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DFV890

Clinical Trial Protocol CDFV890A12201 / NCT04868968

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

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List of abbreviations

AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALB	Albumin
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
anti-HBc	Hepatitis B core antibody
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase

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b.i.d.	bis in die / twice a day
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CAPS	Cryopyrin-Associated Periodic Syndromes
CINCA	Chronic, Infantile, Neurological, Cutaneous and Articular Syndrome
CK	Creatine Kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
ClinRO	Clinician Reported Outcomes

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CMO & PS	Chief Medical Office and Patient Safety
CO	Country Organization
COA	Clinical Outcome Assessment
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	Trough concentration
CV	Coefficient of Variation
CXCL10	C-X-C motif chemokine ligand 10
CYP	Cytochrome P450
DDE	Direct Data Entry
DDI	Drug-Drug Interaction
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
eSource	Electronic Source

FCAS	Familial Cold Autoinflammatory Syndrome
FIH	First in Human
FMF	Familial Mediterranean Fever
FSH	Follicle Stimulating Hormone
G-GT	Gamma-Glutamyl Transferase
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
h	Hour
HBsAg	Hepatitis B surface antigen
hCG	Human Serum Chorionic Gonadotropin
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus

IB	Investigator's Brochure
IC50	Half maximal inhibitory concentration
IC90	Concentration required to achieve 90% of inhibition
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFN-γ	Interferon-gamma
IL-1	Interleukin-1
IL-18	Interleukin-18
IL-18BP	IL-18 binding protein
IL-1β	Interleukin-1beta
IL-6	Interleukin-6
IN	Investigator Notification
INR	International Normalized Ratio
IRB/IEC	Institutional Review Board / Independent Ethics Committee
IUD	Intrauterine Device
IUS	Intrauterine System
KIM-1	Kidney Injury Molecule-1
LC-MS/MS	Liquid chromatography coupled with tandem mass spectrometry
LDH	Lactate Dehydrogenase
LFT	Liver Function Test

LPLV	Last Participant Last Visit
LPS	Lipopolysaccharide
MAD	Multiple Ascending Dose
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)

MWS	Muckle-Wells Syndrome
NGAL	Neutrophil Gelatinase-Associated Lipocalin
NLRP3	Nucleotide-binding oligomerization domain-like receptor family, pyrin domain-containing 3
NOAEL	No Observed Adverse Effect Level
NOMID	Neonatal Onset Multisystem Inflammatory Disease
NSAID	Non-Steroidal Anti-Inflammatory Drug
PBMC	Peripheral Blood Mononuclear Cells
PCR	Protein-Creatinine Ratio
PD	Pharmacodynamic(s)
PI	Principal investigator
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PRO	Patient Reported Outcomes
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
q.d.	quaque die / once a day
QTcF	QT interval corrected by Fridericia's formula
R Value	ALT/ALP x ULN
RBC	Red Blood Cell(s)
RNA	Ribonucleic acid
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SAD	Single Ascending Dose
SAE	Serious Adverse Event
SD	Standard Deviation
SDD	Spray-Dried Dispersion
SoC	Standard of Care
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total Bilirubin
TLR	Toll-like receptor
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ULN	Upper Limit of Normal
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WCC	White Cell Count
WHO	World Health Organization
WOCBP	Women of child bearing potential

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Baseline	Refers to the information found prior to initiating a treatment or after all effects triggered by a treatment have ceased
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Control drug	A study drug (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
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 paper source forms 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 or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and eCRFs into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Estimand	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 patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
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 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
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.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
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
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
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 a 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.

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Protocol summary

Protocol number	CDFV890A12201
Full title	An open-label, single arm phase II study of DFV890 to assess the safety, tolerability and efficacy in participants with familial cold auto-inflammatory syndrome (FCAS)
Brief title	Study of safety, tolerability and efficacy of DFV890 in participants with familial cold auto-inflammatory syndrome (FCAS)
Sponsor and Clinical Phase	Novartis, Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this phase II study is to assess the safety, tolerability and efficacy of DFV890 in participants with FCAS
Primary Objective(s)	The primary objective of this study is to assess the efficacy of DFV890 to reduce cold-induced inflammation in participants with FCAS
Secondary Objectives	The secondary objectives of the study are: • To assess safety and tolerability of DFV890 • To assess the efficacy of DFV890 to improve the signs and symptoms of FCAS • To assess the effect of DFV890 on patient reported outcomes
Study design	This is an open-label, single-arm, multiple dose, phase II study to assess safety, tolerability and clinical efficacy of DFV890 in participants with FCAS. The study includes three periods: • Screening period including a screening cold challenge up to 6 months (and up to 12 months for participants with a historical screening cold challenge prior to protocol amendment 04) • Treatment period including a second cold challenge (total of 5 days duration) • Follow up period concluded with a Study completion visit (10 days after dose administration) At most, the study will last up to 7 months (and up to 13 months for participants with a historical screening cold challenge prior to protocol amendment 04)
Study population	Approximately 6 adult male or female participants with FCAS, who show evidence of inflammatory activity after the cold challenge performed during screening, will be included into the study

Key Inclusion criteria	• Written informed consent must be obtained before any study-specific assessment is performed • Male and female participants aged between 18-80 years inclusive (for France 18-60) • Body mass index within the range of 18-35 kg/m^2 • Participants with a genetic diagnosis of FCAS • Participants with a clinical history and investigations consistent with FCAS, in the absence of a history or diagnosis of amyloidosis and/or organ damage (e.g. deafness, periorbital edema, lymphadenopathy, and serositis) • Participants who have evidence of inflammatory activity after the screening cold challenge, as assessed by a relative increase in WCC of at least 40 % compared to pre-challenge • Evidence of inflammatory disease activity during the screening period before the admission to the screening cold challenge, captured by the Physician global assessment of autoinflammatory disease activity > minimal, recorded at Screening Cold Challenge Admission visit
Key Exclusion criteria	• Commercially Confidential Information • Anti-rejection and/or immunomodulatory drugs must be discontinued: ▪ Anakinra at least 1 day prior to the screening cold challenge and until study completion ▪ Canakinumab and rilonacept at least 3 half-lives prior to the screening cold challenge, at least 5 half-lives prior to Day 1 and until study completion ▪ Other anti-rejection/immune modulatory therapies must be discontinued at least 3 half-lives prior to screening cold challenge, at least 5 half-lives prior to Day 1 and until study completion ▪ Ad hoc use of anakinra is permitted for the interval between the screening cold challenge and Day 1, if it can be discontinued at least 5 half-lives prior to Day 1 ▪ Ad hoc use of paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs, as per local regulations/practice) is permitted for symptomatic relief • Clinically significant, suspected active or chronic bacterial (including *Mycobacterium tuberculosis*), viral or fungal infection within 30 days prior to Day 1 • Participants with innate (e.g. TLR immunodeficiencies, defects in IFN-γ signaling) or acquired immune deficiencies (e.g. AIDS) • Presence of human immunodeficiency virus (HIV) infection, hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (anti-HBc), or hepatitis C antibodies at screening • Live vaccines within 4 weeks of Day 1 • Absolute peripheral blood neutrophil count of ≤1000/mm^3

	• A history of renal disease, including nephrolithiasis, and/or an estimated GFR (eGFR) ≤90 mL/min/1.73m^2 (based on Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula) • History or current diagnosis of ECG abnormalities indicating significant safety risk for participant enrolled • Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human serum chorionic gonadotropin (hCG) laboratory test • Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 10 days after stopping of study treatment • Any significant concurrent medical condition (e.g. anemia) that, in the opinion of the investigator, could affect the participant's ability to tolerate or complete the study
Study treatment	DFV890 100 mg b.i.d. orally for 3 days and once in the morning of the fourth day
Treatment of interest	The study treatment is DFV890 (no placebo or comparator will be administered)
Efficacy assessments	• White Cell Count (WCC) • Physician global assessment of autoinflammatory disease activity • Physician's severity assessment of autoinflammatory disease signs and symptoms • Patient's global assessment of disease activity
Key safety assessments	• Physical examination • Vital signs • ECG parameters • Pregnancy and assessment of fertility • Monitoring of laboratory markers in blood and urine • Adverse event and serious adverse event monitoring
Other assessments	• Commercially Confidential Information
Data analysis	The primary objective will be achieved and DFV890 will be considered efficacious in treating cold-induced inflammation in participants with FCAS if the estimated ratio of fold change from pre-challenge to highest post challenge WCC between treatment and screening period is: statistically significant ($p<0.10$) **and** less than 80%. Commercially Confidential Information

Key words	Familial Cold Auto-inflammatory Syndrome (FCAS), DFV890, NLRP3 inhibitor, inflammasome inhibition, Cryopyrin-associated periodic syndromes (CAPS)

1 Introduction

1.1 Background

Cryopyrin-associated periodic syndromes (CAPS) is a group of rare diseases characterized by skin, musculoskeletal, ocular, and neurological symptoms and chronic systemic inflammation that may lead to organ damage and/or amyloidosis and are caused by heterozygous gain-of-function mutations in the nucleotide-binding oligomerization domain-like receptor family, pyrin domain-containing 3 (NLRP3) gene. CAPS are classified into three clinical phenotypes based on a spectrum of disease severity: familial cold autoinflammatory syndrome (FCAS), Muckle Wells syndrome (MWS) and neonatal onset multisystem inflammatory disease (NOMID) also called chronic, infantile, neurological, cutaneous and articular syndrome (CINCA) (Hoffman et al 2019).

