 and IL-18bp
- CVD-related biomarkers
  - Lipid parameters: Total cholesterol, high-density lipoprotein (HDL), triglycerides (TGs), LDL, 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)
- Genetic markers that may impact primary and exploratory readouts or PK (to be done as part of the EOS analysis and will not be used for eligibility purposes)
  - CHIP mutations and variant allele frequency at baseline and 12 weeks
  - 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, CVD, and/or PK. This may include, but is not limited to additional analysis for bioanalytical purposes, protein binding, metabolite profiling or quantification, indicators of transporter or enzymatic activity, assessment of impact on clinical outcome, and the identification of potential biomarkers that may be predictive of benefit from treatment with DFV890 or MAS825. 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 MAS825, 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

IG samples will be obtained from all patients and evaluated in all patients who received MAS825.

8.9.1 Immunogenicity blood sample collection and handling

Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing, and shipment.

8.9.2 Immunogenicity analytical method(s)

For MAS825, IG (production of anti-MAS825 antibodies) will be evaluated in serum in a validated three-tiered assay approach. All samples, as defined in the assessment schedule, will be screened for potential anti-MAS825 antibodies. Any positive screen results are confirmed using a confirmatory assay where sample screening signal suppression upon addition of drug in excess is investigated. Samples that are confirmed positive for the presence of anti-MAS825 antibodies will be further analyzed using a titration assay. Further details on sample collection, numbering, processing and shipment are provided in the central laboratory manual.

The detailed methods for IG assessment will be described in the Bioanalytical Data Report.

8.10 Health economics OR 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 MAS825, a given dose level of DFV890, or placebo (placebo, DFV890 10 mg, DFV890 25 mg, DFV890 50 mg, DFV890 100 mg, or MAS825). 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.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation (SD), median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented where applicable.

9.2.3 Treatments

The Safety set will be used for the analyses below. Data for study drug administration and concomitant medications and significant non-drug therapies will be listed by treatment and subject.

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, SD, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in weeks to investigational drugs will be summarized by means of descriptive statistics using the safety set.

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 reported as (1) the percentage of participants who took 80% of doses within a dosing period and (2) the percentage of patients that took all doses within 2 days of the dosing period.

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

The primary endpoints are the ratio to baseline in IL-6 and the ratio to baseline in IL-18.

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 for DFV890 and the serum level of IL-6 at Week 3 for the single dose of MAS825.

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

9.3.2 Statistical model, hypothesis, and method of analysis

The primary analysis for DFV890 will assess the effect 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 for 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 Statistical Analysis Plan (SAP).

From the model, the predicted response at each treatment and associated 80% CI will be extracted, along with the difference to placebo for each DFV890 dose level, the corresponding 2-sided 80% CI. 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 (LS) mean and associated 80% CI for each treatment, and the estimated mean difference to placebo for each DFV890 dose level and 2-sided 80% CI will be extracted from the model and back-transformed to the ratio scale for reporting.

The primary analysis for MAS825 will assess the effect on the change in IL-6 compared to placebo after 3 weeks of treatment. For this analysis, the Week 3 measurements of IL-6 on MAS825 and all Week 3 (i.e., Dosing Period 1) placebo measurements from the other sequences will be used.

A linear model of IL-6 at Week 3 with treatment as a fixed effect, and the baseline value of the biomarker as a covariate will be used for the analysis. All biomarker measurements will be logarithm-transformed prior to the analysis.

The LS mean and associated 80% CI for each treatment, and the estimated mean difference to placebo, the p-value, and 2-sided 80% CI will be extracted from the model and back-transformed to the ratio scale for reporting.

A time course profile of Treatment Sequence 1 (MAS825 as compared to corresponding Dosing Period 1 placebo) will be plotted to investigate how long the effect is sustained.

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 SoC CVD 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 for DFV890 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

A supplementary analysis will be used to examine the response to treatment with MAS825 and DFV890 within each CHIP subtype (*TET2*, *DNMT3A*) randomized in the study. This will be explored in the primary model as specified for each compound. Details will be described in the SAP.

As an additional supplementary analysis, the primary analyses may be performed as described, except that some or all biomarker measurements collected after any change in SoC CVD prevention medication may be excluded from the analysis.

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

Not applicable.

9.4.1 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment sequence.

Adverse events

The number (and percentage) of participants with treatment emergent AEs will be summarized by overall count, by treatment/dose , primary system organ class, and preferred term. An additional summary by treatment sequence primary system organ class, preferred term, and maximum severity will be reported.

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.

All information obtained on AEs will be displayed by treatment sequence and participant.

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

AEs which will be counted for a specific treatment period are those which are treatment-emergent. These events are those with an onset after the start of the treatment period, or which were present prior to the start of the treatment 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 treatment period.

Vital signs

All vital signs data will be summarized by overall count (%) and by treatment/dose and visit/time.