FCAS represents the mildest CAPS clinical phenotype and symptoms are typically limited to low grade fever, general rash, conjunctivitis and polyarthralgia, triggered 1-2 hours following cold exposure and resolve within 24 hours with warmth (Shpall et al 2004). Clinically it is important to distinguish between FCAS and cold urticaria, that are not related, are distinct in their etiology, clinical presentation, response to type of cold exposure (generalized for FCAS versus local for cold urticaria), pathophysiology (IL-1β mediated for FCAS versus histamine for cold urticaria) and natural history (throughout life for FCAS versus spontaneous resolution for cold urticaria) (Wanderer and Hoffman 2004). In addition, many patients with FCAS also show evidence of chronic inflammation between attacks, particularly a daily pattern of rash developing in the afternoon that can be associated with headache, myalgia, and fatigue by the evening though chronic inflammation rarely leads to amyloidosis (~2%) in this patient population (Hoffman et al 2019).

Chronic inflammation and abnormal immune activity underlie and drive many serious human diseases ranging from rare and acute inflammatory diseases, rheumatologic indications, cardiovascular and metabolic diseases, neurodegenerative diseases, and cancer. In these settings, molecular danger signals produced by dying cells, metabolic dysregulation, environmental toxins, or the diet may function as stimuli to activate NLRP3 inflammasome (Mangan et al 2018). Once activated, NLRP3 nucleates assembly of an inflammasome complex that orchestrates innate and adaptive immune responses to drive a strong inflammatory response (Evavold and Kagan 2018). Inflammasomes are large cytoplasmic, multimeric protein complexes assembled in response to danger signals, and inflammasome activation results in caspase-1 mediated production of interleukin-1β (IL-1β) and interleukin-18 (IL-18) as well as pyroptosis (inflammatory mediated cell death) (Dinarello 2011).

The role of IL-1β in several diseases has been well established in the clinic. The drugs anakinra (recombinant soluble IL-1 receptor antagonist) and canakinumab (anti-IL-1β) are approved for treatment of a range of autoinflammatory diseases including CAPS and familial Mediterranean fever (FMF). Canakinumab (anti-IL-1β monoclonal antibody) reduces cardiovascular risk in patients who have previously had a myocardial infarction (Ridker et al 2017a). Further analysis of the CANTOS study found that canakinumab treatment reduced lung cancer incidence (Ridker et al 2017b) and knee and hip replacements in osteoarthritis patients (Schieker et al 2020), suggesting that IL-1β blockade could be beneficial in a broad range of common inflammatory diseases. Potentially NLRP3 inhibition with DFV890, blocking IL-1β,

IL-18, and pyroptosis, in these and other settings may provide a treatment for conditions where persistent inflammasome activation results in pathology (Ridker et al 2018). To support this extrapolation from clinical experience with IL-1β blockade to NLRP3 inhibition, an extensive body of published literature based on genetic knockout or pharmacologic inhibition of NLRP3 provides validation for the assessment that NLRP3 is a promising therapeutic target (Mangan et al 2018).

DFV890 is a potent small molecule inhibitor of NLRP3.

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DFV890 is a small molecule NLRP3 inhibitor that has reached clinical stage, and its therapeutic benefits in a NLRP3-driven disease has yet to be shown in humans. CCI

Therefore, we propose a proof of concept for DFV890 in participants with FCAS, a known NLRP3-specific disease, to understand its clinical response profile.

1.1.1 DFV890

DFV890 was developed as an orally administered small molecule to treat diseases in which inflammation or aberrant immune responses caused by activation of the NLRP3 inflammasome initiates or mediates pathology. Commercially Confidential Information
inflammasome has been implicated as a major driver of inflammation associated with autoinflammatory, acute and chronic inflammatory diseases, such as CAPS.

1.1.2 Non-clinical data

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1.1.3 Clinical data

Clinical human pharmacokinetics

DFV890 is a highly permeable compound with solubility-limited absorption of crystalline material at high doses.

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Specific studies to investigate drug-drug interactions (DDIs) have not been conducted with DFV890. Weak to moderate DDI effects are expected for DFV890 as a victim with concomitant administration of strong and moderate CYP2C9 and CYP3A4 inhibitors for patients, who are

normal and intermediate CYP2C9 metabolizers. High DDI risk (≥5 up to 25-fold increase in DFV890 AUC) is expected for patients, who are poor CYP2C9 metabolizers. When dosed with a strong CYP3A4 inducer or moderate dual CYP2C9/CYP3A inducer, moderate DFV890 exposure reduction by ~4-fold is predicted for normal CYP2C9 metabolizers. Weaker effect of inducers is expected for patients with reduced CYP2C9 activity. As a perpetrator, DFV890 has weak potential to induce CYP3A4 and therefore may reduce AUC of strong CYP3A4 substrates by up to ~2-fold (refer to the Investigator's Brochure for further details).

Clinical safety

As of 17-May-2022, 266 subjects have been enrolled into the DFV890 clinical development program, of which approximately 164 subjects or patients have received DFV890 at various doses and 100 placebo or standard of care (SoC). The final clinical study report is available for Commercially Confidential Information CDFV890D12201 (COVID-19) studies.

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In the completed Phase 2 study (CDFV890D12201) in patients with COVID-19 pneumonia and impaired respiratory function, 143 participants were enrolled to the study (DFV890+SoC or SoC alone groups), of whom 70 participants received DFV890 at a dose of 50 mg b.i.d. for 14 days. DFV890 was generally well tolerated with drug exposures as expected CCI . The overall incidences of reported AE and SAE were similar between the DFV890 and SoC groups with no unexpected or new safety findings in this COVID-19 population. There were no events related to the musculoskeletal/connective tissue systems for DFV890 or SoC arms and no unexpected renal events or serious infections in hospitalized COVID-19 population. There was as anticipated a higher incidence of mild to moderate rash events observed in participants who received DFV890. Maculopapular/pruritic skin rashes considered related to DFV890 were reported in 7 participants (approximately 10%), 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.

In summary, there were no unexpected events for this disease indication and patient population. The safety findings are consistent with the early clinical safety profile CCI

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A Phase 2 study is currently ongoing (CDFV890B12201) in participants with symptomatic knee osteoarthritis

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1.2 Purpose

The purpose of this phase II study is to assess the safety, tolerability and efficacy of DFV890 in participants with FCAS.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the efficacy of DFV890 to reduce cold-induced inflammation in participants with FCAS	• Ratio of fold change from pre-challenge to the highest post-challenge value of white cell count (WCC) between treatment and screening period
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess safety and tolerability of DFV890	• Safety endpoints (including vital signs, ECG parameters, safety laboratory assessment and adverse events)

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

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

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2.1 Primary estimand

The primary clinical question of interest is: does DFV890 prevent flares triggered by the cold challenge as indicated by proportional reduction in the fold change from pre-challenge to the highest post-challenge value of WCC between treatment and screening periods in participants with FCAS?

It has been shown (Hoffman et al 2004) that the fold change in WCC from pre-challenge to post-challenge can capture the treatment effect in the acute flare situation triggered by the cold challenge. Hence the choice of the primary estimand is considered as the ratio of fold change from pre-challenge to highest post-challenge WCC values between treatment and screening.

The primary estimand is described by the following attributes:

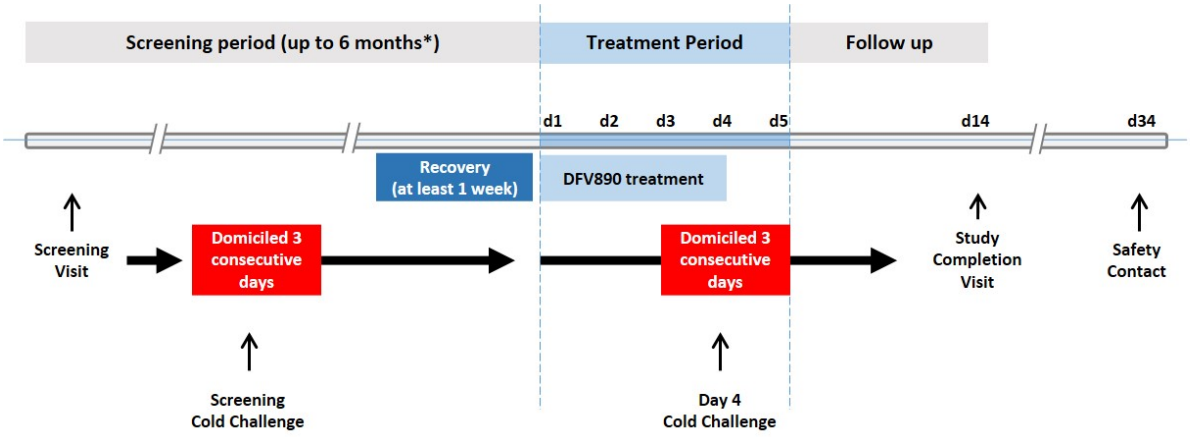
1. Population: participants with a genetic diagnosis of FCAS in association with a clinical history and investigations consistent with FCAS, who show evidence of inflammatory activity after the cold challenge performed during screening. Further details about the population are provided in Section 5.
2. Endpoint: fold change from pre-challenge to the highest post-challenge value of WCC. This is measured as the ratio of highest post-challenge and the pre-challenge value of WCC. The highest post-challenge value is based only on post-challenge measurements within the cold challenge visit (up to and including 8 hours post-challenge; i.e. 9 hours post-dose).
3. Treatment of interest: DFV890
4. Summary measure: ratio of treatment fold change and screening fold challenge of WCC value.

3 Study design

This is an open-label, single-arm, multiple dose, phase II study to assess safety, tolerability and efficacy of DFV890 in participants with FCAS who show evidence of inflammatory activity after the cold challenge performed during screening. Approximately 6 participants with FCAS and confirmed NLRP3 gain-of-function mutations will be enrolled in the CDFV890A12201 study.

The study consists of three periods: screening, treatment and follow-up. During the screening period the participant's eligibility will be assessed at a screening visit and a cold challenge will be performed. Eligible participants (defined as those participants who respond to the cold challenge) will then enter the treatment period where they will be administered oral DFV890 100 mg b.i.d. for 3 days, one last dose will be administered in the morning of Day 4 followed by a cold challenge. The Study completion visit will be conducted approximately 10 days after last dose and a post study safety contact will occur 30 days after last dose. Assessments are outlined in the assessment schedule (Table 8-1). The total study duration from screening until study completion is expected to be up to 7 months (and up to 13 months for participants with a historical screening cold challenge prior to protocol amendment 04).

Figure 3-1 Study Design



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

Screening period

A period of up to 6 months (and up to 12 months for participants with a historical screening cold challenge prior to protocol amendment 04), to confirm that the study eligibility criteria are met and to conduct the first cold challenge. The required assessments may be conducted over several days if it is in the best interest of the participant, or for logistical reasons. The screening period also allows for the safe treatment discontinuation in participants treated with therapeutics targeting the IL-1β pathway.

Screening visit: Informed consent will be collected, and participants evaluated for eligibility. For those participants that qualify for the screening cold challenge, prohibited medication will be stopped (Section 6.2.2). Results from laboratory samples collected at the Screening visit, as well as reports of active disease from the participant, must be available prior to scheduling the screening cold challenge.

Screening Cold Challenge: The participants will be domiciled for three days in connection with the screening cold challenge. On the first day (Day -10), the participants will be admitted in the morning, go through safety assessments and then stay in a room with ambient temperature, preferably above 23°C, to ensure stable conditions prior to the cold challenge. On the second day (Day -9), after pre-challenge assessments and breakfast, participants will undergo a cold challenge for 45 minutes (see Section 16.3 for further details) followed by monitoring over the

next 23 hours. On the third day (Day -8), the participants will be discharged after the last assessment, or later at the discretion of the investigator. Participants should have a minimum of one week of recovery from cold challenge prior to enrollment and initiation of treatment. The screening cold challenge can be conducted any time during the screening period, provided that Day 1 is conducted within 6 months (and within 12 months for participants with a historical screening cold challenge prior to protocol amendment 04; see below) of the Screening visit and all inclusion and none of the exclusion criteria are met. Historical screening cold challenge conducted in this study under the previous protocol version is acceptable, provided that Day 1 is conducted within 12 months of the Screening visit, and all inclusion and none of the exclusion criteria based on this amendment are met.

To mitigate potential SARS-CoV-2 infections among participants, guidance and requirements provided by the local regulatory authorities or local site-specific standard operating procedures (SOPs) will be followed (e.g. participants may be screened for SARS-CoV-2 by polymerase chain reaction or comparable approved methodology prior to admission at the study/hospital site for any overnight stays following local site-specific SOPs).

Treatment period

Treatment initiation visit: Participants who meet all inclusion and no exclusion criteria, including showing evidence of inflammatory activity after the cold challenge performed during screening, will be enrolled on Day 1 and treatment will be initiated. Evidence of inflammatory activity is defined in Inclusion criterion 8, Section 5.1.

The first dose of DFV890 will be administered in the clinic and study treatment will be dispensed to the participant for continued treatment at home. Participants may be domiciled during the treatment period for convenience of the participants and/or logistical aspects, at the discretion of the participant and investigator.

Cold Challenge: Participants will be admitted to the clinic in the morning of Day 3, the day prior to cold challenge, and will be domiciled for a total of three days or longer if mandated by the investigator or by local regulations. On Day 3, participants will undergo safety assessments and then stay in a room with ambient temperature, preferably above 23°C, to ensure stable conditions prior to the cold challenge. On the morning of Day 4, pre-challenge assessments will be performed and breakfast will be served. Directly after breakfast, a pre-dose PK sample will be collected and the last dose of study treatment will be administered. One hour after study treatment administration, another PK sample will be collected, and the cold challenge will be initiated. The cold challenge lasts for 45 minutes. After the end of the cold challenge, participants will be monitored until the next morning (Day 5). The participants will be discharged after the last assessment on Day 5 or later, at the discretion of the investigator.

Follow up period

Participants will be followed-up for an end of study evaluation at the Study completion visit, approximately 10 days after last dose. The Study completion visit may be performed at an alternative Sponsor-approved site (e.g. satellite site that may be more convenient to the participant) if agreed by the principal investigator (PI) who will maintain the investigator responsibilities, and only as permitted by local regulations.

Unscheduled visits

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

4 Rationale

4.1 Rationale for study design

Study design

The design supports the assessment of the safety, tolerability, as well as the evaluation of the proof of concept and efficacy of DFV890 in participants with FCAS.

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This study design includes a cold challenge that was developed to study the acute inflammatory mechanisms after general cold exposure in FCAS patients and to investigate the effect of pretreatment with IL-1 blocking therapeutics to enable the clinical development of such therapeutics to treat FCAS patients (Hoffman et al 2004, Ross et al 2008).

Based on the analysis of the results from Hoffman et al 2004, the sample size (6 patients) is calculated assuming that the geometric mean of the ratio in fold changes of WCC between treatment and screening periods will be at most 50% (see Section 12.8.1 for further details). This approach also excludes non-responders during the screening/control period, lowering the risk of false negatives and ensuring only those participants with FCAS who respond to the cold challenge are administered DFV890 and undergo a second cold challenge as part of the study. In addition, the primary endpoint (WCC) is unlikely subject to bias, further justifying the open-label design.

The **Screening visit** will be used to confirm that the study inclusion and exclusion criteria are met and for performing clinical observations and biological sampling.

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The screening cold challenge will be conducted and treatment phase started as soon as the defined wash-out for background therapy is fulfilled. This wash-out period for previously treated participants ensures that only participants with sufficient wash-out of background medication will undergo the screening cold challenge.

Following the screening cold challenge only the participants who have evidence of inflammatory activity (e.g. elevation in WCC) will be enrolled to the **treatment period** and will be administered DFV890 prior to a second cold challenge. The DFV890 treatment is anticipated to provide full inhibition of the NLRP3 inflammasome in FCAS participants potentially reducing or ablating inflammatory responses to cold temperatures.

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Pre-challenge and post-challenge measurements of WCC, CCI as well as clinical signs and symptoms using physician and patient reported outcomes (PROs) will be conducted. These assessments have been widely used in clinical studies of inflammation.

The **follow-up period** ensures participants' safety after discontinuation of DFV890 and recovery from the cold challenge.

Targeted study population

The rationale for including participants with FCAS is the following: FCAS is a mild CAPS phenotype that may not require treatment. Furthermore, in the case of participants on treatment, it is safe to temporary discontinue treatment as per medical judgment for the limited period of the study. Participants with a history of CAPS-related organ damage and/or amyloidosis will be excluded to ensure no overlap with MWS. A potential risk of DFV890 and in general for small molecule inhibitors of NLRP3 is the recently described differential binding affinities of such molecules to wild type versus mutant NLRP3, resulting in reduced efficacy in the latter (Vande Walle et al 2019). Therefore, participants carrying NLRP3 gene mutations not responsive to DFV890 inhibition including but not limited to L353P carriers, will be excluded. As an experimental cold challenge is used to trigger an inflammatory response, only participants showing evidence of inflammatory activity after the cold challenge during screening (as defined above) will be included.

Duration of study periods

A screening period of up to 6 months (and up to 12 months for participants with a historical screening cold challenge prior to amendment 04) has been selected to allow for wash-out of previous IL-1β/NLRP3 blocking therapy, the conduct of the screening cold challenge, as well as to accept historical screening cold challenge conducted in this study under the previous protocol version.

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4.2 Rationale for dose/regimen and duration of treatment

A dose of 100 mg administered b.i.d. as a tablet has been selected for this study. DFV890 tablets will be administered shortly after completion of a meal and all doses should be taken approximately 12 h apart (±1h). Commercially Confidential Information

Commercially Confidential Information

Considering the short treatment duration of 4 days and sufficient safety margins, administration of DFV890 in this study is considered safe.

4.3 Rationale for choice of control drugs (comparator/placebo)

Not applicable.

4.4 Rationale for public health emergency mitigation procedures

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

4.5 Purpose and timing of interim analyses/design adaptations

No interim analysis is planned for this trial.

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

4.6 Risks and benefits

4.6.1 Potential benefits to study participants

There is no benefit expected for participants in this study given the limited duration of DFV890 treatment, though participants with FCAS will contribute to the development of a potential new oral therapy.

From a patient perspective, there exists significant unmet medical need for large segments of patients across the diseases in which NLRP3 is a driver of inflammation and mediates consequent immune damage. For patients with NLRP3-driven diseases who do not respond to approved therapies, and therefore for whom no standard therapeutic alternatives are available or for whom available therapeutic alternatives are associated with significant risks of side effects, DFV890 represents a promising alternative.

4.6.2 Potential risks to study participants

The risk to participants with FCAS in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring, follow-up, minimal duration of the study treatment and pre-specified study stopping rules.

The cold challenge procedure was developed to study the acute inflammatory mechanisms after general cold exposure in FCAS patients and to investigate the effect of pretreatment with IL-1 blocking therapeutics to enable the clinical development of such therapeutics. Participants with a clinical history of transient self-limiting rash, fever and/or arthralgia that are pathognomonic of FCAS following cold exposure that resolve with warmth will undergo two controlled cold challenges while domiciled at the clinical site under medical supervision to trigger a transient and monitorable inflammatory response. Following the 45-minute cold challenge, participants will be returned to an ambient temperature of approximately 23°C for at least 24 hours at the clinical site, to ensure resolution of the inflammatory response.