12-lead ECG

All ECG data will be summarized by overall count (%) and by treatment/dose and visit/time.

Clinical laboratory evaluations

All laboratory data will be summarized by overall count (%) and by treatment/dose, and visit/time. An additional summary by treatment sequence, will be reported.

Immunogenicity

All IG results will be listed by overall count (%) and by treatment/dose, participant, and visit/time. An additional summary by treatment sequence, will be reported.

9.4.2 Pharmacokinetics

Descriptive summary statistics of DFV890, IBW042 and MAS825 plasma or serum concentration data will be provided by treatment, and visit/sampling time point, including the frequency of concentrations below the LLOQ and reported as zero.

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

Drug concentrations below LLOQ will be treated as missing for the calculation of the geometric means and geometric CV%, and as zero for all other calculations including calculation of PK parameters.

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

Plasma Ctrough of DFV890 and its metabolite, IBW042, by CYP2C9 genotype will be summarised

9.5.1 Biomarkers

The following inflammation-related exploratory biomarkers (hsCRP, soluble ASC, CXCL9, CXCL10, hsIFN-γ, IL-1β, 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 studies are designed to investigate the association between genetic factors (genotypes) and clinical assessments (phenotypes) which are collected during the clinical trial. These can include, but are not limited, to longitudinal changes of CHIP VAF, additional to the planned baseline and week 12 assessments. 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 randomized 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 PoC criteria or information needed for planning/modifying another study) to relevant Novartis teams for information, consulting and/or decision purposes.

A blinded assessment of variability of IL-6 and IL-18 may be performed after approximately 50% of participants have completed Dosing Period 4.

9.9 Sample size determination

9.9.1 Primary endpoint(s)

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

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

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

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

1. At least one of the following is observed in relation to placebo at the 100 mg dose:

- IL-6 reduction ≥ 25%, or
- IL-6 reduction ≥ 20% + IL-18 reduction ≥ 10%, or
- IL-6 reduction ≥ 15% + IL-18 reduction ≥ 20%.

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

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

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

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

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 (CIOMS) international ethical guidelines
- Applicable ICH Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, 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, 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

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations (including European Directive 2001/20/EC or European Clinical Trial Regulation 536/2014, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

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.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her level of understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

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 also 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:

- Main study consent, which also included:
  - 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
- 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 sub studies/ 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 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.

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

Designated Investigator staff will enter the data required by the protocol into the 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 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 study 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). Definition of what constitutes source data and its origin can be found in, e.g., source data acknowledgment or monitoring guidelines.

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 and as required in CTIS public website. In addition, after study completion (defined as global 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 or CTIS public website 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 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

ADA	Anti-drug antibodies
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute neutrophil count
APTT	activated partial thromboplastin time
AST	Aspartate Aminotransferase
b.i.d.	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
CCUS	Clonal cytopenia of unknown significance
CHIP	Clonal Hematopoiesis of Indeterminate Potential
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine Kinase
cm	Centimeters
CMO&PS	Chief Medical Office and Patient Safety
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
CTC	Common Terminology Criteria
Ctrough	Trough concentrations
CTT	Clinical Trial Team
CV	coefficient of variation
CVD	Cardiovascular disease
CYP	Cytochrome P450
DBP	Diastolic Blood Pressure
DDI	drug-drug interaction
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EOS	End of Study
EOT	End of treatment
FIH	First in Human
GCP	Good Clinical Practice
GCS	Global Clinical Supply

GGT	Gamma-glutamyl transferase
GLDH	Glutamate Dehydrogenase
GLP	Good laboratory practice
h	Hour
HDL	High-density lipoprotein
HDPE	High Density Polyethylene
HIV	Human immunodeficiency virus
HS	Hidradenitis suppurativa
hsCRP	high-sensitivity C-reactive protein
i.v.	intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
IFN-γ	interferon-γ
IG	Immunogenicity
IgG	Immunoglobulin G
IL-1β	interleukin-1β
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRT	Interactive Response Technology
IUD	Intrauterine device
kg	Kilogram
LDH	lactate dehydrogenase
LDL	Low density lipoprotein
LDLR	Low density lipoprotein receptor
LLOQ	lower limit of quantification
LPLV	Last Patient Last Visit
LPS	lipopolysaccharides
LS	Least square
mAb	Monoclonal antibody
MACE	Major adverse cardiovascular event
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
MI	myocardial infarction
mL	milliliter(s)
NLPR3	NOD-, LRR- and pyrin domain-containing protein 3
NLRC4	Nucleotide-binding oligomerization domain-like receptor family caspase activation and recruitment domain-containing 4 protein
NLRC4-GoF	nucleotide-binding oligomerization domain-like receptor family caspase activation and recruitment domain-containing 4 protein gain-of-function
NYHA	New York Heart Association