The design of the cold challenge procedure is based on the clinical characteristics of the acute episodes in FCAS patients where a mean duration of generalized cold exposure of 52 minutes (range 5-180 minutes) was reported to trigger a self-limiting episode with onset of symptoms 150 minutes (range 10-480 minutes) after generalized cold exposure, with the absolute change in temperature (ambient to low) being an important factor in precipitating episodes (Hoffman et al 2001, Johnstone et al 2003). Importantly, environmental generalized cold exposure (e.g. cold damp weather) would similarly cause an inflammatory episode in many untreated FCAS patients experiencing baseline daily symptoms, often with diurnal pattern of episodes in the afternoon or evening that resolve by morning following rewarming in bed overnight. The cold challenge as described in the present protocol models the real life situation of exposure to mildly cold weather conditions and is expected to trigger typical signs and symptoms of an acute episode in FCAS patients including a low-grade fever, rash and arthralgia beginning approximately 1 hour after challenge, peaking at 4-8 hours and abating with warming by the next day with no reports of acute complications during the challenge or long-term sequelae in patients (Hoffman et al 2004, Ross et al 2008).

Importantly, the cold challenge induces cold stress (body temperature 35.0-37.0°C (Dow et al 2019)) but not hypothermia (body temperature 35.0-32.0°C, clear consciousness with shivering (Durrer et al 2003)) requiring treatment. FCAS patients are able to normally function during the challenge with physiological responses to cold including shivering to raise body temperature and metabolic rate. This is followed by IL-1β mediated response post challenge that includes a self-limiting low-grade fever that resolves on warming (Ross et al 2008).

Study specific assessments will be performed following local procedures by investigators and site staff experienced in the care of FCAS patients. Participants with FCAS will be domiciled for the cold challenges to ensure close clinical monitoring during the rewarming until discharge (approximately 22 hours after end of cold challenge), and the protocol contains a recovery period of more than one week between the first and second challenge in eligible patients. The use of paracetamol/acetaminophen or NSAIDs is also permitted for symptom relief. The cold challenge as described in this protocol (see Section 16.3) models the real-world exposure of FCAS patient to mild cold weather conditions for a limited duration with careful monitoring under medical supervision during and after the cold challenge including pre specified stopping

rules for the cold challenge. Based on the available clinical, safety and laboratory assessments and the clinical experience of the cold challenge in FCAS patients and the CDFV890A12201 protocol specific measures, the overall risk-benefit of the cold challenge is considered acceptable. Any potential risks are considered to be adequately mitigated with the indicated measures.

The potential risks of DFV890 summarized below are based on preclinical and clinical data from the completed Commercially Confidential Information CDFV890D12201 COVID-19 studies, based on the final clinical study report from both studies. Recommended guidelines for management of study AEs are provided in Section 6.6.2.

4.6.3 Potential risk and recommended management of skin rash

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In the completed CDFV890D12201 Phase 2 study in COVID-19, 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.

To reduce the potential risks of the development of maculopapular and/or pruritic rashes, for early patient studies b.i.d. dosing will be employed to achieve maximal, sustained inhibition of the NLRP3 target while minimizing DFV890 Cmax and the potential for triggering skin rash if driven by Cmax. Commercially Confidential Information

Investigators should be vigilant for symptoms of pruritus and signs of rashes (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 6.6.2 for recommended management of maculopapular/pruritic rashes).

4.6.4 Potential risk of renal abnormalities and recommended monitoring

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Although it is not clear whether there are potential effects of DFV890 on kidney in humans, markers of renal function including electrolytes, creatinine and BUN/Urea, urine-creatine ratio and urinalysis will be monitored in this study (see Section 10.2.2 for further details and guidance).

4.6.5 Potential risk and recommended monitoring of hematological parameters

Transient asymptomatic decreases in ANC and WCC were observed in the CCI and CDFV890D12201 COVID-19 studies. These transient self-limiting decreases in CCI were not associated with an increased risk of infection which could be consistent with a PD effect of DFV890 CCI

To reduce the risk of developing neutropenia in participants treated with DFV890, all participants with evidence of an ANC count < 1000/mm^3 should be excluded from entry into this study (see Section 5.2).

4.6.6 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. Commercially Confidential Information

. To mitigate potential risks of immune suppression and infection in this study, exclusion criteria include other immune suppressive treatments administered 28 days or 5 half-lives, whichever is longer, prior to screening cold challenge, or concurrent use thereof. Participants will also be excluded with known or suspected immunodeficiency state or evidence of active or latent, serious bacterial, fungal or viral infections. See Section 5.2.

In response to the COVID-19 pandemic site-specific procedures should be implemented to minimize COVID-19 infection risks for participants and site staff as per local guidance. These documents may cover, but are not limited to, local COVID-19 testing, infection prevention/control, hygiene and social distancing measures.

Investigator must instruct participants to contact the investigator immediately if the participants develop any symptoms and/or signs of infection (e.g. fever, loss of smell, loss of taste, muscle aches, persistent or productive cough, abdominal pain, vomiting, nausea, shortness of breath, dysuria and/or diarrhea).

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

4.6.7 Potential risk and guidance on vaccinations

To mitigate the risk from live vaccinations, participants who have received live vaccinations within 1 month prior to the first dose of study will be excluded from entry into this study. Additionally, it is recommended that all participants should complete all immunizations in accordance with current immunization guidelines at least 1 month prior to administration of the first dose DFV890.

Approved (including Health Authorities' conditional marketing authorization) killed, inactivated, peptide, DNA and RNA vaccines may be permitted according to the investigator's discretion and per local guidance. Due to the mechanism of action of DFV890, specifically targeting the NLRP3 inflammasome, it is unlikely that treatment with this compound would interfere with vaccination responses. However, no specific preclinical or clinical investigations have been conducted to date with DFV890.

4.6.8 DFV890 potential for higher systemic exposure and for drug-drug interactions

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Clinical studies to investigate drug-drug interactions between DFV890 and CYP3A and or CYP2C9 substrates/modulators have not been performed yet. CCI

Commercially Confidential Information Restrictions on concomitant medications are described in Section 6.2.

4.6.9 Potential risk to women of child-bearing potential

At this stage of development, DFV890 has not been assessed in developmental and reproductive toxicity studies or experience in human pregnancies and all menarchal females and sexually active males must be informed that exposure to DFV890 may involve unknown risks to the fetus if pregnancy were to occur. Therefore, pregnant women are excluded from enrollment into this study, and women of child-bearing potential (WOCBP) and sexually active males must agree to that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria (Section 5.2). If there is any question that the participant will not reliably comply, they should not be enrolled or continue the study.

4.6.10 Blood sample volume

A volume equivalent to a typical blood donation is planned to be collected over a period of 13 months, from each participant as part of the study. A maximum blood volume of 150 mL will be collected during the Screening period, 210 mL during the Treatment period (plus 25 mL in case an unscheduled visit has to take place) and 35 mL at the Study completion visit. Additional samples may be required for safety monitoring.

Sample volume may vary according to local laboratory standard. A total maximal volume of 420 mL of blood per participant will be collected during his/her participation in the study.

Timings of blood sample collection are outlined in the assessment schedule (Table 8-1).

See the Section 8.5.3.2 on the potential use of residual samples.

4.6.11 Overall Risk Benefit

Based on the clinical experience with DFV890 in the Commercially Confidential Information , the CDFV890D12201 phase II study in COVID-19, relevant nonclinical findings, the biological understanding of the pathways and their relevance to FCAS, the overall risk-benefit of DFV890 is, to date, considered favorable. The clinical, safety and laboratory assessments from the completed CCI COVID-19 studies show that DFV890 is generally well tolerated and has a manageable safety profile. Commercially Confidential Information

In addition to the risks noted above, there may be risks to DFV890 that are serious and unforeseen. Therefore, the risks to FCAS participants in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring including markers of renal function, frequent follow up, minimal duration of the study and stopping rules.

5 Study Population

The study population includes approximately 6, but not more than 10, adult participants with FCAS who show evidence of inflammatory activity after the cold challenge performed during screening.

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 study-specific assessment is performed.
2. Participants must be able to communicate well with the investigator and to understand and comply with the requirements of the study.
3. Male and female participants aged between 18 - 80 years (for France 18 - 60 years) inclusive at the time of screening will be included.
4. Participants must have a body mass index (BMI) within the range of 18 - 35 kg/m^2 (BMI = Body weight (kg) / [Height (m)]^2) at Screening, Screening Cold Challenge Admission visit and Day 1 pre-dose.
5. Participant with a genetic diagnosis of FCAS (this analysis may be performed as part of screening if not readily available).
6. Clinical history and investigations consistent with FCAS, in the absence of a history or diagnosis of amyloidosis and/or organ damage (e.g. deafness, periorbital edema, lymphadenopathy, and serositis).
7. Evidence of inflammatory disease activity during the screening period before the admission to the screening cold challenge, captured by the Physician global assessment of autoinflammatory disease activity > minimal, recorded at Screening Cold Challenge Admission visit.
8. Participants who have evidence of inflammatory activity after the screening cold challenge, as assessed by a relative increase in WCC of at least 40% compared to pre-challenge.

5.2 Exclusion criteria

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

1. Commercially Confidential Information

2. Anti-rejection and/or immunomodulatory drugs must be discontinued (see Section 6.2.2):
   - Anakinra at least 1 day prior to the screening cold challenge and until study completion
   - Canakinumab and rilonacept at least 3 half-lives prior to the screening cold challenge, at least 5 half-lives prior to Day 1 and until study completion
   - Other anti-rejection/immune modulatory therapies at least 3 half-lives prior to screening cold challenge, at least 5 half-lives prior to Day 1 and until study completion
   - Ad hoc use of anakinra is permitted for the interval between the screening cold challenge and Day 1, if it can be discontinued at least 5 half-lives prior to Day 1
   - Ad hoc use of paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs, as per local regulations/practice) is permitted for symptomatic relief
3. Participants currently being treated with drugs known to be strong or moderate inducers of isoenzyme CYP2C9 and/or strong inhibitors of CYP2C9 and/or strong inducers of

cytochrome P450, family 3, subfamily A (CYP3A) or dual strong or moderate inhibitors of CYP2C9/CYP3A (see list of prohibited drugs Table 6-3) and the treatment cannot be discontinued or switched to a different medication by 5 half-lives or 1 week (whichever is longer) prior to Day 1 and for the duration of the study.

4. Participation in any other investigational trials within 5 half-lives or within 30 days of screening (e.g. investigational small molecules) or until the expected PD effect has returned to baseline (e.g. investigational biologics), whichever is longer; or longer if required by local regulations with the exception of treatment with anakinra, canakinumab, rilonacept and/or other investigational IL-1/NLRP3 binding or blocking therapy.
5. Participants with innate (e.g. Toll-like receptor (TLR) immunodeficiencies, defects in interferon-gamma (IFN-γ) signaling) or acquired immune deficiencies (e.g. AIDS).
6. Presence of human immunodeficiency virus (HIV) infection, hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (anti-HBc), or hepatitis C antibodies at Screening.
7. Participants who have undergone solid organ or stem cell transplantation.
8. Live vaccines within 4 weeks of Day 1.
9. Clinically significant, suspected active or chronic bacterial (including *Mycobacterium tuberculosis*), viral or fungal infection within 30 days prior to Day 1.

   COVID-19 specific: It is highly recommended that testing with polymerase chain reaction or other approved diagnostic methodology for COVID-19 to be completed within 1 week prior to first dosing. If testing is performed, negative test results are required prior to enrolment into the study. Additional testing may occur at the discretion of the investigator. 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.
10. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in situ* cervical cancer), treated or untreated, within the past 5 years prior to Screening, regardless of whether there is evidence of local recurrence or metastases.
11. Absolute peripheral blood neutrophil count of $\leq 1000/mm^3$ at Screening, Screening Cold Challenge Admission visit and at Day 1 pre-dose.
12. A history of renal disease, including nephrolithiasis, and/or an estimated GFR (eGFR) ≤90 $mL/min/1.73m^2$ (based on Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula) at Screening, Screening Cold Challenge Admission visit and at Day 1 pre-dose.
13. History of clinically significant liver disease or liver injury as indicated at Screening, Screening Cold Challenge Admission visit and at Day 1 pre-dose by abnormal liver function tests (as defined below) such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), or serum bilirubin. The Investigator should be guided by the following criterion:
    - Any single parameter may not exceed 2x upper limit of normal (ULN).
14. History or current diagnosis of ECG abnormalities indicating significant safety risk for participant enrolled in the study such as:

- Concomitant clinically significant cardiac arrhythmias; e.g. sustained ventricular tachycardia, and clinically significant second- or third-degree atrioventricular block without a pacemaker
- History of familial long QT syndrome or known family history of Torsades de Pointes

15. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human serum chorionic gonadotropin (hCG) laboratory test.
16. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 10 days after stopping of study treatment. *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 intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
    - In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
    - 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 (Section 4.6.8), therefore hormonal contraception must be supplemented with a barrier method, preferable a male condom.

    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 ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential. Refer to Section 8.4.3 (Pregnancy and Assessments of Fertility).

17. Sexually active males unwilling to use a condom during intercourse while taking study treatment and for 10 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 while taking study treatment and for 10 days after stopping study treatment.
18. Participants unwilling to comply with restrictions related to use of alcohol (see Section 6.2.4.1).
19. Participants with the CYP2C9 *3/*3 genotype defined as homozygous carriers of the CYP2C9*3 allele.
20. Donation or loss of 400 mL or more of blood within 8 weeks prior to Screening, or longer if required by local regulation, plasma donation (>200 mL) within 30 days prior to Day 1.
21. History of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes.
22. Any significant concurrent medical condition (e.g. anemia) that, in the opinion of the investigator, could affect the participant's ability to tolerate or complete the study.
23. Participants with cold urticaria (e.g. acquired cold urticaria) or immediate systemic reactions (e.g. tachycardia, hypotension, fainting) to cold or during aquatic activities

6 Treatment

6.1 Study treatment

Details on the requirements for storage and management of study treatment, and instructions to be followed for prescribing/dispensing, and taking study treatment are outlined in Section 6.1.1 and Section 6.7. A separate Pharmacy Manual will not be provided.

6.1.1 Investigational and control drugs

The investigational drug DFV890 25 mg tablets will be provided by Novartis Global Clinical Supply. Investigational drug will be supplied to the investigator as open-label participant-specific supplies. DFV890 100 mg will be administered orally shortly after completion of a meal b.i.d. approximately 12 hours apart (morning and evening). The investigational drug should not be stored above 25 °C.

Table 6-1 Investigational drug

Investigational Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
DFV890 25 mg	Film coated tablet	Oral	Open label participant-specific supplies	Novartis Pharma AG

6.1.2 Additional study treatments

No other treatment beyond investigational drug is included in this trial.

6.1.3 Treatment arms/group

All study participants will receive 100 mg of DFV890 b.i.d. for 3 days and 100 mg of DFV890 in the morning on the fourth day, starting on morning of Day 1. At each administration, 4 tablets of 25 mg DFV890 each will be taken.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

Participants should remain on their current medication wherever possible for the duration of the study; if additions to chronic medications are required, these should be discussed with the sponsor.

The investigator must instruct the participants to notify the study site about any new medications he/she takes after the participant provided consent to the study.

All relevant medications , procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered from 30 days prior to the participant's consent until the Study completion visit must be recorded on the appropriate electronic Case Report Forms (eCRF). Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Novartis medical monitor before enrolling 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.

Decisions regarding replacements of participants requiring concomitant medication will be discussed with the sponsor on a case-by-case basis.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Clinical studies to investigate DDIs with Cytochrome P450 (CYP) substrates/modulators and DFV890 have not been performed yet.

In this clinical study protocol, modulators (strong or moderate inducers and strong inhibitors) of CYP2C9 and/or strong inducers of CYP3A are prohibited (Section 6.2.2) and hormone-based contraceptives must be supplemented with a barrier method, preferable a male condom.

Investigators at their discretion may administer concomitant medications known to be metabolized by CYP3A4/5. Participants receiving such medications may require dose titration or increase of the concomitant drug. Particularly, caution is advised when DFV890 is co-administered with drugs that are sensitive substrates of CYP3A and/or have a narrow therapeutic index (Table 6-2). Strong and moderate inhibitors of CYP3A should be avoided. If they cannot be replaced by other medications, investigators may, after consultation with the sponsor, co-administer known strong or moderate inhibitors of CYP3A, but their duration should be kept as short as possible, and participants must be closely monitored.

Table 6-2 Concomitant medications to be used with caution

Category	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], nirmatrelvir/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, grapefruit juice, imatinib, isavuconazole, istradefylline, lefamulin, letermovir, Magnolia vine (*Schisandra sphenanthera*)[3], netupitant, nilotinib, ravuconazole, tofisopam, verapamil, voxelotor
Narrow therapeutic index substrates of CYP3A	abemaciclib, acalabrutinib, alectinib amiodarone, amitriptyline, astemizole, axitinib, baricitinib, bosutinib, brigatinib, cabazitaxel, cabozantinib, ceritinib, clomipramine, cobimetinib, conivaptan, copanlisib, crizotinib, cyclosporine, dabrafenib, dasatinib, dihydroergotamine, docetaxel, dronedarone, entrectinib, erdafitinib, ergotamine, everolimus, imipramine, ixazomib, lomitapide, midostaurin, neratinib, nilotinib, panobinostat, pexidartinib, pimozide, ponatinib, quinidine, regorafenib, romidepsin, sirolimus, sonidegib, sorafenib, sunitinib, tacrolimus, tamoxifen, temsirolimus, tolvaptan, trabectedin, venetoclax, vinblastine, zanubrutinib

Category	Drug Names
Sensitive substrates of CYP3A	abemaciclib, acalabrutinib, alisporivir, almorexant, alfentanil, alpha-dihydroergocryptine, aplaviroc, aprepitant, asunaprevir, atazanavir, atorvastatin, avanafil, avapritinib, blonanserin, bosutinib, brecanavir, brigatinib, brotizolam, budesonide, buspirone, cabazitaxel, capravirine, casopitant, cobicistat, cobimetinib, conivaptan, cyclosporine, danoprevir, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eliglustat, elvitegravir, entrectinib, eplerenone, everolimus, felodipine, fluticasone, grazoprevir, ibrutinib, indinavir, isavuconazole, itacitinib, ivabradine, ivacaftor, levomethadyl (LAAM), lomitapide, lopinavir, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, midostaurin, morphothiadin, naloxegol, neratinib, nisoldipine, paritaprevir, perospirone, quetiapine, ridaforolimus, saquinavir, sildenafil, simeprevir, simvastatin, sirolimus, tacrolimus, ticagrelor, tilidine, tipranavir, tolvaptan, triazolam, ubrogepant, ulipristal, vardenafil, venetoclax, vicriviroc, vilaprisan, voclosporin, voriconazole, zanubrutinib

[1] Combination therapy

[2] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent

[3] Herbal product

6.2.2 Prohibited medication

Use of topical and systemic treatments displayed in the below table are not allowed during the time period noted below.

Novartis qualified medical personnel will be readily available to advise investigators on trial related medical questions about concomitant therapy and prohibited medications.