OHP	Off-site Healthcare Professional
PCI	percutaneous coronary intervention
PCR	Protein-creatinine ratio
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PMBC	Peripheral blood mononuclear cells
PT	prothrombin time
PTT	Partial Thromboplastin Time
QD	Once a day
QTcF	QT interval corrected by Fridericia's formula
RU	Resource Utilization
s.c.	subcutaneous
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	standard deviation
SDD	Spray-dried dispersion
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SoA	Schedule of Activities
SoC	Standard of Care
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBIL	Total bilirubin
TG	Triglycerides
ULN	upper limit of normal
VAF	Variant allele frequency
WBC	white blood cell
WHO	World Health Organization
WOCBP	Women of child-bearing potential

10.2.2 Definitions

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
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
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 once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (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
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 Product/ Investigational Medicinal product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference (such as an active comparator) in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Medication number	A unique identifier on the label of medication kits
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
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.
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
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
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
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 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
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 informed consent form.

10.3 Appendix 3: Clinical laboratory tests

10.3.1 Clinically notable laboratory values and vital signs

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
- Individual study results - 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 TBIL normal at baseline:	• ALT or AST > 5 × ULN • TBIL > 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 TBIL > 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 AE 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, CK, and GLDH in 48-72 hours. • Follow-up for symptoms. • Initiate close monitoring
	If elevated at baseline: ALT > 3 x baseline AND >5x ULN for more than two weeks or ALT ≥5x baseline AND ≥8x ULN			

	ALT	TBL	Liver Symptoms	Action
	If normal at baseline: ALT > 8 x ULN	Normal	None	and workup for competing etiologies. • Study treatment can be restarted only if another etiology is identified and liver enzymes return to baseline.
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 Bilirubin (isolated)		
>1.5 – 3.0 ULN	• Maintain treatment • Repeat LFTs within 48-72 hours	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 48-72 hours • 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, TBIL, 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, TBIL, 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 24-48 hours 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 Section 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 hours 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 24-48 hours if possible • Repeat laboratory values within 48 hours 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 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

Renal Event	Actions
	• Repeat assessment to confirm • 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

Bugelski PJ, Treacy G (2004) Predictive power of preclinical studies in animals for the immunogenicity of recombinant therapeutic proteins in humans. Curr Opin Mol Ther; 6:10-6.

Duewell P, Kono H, Rayner KJ, et al (2010) NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals. Nature; 464(7293):1357-61.

Fuster JJ, Maclauchlan S, Zuriaga MA, et al (2017) Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice. Science; 355:6327.

Hettwer J, Hinterdobler J, Miritsch B, et al (2022) Interleukin-1β suppression dampens inflammatory leucocyte production and uptake in atherosclerosis. Cardiovasc Res; 118(13):2778-91.

Jaiswal S, Natarajan P, Silver A, et al (2017) Clonal Hematopoiesis and Risk of Atherosclerotic Cardiovascular Disease. N Engl J Med; 377:111-21.

Marnell C, Bick A, Natarajan P (2021) Clonal hematopoiesis of indeterminate potential (CHIP): Linking somatic mutations, hematopoiesis, chronic inflammation and cardiovascular disease. J Mol Cell Cardiol; 161:98-105.

Palmeira P, Quinello C, Silveira-Lessa AL, et al (2012) IgG placental transfer in healthy and pathological pregnancies. Clin Dev Immunol; 2012:985646.

Ridker PM, Everett BM, Thuren T, et al (2017) Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med; 377(12):1119-31.

Ridker PM, MacFadyen JG, Thuren T, et al (2020) Residual inflammatory risk associated with interleukin-18 and interleukin-6 after successful interleukin-1β inhibition with canakinumab: further rationale for the development of targeted anti-cytokine therapies for the treatment of atherothrombosis. Eur Heart J; 41(23):2153-63.

Rojko JL, Evans MG, Price SA, et al (2014) Formation, clearance, deposition, pathogenicity, and identification of biopharmaceutical-related immune complexes: review and case studies. Toxicol Pathol; 42:725-64.

Roth GA, Mensah GA, Johnson CO, et al (2020) Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol; 76(25):2982-3021.

Sano S, Oshima K, Wang Y, et al (2018) CRISPR-Mediated Gene Editing to Assess the Roles of Tet2 and Dnmt3a in Clonal Hematopoiesis and Cardiovascular Disease. Circulation Research; 123:335-41.

Steensma DP, Bejar R, Jaiswal S, et al (2015) Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. Blood; 126(1):9-16.

Svensson EC, Madar A, Campbell CD, et al (2022) TET2-driven clonal hematopoiesis and response to canakinumab: an exploratory analysis of the CANTOS randomized clinical trial. JAMA Cardiol; 7(5):521-28.

Thygesen K, Alpert JS, White HD, et al (2007) Universal Definition of Myocardial Infarction. Circulation; 116:2634-53.