Table 6-3 Prohibited medication

Medication	Prohibition period	Action taken
Anakinra[a]	At least 1 day prior to screening cold challenge, at least 1 day prior to Day 1 and until study completion	Screen fail participant/ Discontinue study treatment
Canakinumab	At least 3 half-lives (78 days) prior to screening cold challenge, at least 5 half-lives (130 days) prior to Day 1 and until study completion	Screen fail participant/ Discontinue study treatment
Rilonacept	At least 3 half-lives (26 days) prior to screening cold challenge, at least 5 half-lives (43 days) prior to Day 1 and until study completion	Screen fail participant/ Discontinue study treatment

Medication	Prohibition period	Action taken
Other anti-rejection/immune modulatory therapies	At least 3 half-lives prior to screening cold challenge, at least 5 half-lives prior to Day 1 and until study completion	Screen fail participant/ Discontinue study treatment
Live vaccine[b]	Four weeks prior to Day 1 (first DFV890 dose) until study completion	Screen fail participant/ Discontinue study treatment
Strong or moderate inducers of CYP2C9 or strong inducers of CYP3A including, but not limited to apalutamide, avasimibe, carbamazepine, enzalutamide, ivosidenib, lumacaftor, mitotane, phenobarbital, phenytoin, rifampicin, rifapentine and St. John's wort (Hypericum perforatum)	5 half-lives or 1 week (whichever is longer) prior to Day 1 (first DFV890 dose) until study completion	Screen fail participant/ Discontinue study treatment
Strong inhibitors of CYP2C9 or dual strong or moderate inhibitors of CYP2C9/CYP3A (including, but not limited to miconazole, sulfaphenazole, fluconazole, tasisulam)	5 half-lives or 1 week (whichever is longer) prior to Day 1 (first DFV890 dose) until study completion	Screen fail participant/ Discontinue study treatment
Other investigational products	5 half-lives or within 30 days of screening visit (e.g. small molecules) or until the expected PD effect has returned to baseline (e.g. biologics), whichever is longer; or longer if required by local regulations, until study completion	Screen fail participant/ Discontinue study treatment

[a] Ad hoc use of anakinra is permitted for the interval between the screening cold challenge and Day 1, if it can be discontinued at least 5 half-lives prior to Day 1. Ad hoc use of paracetamol and NSAIDs is permitted for symptomatic relief or as recue medication (as per local regulations/practice) (Section 6.2.3).

[b] No live vaccinations within 4 weeks prior Day 1 (first dose of DFV890) until study completion. Approved killed, inactivated, peptide, deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) vaccines may be permitted according to the investigator's discretion and per local guidance.

6.2.3 Rescue medication

The use of paracetamol/acetaminophen or NSAID is allowed as rescue medication for symptomatic relief.

Ad hoc use of anakinra is permitted for the interval between the screening cold challenge and Day 1, if it can be discontinued at least 5 half-lives prior to Day 1.

Any use of rescue medication must be recorded on the appropriate eCRF.

6.2.4 Restriction for study participants

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

6.2.4.1 Dietary restrictions and smoking

1. No alcohol use 24 hours prior to and during the first cold challenge and for 48 hours thereafter. No alcohol use 24 hours prior to the initiation of the treatment, during treatment and until 48 hours after the second cold challenge.
2. Grapefruit or grapefruit juice should not be consumed for 14 days prior to dosing until 7 days following the last dose.
3. Participants should take DFV890 b.i.d. at approximately the same time each day (±1 hour if possible) in the morning and evening shortly after completion of a meal and with a glass of water. The morning meal should consist of at least a continental breakfast.

6.2.4.2 Other restrictions

- Participants will be required to adhere to the measures and procedures outlined by the study site, to prevent SARS-CoV-2 infections among trial participants and clinical site staff.
- Strenuous physical exercise (e.g. heavy weight training, aerobics, football) should not be performed within 24 hours prior to any study visit, during the two cold challenges and during the treatment period.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 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 re-screened. The Participant No. consists of the Center Number (Center 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 re-screen the participant after a participant has screen failed, and the participant will be assigned a new Participant No.

6.3.2 Treatment assignment, randomization

This is an open label single arm study. No randomization will be performed.

6.4 Treatment blinding

Not applicable.

6.5 Dose escalation and dose modification

Investigational treatment dose adjustments and/or interruptions are not permitted. In the case that the Day 3 /Admission visit must be delayed, the treatment should be prolonged with one day (b.i.d. Day 4, once daily Day 5). This option should only be used under exceptional circumstances.

6.6 Additional treatment guidance

6.6.1 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. Participants will be provided with a diary to capture date and time of study treatment intake as well to confirm the study treatment was taken shortly after completion of a meal. All completed diaries will be kept at the site as source documentation. The diaries will not be collected by the sponsor. The participant must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts (if applicable) and information provided by the participant. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.6.2 Recommended treatment of adverse events

Treatment and management of skin rashes

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. pruritus, burning)) with symptomatic treatment (e.g. topical steroids) with close monitoring of the participant's response.

For skin rashes covering > 10% body surface area, 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 corticoids steroid (e.g. prednisone 1 to 2 mg/kg per day for five to seven days) may be considered.

Treatment of Overdose

There is no clinical experience with DFV890 overdose. Should an overdose occur, the participant should be carefully monitored for any potential symptoms, and if necessary, appropriate supportive care should be provided until the participant has recovered.

At present there is insufficient information to provide specific recommendations regarding treatment of other potential AEs in this patient population. Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies eCRF.

6.6.3 Emergency breaking of assigned treatment code

Not applicable.

6.7 Preparation and dispensation

Each study site will be supplied with study treatment in packaging as described under investigational and control drugs section (Section 6.1.1).

A unique medication number is printed on the study treatment label. Investigator staff will dispense the study treatment to the participant. The study treatment has a 2-part label (base plus tear-off label), immediately before dispensing the bottle to the participant, site personnel will detach the outer part of the label from the bottle and affix it to the participant's source document.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 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 investigational treatment must be stored according to the instructions specified on the labels.

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

Medication labels will be in the local language (or in English in case allowed according to local regulation) and comply with the legal requirements of each country. They will include storage conditions for the investigational treatment but no information about the participant except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of investigational treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Participants will be asked to return all unused investigational treatment upon last dose.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused investigational 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. Alternatively following written approval from the Sponsor, destruction of all unused study treatment and packaging/drug labels may be performed at the site as per the site's Standard Operating Procedure (SOP). A copy of the destruction form and final drug accountability will then be provided to the Novartis address provided in the Investigator folder at the site.

6.7.2 Instruction for prescribing and taking study treatment

Participants should take DFV890 b.i.d. at approximately the same time each day (+/- 1 hour if possible) in the morning and evening shortly after completion of a meal and with a glass of water. The morning meal should consist of at least a continental breakfast.

Participants should be instructed to swallow whole tablets and not to chew them.

If vomiting occurs during the course of treatment, participants should not take the study treatment 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 4 hours after the approximate time of the usually daily dosing. That dose should be omitted, and the participant should continue treatment with the next scheduled dose.

The first dose will be administered in the clinic, subsequent doses on Day 1 and 2 will be self-administered by the participant. Participants will be provided with individual diary cards to record each intake of study treatment and to confirm that study treatment was taken shortly after completion of a meal. The diary will be checked by site staff on Day 3.

On Day 3, the participant will administer the morning and evening dose of DFV890 after admission to the clinic, when instructed by the study staff. The last dose will be administered on the morning of Day 4. Participants will be provided a breakfast which should be consumed within 30 minutes. The study treatment should be administered within 5 minutes after completion of the meal.

Table 6-4 Dose and treatment schedule

Investigational Drug (Name and Strength)	Dose	Frequency and/or Regimen
DFV890 25 mg	100 mg (4 x 25 mg)	Twice daily (Day 1-3) Once daily (Day 4)

7 Informed consent procedures

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

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.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the participant informed consent and should be discussed with the participant 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 investigator notification (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 investigator may conduct any informed consent discussion remotely (e.g. via telephone or videoconference) where feasible as per medical judgment. Guidance issued on this by local regulatory bodies prevails and must be appropriately implemented and documented (e.g. the

presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

The following informed consents are included in this study:

- Main study consent, which also includes:
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
  - Optional consent for activities that may be done outside of the study site
- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the female partners of any male participants who took study treatment
- Patient information sheet for female partners of any male participants who took study treatment
- Commercially Confidential Information

Women of child bearing potential 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.

Male participants must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

Commercially Confidential Information

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

The study includes the option for the participant to have certain study procedures performed off-site by an off-site healthcare professional instead of at the study site, for which a separate signature is required if the participant agrees, as permitted by national and local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments and when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the eCRF.

Unscheduled visits and the Study completion visit may be performed at an alternative Sponsor-approved site (e.g. satellite site that may be more convenient to the participant) if agreed by the principal investigator who will maintain the investigator responsibilities, and only as permitted by local regulations.

As per Section 4.4, 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) 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 off-site healthcare professional, 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 8-1 Assessment Schedule

Epoch	Screening[27]										Open Label Treatment										
Visit Name	**Screening**	**Admission [18,19]**	**Screening Cold Challenge[18]**							**Discharge [18]**	**Day 1[2,20]**	**Day 3/Admission[3,4]**	**Day 4/ Cold Challenge**							**Day 5/Discharge**	**Rash [21, 22]**
Visit Numbers[1]	**1**	**2**	**3**							**4**	**101**	**102**	**103**							**104**	**105**
Days	**-183 to -11**	**-10**	**-9**							**-8**	**1**	**3**	**4**							**5**	**unscheduled**
Time (post-dose)[26]	**-**	**-**	**-1h**	**0h**	**1h**	**2h**	**3h**	**5h**	**9h**	**24h**	**-**	**-**	**-1h**	**0h**	**1h**	**2h**	**3h**	**5h**	**9h**	**24h**	**-**
Informed consent	X																				
Commercially Confidential Information																					
Inclusion / Exclusion criteria	X	X									X										
Medical history/current medical conditions	X										X										
Smoking history	X																				
Demography	X																				
Hepatitis and HIV Screen	S										S[23]										
Tuberculosis test	S										S[23]										
Pregnancy test and assessment of fertility[25]	S	S									S										
Physical Examination (full)	S										S										
Physical Examination (short)			S			S	S	S	S	S		S	S			S	S	S	S	S	S
Vital signs and body measurements	X	X	X		S[16]	X	X	X	X	X	X	X	X		S[16]	X	X	X	X	X	X
Body Height	X																				
Body Weight	X	X									X										

Epoch	**Screening[27]**										**Open Label Treatment**										
Visit Name	**Screening**	**Admission [18,19]**	**Screening Cold Challenge[18]**							**Discharge [18]**	**Day 1[2,20]**	**Day 3/Admission[3,4]**	**Day 4/ Cold Challenge**							**Day 5/Discharge**	**Rash [21, 22]**
Visit Numbers[1]	**1**	**2**	**3**							**4**	**101**	**102**	**103**							**104**	**105**
Days	**-183 to -11**	**-10**	**-9**							**-8**	**1**	**3**	**4**							**5**	**unscheduled**
Time (post-dose)[26]	**-**	**-**	**-1h**	**0h**	**1h**	**2h**	**3h**	**5h**	**9h**	**24h**	**-**	**-**	**-1h**	**0h**	**1h**	**2h**	**3h**	**5h**	**9h**	**24h**	**-**
Electrocardiogram (ECG)	X										X	X									
Participants domiciled[6]		S										S									
Study drug administration											X	X		X							
Meal record				S							S										
Cold challenge[7]					X										X						
Patients Global Assessment of Disease Activity			X			X	X	X	X	X	X	X	X			X	X	X	X	X	
Physician Global Assessment of Autoinflammatory Disease Activity		X[17]	X			X	X	X	X	X	X	X	X			X	X	X	X	X	
Physician's Severity Assessment of Autoinflammatory Disease Signs and Symptoms			X			X	X	X	X	X	X	X	X			X	X	X	X	X	
Urinalysis	X	X									X[24]	X	X							X	X
Hematology	X	X									X[24]		X							X	X
Clinical Chemistry	X	X									X[24]		X							X	X

Epoch	**Screening[27]**										**Open Label Treatment**										
Visit Name	**Screening**	**Admission [18,19]**	**Screening Cold Challenge[18]**							**Discharge [18]**	**Day 1[2,20]**	**Day 3/Admission[3,4]**	**Day 4/ Cold Challenge**							**Day 5/Discharge**	**Rash [21, 22]**
Visit Numbers[1]	**1**	**2**	**3**							**4**	**101**	**102**	**103**							**104**	**105**
Days	**-183 to -11**	**-10**	**-9**							**-8**	**1**	**3**	**4**							**5**	**unscheduled**
Time (post-dose)[26]	**-**	**-**	**-1h**	**0h**	**1h**	**2h**	**3h**	**5h**	**9h**	**24h**	**-**	**-**	**-1h**	**0h**	**1h**	**2h**	**3h**	**5h**	**9h**	**24h**	**-**
Mandatory CYP2C9 genotyping for confirmation of eligibility[5]	X																				

Commercially Confidential Information

Adverse Events	As Required																				
Serious Adverse Events	As Required																				
Concomitant medications	As Required																				
Study completion information																					
Safety Follow up Call																					

Epoch	**Post-Treatment Follow-Up**	**Post-Treatment Follow-Up**
Visit Name	**Study Completion**[14, 22]	**Post Study Safety Contact**[15]
Visit Numbers[1]	**201**	**301**
Days	**14** **-0 +7**	**34** **±3**
Time (post-dose)	**-**	**-**
Informed consent		

Commercially Confidential Information

Inclusion / Exclusion criteria		
Medical history/current medical conditions		
Smoking history		
Demography		
Hepatitis and HIV Screen		
Tuberculosis test		
Pregnancy test and assessment of fertility[25]	S	
Physical Examination (full)		
Physical Examination (short)	S	
Vital signs and body measurements	X	
Body Height		
Body Weight		
Electrocardiogram (ECG)	X	
Participants domiciled[6]		
Study drug administration		

Epoch	**Post-Treatment Follow-Up**	**Post-Treatment Follow-Up**
Visit Name	**Study Completion**[14, 22]	**Post Study Safety Contact**[15]
Visit Numbers[1]	**201**	**301**
Days	**14 -0 +7**	**34 ±3**
Time (post-dose)	**-**	**-**
Meal record		
Cold challenge[7]		
Patients Global Assessment of Disease Activity	X	
Physician Global Assessment of Autoinflammatory Disease Activity	X	
Physician's Severity Assessment of Autoinflammatory Disease Signs and Symptoms	X	
Urinalysis	X	
Hematology	X	
Clinical Chemistry	X	
White Cell Count with differentials[8]	X	

Adverse Events	As Required	
Serious Adverse Events	As Required	
Concomitant medications	As Required	
Study completion information	X	
Safety Follow up Call		S

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Visit Numbers given for internal programming purpose only
[2] Assessments to be conducted prior to first dose
[3] Assessments to be conducted prior to the morning dose
[4] Admission can be delayed with a maximum of one day and treatment hence prolonged to with one day. This option should only be used under exceptional circumstances
[5] To confirm eligibility, available historical CYP2C9 genotyping results confirming the absence of the CYP2C9*3/*3 variant previously issued in frame of this study are acceptable for re-screened participants
[6] Participant domiciliation may be prolonged at the discretion of the investigator and patient
[7] The start of the cold challenge is at 1 h and the duration is 45 minutes. The screening cold challenge should be initiated 1 h after meal and treatment cold challenge 1 h after treatment administration.
[8] Where possible, white cell count should be included as part of hematology sampling, rather than collecting a separate sample
[9] Commercially Confidential Information
[10] To be collected at 0 h prior to morning dose and 12 h after previous evening dose the day before
[11] To be collected at 1 h postdose, prior to initiation of cold challenge
[12] Commercially Confidential Information
[13]
[14] Also applicable in case of early discontinuation
[15] 30 days after last dose
[16] Vital signs to be collected every 10 minutes during the cold challenge and at the end of the cold challenge
[17] The Physician Global Assessment of Autoinflammatory Disease Activity conducted at the Screening Cold Challenge Admission visit must capture evidence of disease flare (> minimal) occurring during the screening period
[18] The screening cold challenge can be conducted any time during the screening period (the visits “Admission”, “Screening Cold Challenge” and “Discharge” must occur on 3 consecutive days), provided that Day 1 is conducted within 6 months (and within 12 months for participants with a historical screening cold challenge prior to protocol amendment 04) of the Screening visit
[19] Participants can be admitted to the Screening Cold Challenge visit only when all eligibility criteria are confirmed, except inclusion criterion 8 which is assessed during the screening cold challenge
[20] Participants can enter the treatment period after at least one week of recovery after the Screening Cold Challenge Discharge visit
[21] An unscheduled visit should be considered based on clinical findings and severity of rash or pruritus
[22] May be performed at an alternative Sponsor-approved site (e.g. satellite site that may be more convenient to the participant) if agreed by the principal investigator who will maintain the investigator responsibilities, and only as permitted by local regulations
[23] Hepatitis and HIV Screen, tuberculosis test may be repeated according to the investigator’s discretion, if performed more than 6 months prior to Day 1
[24] Hematology, clinical chemistry and urinalysis results must be available before the first dose is administered on Day 1 to confirm eligibility of the participant. For logistical reasons sampling may be performed the day before Day 1 instead of Day 1
[25] Serum pregnancy test should be performed at Screening and Study completion visits, urine pregnancy test at all other visits
[26] The sampling time points during the screening period are referring to pre/post-meal, since there is no dose administered during the screening period
[27] The screening period is up to 6 months (and up to 12 months for participants with a historical screening cold challenge prior to protocol amendment 04)

8.1 Screening

Screening

It is permissible to re-screen a participant if s/he fails the assessments done during the screening period; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

In the case where a safety laboratory assessment at screening is outside of the range specified in the exclusion criteria, the assessment may be repeated once prior to enrolment. If the repeat value remains outside of the specified ranges, the participant must be excluded from the study.

8.1.1 Eligibility screening

8.1.1.1 Hepatitis screen, HIV screen

All participants will be screened for Hepatitis B surface antigen (HBsAg) and, if standard local practice, Hepatitis B core antigen (HBcAg). Screening for Hepatitis C will be based in Hepatitis C Virus (HCV) antibodies and if positive, HCV RNA levels should be determined.

Evaluation for HIV seropositivity will be performed, and, if positive, confirmation by a second technique available at the laboratory site; e.g. Western blot. Appropriate counseling will be made available by the Investigator in the event of a positive confirmatory test. Notification of state and federal authorities, as required by law, will be the responsibility of the Investigator.

Samples will be collected and processed according to local procedures and analyzed at the local laboratory.

Hepatitis and HIV Screen may be repeated according to the investigator's discretion, if performed more than 6 months prior to Day 1.

8.1.1.2 Tuberculosis (TB) testing

In order to evaluate the tuberculosis (TB) status of the participants, a TB test should be performed at Screening as per local regulations/guidelines using one or both of the following methods:

- QuantiFERON®-TB assay
- Tuberculin skin testing

Samples will be collected and processed according to local procedures and analyzed at the local laboratory. Negative test results from the previous 3 months may be used if available.

Tuberculosis test may be repeated according to the investigator's discretion, if performed more than 6 months prior to Day 1.

Any significant findings will be recorded in the Relevant medical history/Current medical conditions section of the eCRF as necessary.

8.1.2 Information to be collected on screening failures

Participants who sign an informed consent form and subsequently found to be ineligible will be considered a screen failure. This applies also to participants who are considered screen failures after the screening cold challenge. The reason for screen failure should be entered on the

applicable eCRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. Additional data may be entered to support the eligibility decision, such as – but not limited to – medical history, relevant prior and concomitant medications, hematology, clinical chemistry. SAEs will also be collected for screen failed participants (see SAE section (Section 10.1.3) for reporting details).

Participants who sign an informed consent and are considered eligible but fail to be started on treatment for any reason will be considered an early terminator. The reason for early termination should be captured on the appropriate disposition eCRF.

8.2 Participant demographics/other baseline characteristics

Demographic information

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with eCRF. Participant race and ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities.

Participant demographics: year of birth (age), sex, race, predominant ethnicity (if permitted), child-bearing potential (women only), relevant medical history/current medical conditions (until date of signature of informed consent), specific NLRP3 mutation (if available) and nicotine use will be recorded in the eCRF. Where possible, the diagnosis and not symptoms should be recorded. Vaccination status (12 months prior to the participant's consent until the Study completion visit) should be recorded as part of the collection of medical history/current medical conditions.

All prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start of the study must be documented. See the protocol Section 6.2.1 Concomitant Therapy for further details on what information must be recorded on the appropriate page of the eCRF.

FCAS medical history and diagnosis

The following should be recorded in the participants medical records

- Molecular diagnosis of NLRP3 mutations
- Absence of L353P mutation
- Presence of mutation with documented responsiveness to DFV890 in *ex vivo* testing if available
- Clear documentation of use of and response to previous treatment therapeutics targeting the IL-1β pathway if available
- Presence of active disease following discontinuation of current treatment as outlined in Section 5.1.
- Any available documentation of previous medical assessments (e.g. auditory brainstem response, neurological and ophthalmological assessments) to document absence of organ damage and/or amyloidosis

8.3 Efficacy

Efficacy assessments will be performed at the timepoints defined in the Assessment Schedule (Table 8-1).

8.3.1 Inflammatory markers

WCC (primary endpoint) Commercially Confidential Information will be assessed at the timepoints defined in the Assessment Schedule (Table 8-1). Samples will be collected and processed according to local procedures and analysed at the local laboratory. Where possible, WCC, CCI will be included as part of hematology and clinical chemistry sampling respectively, rather than collecting separate samples.

8.3.2 Clinical Outcome Assessments (COAs)

Two Clinician Reported Outcomes (ClinRO), the physician global assessment of autoinflammatory disease activity and physician's severity assessment of autoinflammatory disease signs and symptoms, as well as one Patient reported outcomes (PRO), the patient's global assessment of disease activity, are described in this section.

As per Section 4.4, 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, COA data may be collected remotely.

Physician global assessment of autoinflammatory disease activity

The physician global assessment on autoinflammatory disease activity (secondary endpoint and to confirm participant eligibility (Section 5.1)) will be performed at the timepoints defined in the Assessment Schedule (Table 8-1). The assessment recorded at the Admission visit prior to the screening cold challenge captures evidence of symptoms occurring during the screening period. It is encouraged that the same Investigator assesses the participant throughout the study to ensure consistency between assessments.

The physician global assessment on autoinflammatory disease activity will be based on a 5-point scale of disease-associated clinical signs and symptoms (see Section 16.4):

0 = Absent

1 = Minimal

2 = Mild

3 = Moderate

4 = Severe

The assessments will be entered in the eCRF. In case an alternative Sponsor-approved site is utilized (e.g. satellite site that may be more convenient to the participant), the main site principal investigator must consult with the additional site investigator either during or shortly after the participant visit to consult and document a signed agreement on the outcome of the physician global assessment of autoinflammatory disease activity.

Physician's Severity Assessment of Autoinflammatory Disease Signs and Symptoms

Physician's severity assessment of autoinflammatory disease signs and symptoms (secondary endpoint) will be performed at the timepoints defined in the Assessment Schedule (Table 8-1). It is encouraged that the same Investigator assesses the participant throughout the study to ensure consistency between assessments.

The following items will be assessed using a 5-point scale (ranging from absent to severe, see Section 16.5):

- Assessment of skin disease (urticarial skin rash)
- Assessment of arthralgia
- Assessment of myalgia
- Assessment of headache/migraine
- Assessment of conjunctivitis
- Assessment of fatigue/malaise
- Assessment of other symptoms related to autoinflammatory syndrome
- Assessment of other symptoms not related to autoinflammatory syndrome

The assessments will be entered in the eCRF. In case an alternative Sponsor-approved site is utilized (e.g. satellite site that may be more convenient to the participant), the main site principal investigator must consult with the additional site investigator either during or shortly after the participant visit to consult and document a signed agreement on the outcome of the physician's severity assessment of autoinflammatory disease signs and symptoms.

Patients Global Assessment of Disease Activity

Patient's global assessment of disease activity (secondary endpoint) will be collected by a handwritten diary. The diary will be completed by the participant prior to any clinical assessments at the timepoints defined in the Assessment Schedule (Table 8-1). The investigator or site staff should not give verbal or non-verbal cues to influence the answers to the diary. The investigator or site staff will only be allowed to review the diary for completeness. The Investigator will review the participant's diary before performing the Physician's global assessment of autoinflammatory disease activity.

The patient global assessment on disease activity will be based on a 5-point scale of disease-associated clinical signs and symptoms (see Section 16.6):

0 = Absent
1 = Minimal
2 = Mild
3 = Moderate
4 = Severe

The diary will be transcribed into the eCRF by the site staff.

8.3.4 Appropriateness of efficacy assessments

The efficacy endpoints selected for this study are clinically relevant and in line with those used in other studies of patients with CAPS (e.g. ACZ885D2307, NCT00288704 (Hoffman et al 2008))

8.4 Safety

Safety assessments are specified below with the assessment schedule (Table 8-1) detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section (Section 10).

As per Section 4.4, 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 for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

Table 8-2 Assessments and Specifications

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A short physical exam will include the examination of general appearance and the skin. 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 eCRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an AE must be recorded as an AE.
Vital Signs	Vital signs will include the collection of CCI , blood pressure (BP) and pulse measurements. Commercially Confidential Information After the participant has been sitting for 3 minutes, with back supported and both feet placed on the floor, systolic and diastolic BP will be measured using an automated validated device with an appropriately sized cuff. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. During the cold challenge the site staff must continuously monitor the participant's vital signs, collecting them at least every 10 minutes and at the end of the cold challenge. Equipment used during the cold challenge may differ from the one mentioned above.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured. BMI will be calculated using the formula below and rounded to the nearest whole number: BMI = Body weight (kg) / [Height (m)]^2 The Screening Visit height measurement will be used for BMI calculations throughout the study.

8.4.1 Laboratory evaluations

Blood and urine samples for the evaluation of safety will be collected at the timepoints defined in the Assessment Schedule (Table 8-1) in accordance with local procedures and analyzed at the local laboratory. Additional parameters may be measured as part of a standard laboratory panel as per local practice however not entered into the eCRF. This would not be considered a protocol deviation.

Results will be entered into the eCRF with the exception of the results of the pregnancy test that is recorded in medical records only. 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, a decision regarding whether the result is of clinical significance or not shall be made by the investigator (in consultation with the sponsor) and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once prior to enrollment. 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.

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.

As per Section 4.4, 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.

Urinalysis

A midstream urine sample (approx. 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments and allow proper assessments. Please follow local procedures for analysis.

Table 8-3 Clinical Laboratory Safety Assessments (local)

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Chemistry	Albumin (ALB), ALP, ALT, AST, Gamma-glutamyl transferase (G-GT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Sodium, Potassium, Creatinine, Creatine kinase (CK), Total Bilirubin (TBL)[a], Total Protein, Triglycerides, BUN or Urea, Uric Acid, Amylase, Lipase, Glucose (*fasting or non-fasting*), SAA, hsCRP
Urinalysis	Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells) Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen)
Coagulation [b]	Prothrombin time (PT), International normalized ratio (INR), Partial thromboplastin time (PTT), Activated partial thromboplastin time (APTT)
Pregnancy Test	Serum pregnancy test

[a] If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated

[b] Coagulation assessment should include only those tests routinely performed according to local standard of care

8.4.2 Electrocardiogram (ECG)

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

The Fridericia QT correction formula (QTcF) must be used for clinical decisions.

Unless auto-calculated by the ECG machine, the investigator must calculate QTcF at the Screening visit to assess eligibility according to the following formula:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

Single 12-lead ECGs are to be collected with ECG machines available at the site. Single 12-lead ECGs are collected, and results are entered into the appropriate eCRF page. The original ECGs on non-heat-sensitive paper and a certified copy on non-heat sensitive paper, appropriately signed, must be collected and archived at the study site.

Each ECG tracing must be labeled with study number, participant initials, participant number, date and time, and filed in the study site source documents.

Investigator should document clinical evaluation in source. For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. Clinically significant ECG findings at Day 1 must be discussed with the sponsor before administration of study treatment.

Clinically significant abnormalities must be recorded on the relevant section of the medical history/Current medical conditions/AE eCRF as appropriate.

8.4.3 Pregnancy and assessments of fertility

Pregnancy

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 should not donate sperm while taking study treatment and for 10 days after stopping study treatment.

All pre-menopausal women who are not surgically sterile will have pregnancy testing performed at the timepoints defined in the Assessment Schedule (Table 8-1). Serum pregnancy testing is required at Screening and Study completion visit, but urine pregnancy testing at all other visits. The samples will be collected in accordance with local procedures and analyzed at the local laboratory. Additional pregnancy testing might be performed if requested by local requirements. Local pregnancy test and associated results will not be collected on eCRF.

As per Section 4.4, 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

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 ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential.

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child-bearing potential must also be available as source documentation in the following cases:

1. Surgical bilateral oophorectomy without a hysterectomy
2. Reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, Follicle Stimulating Hormone (FSH) testing is required of any female participant regardless of reported reproductive/menopausal status at screening.

8.4.4 Appropriateness of safety measurements

The safety assessments selected are appropriate for this protocol, which utilizes a compound which has not previously been used in this patient population and where the safety profile has not therefore been established. The assessments will enable determination of both safety and therapeutic response in this setting.

8.5 Additional assessments

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9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

Discontinuation of cold challenge

The cold challenge will be stopped, if any of the following criteria are met:

- The participant requests to discontinue the cold challenge
- The participant's body temperature is 35.0 °C or below (mild hypothermia*) on two consecutive temperature readings
- The criteria for an overall study stopping rule are met Section 9.1.4

Following stopping of the cold challenge the participant should immediately proceed to rewarming with monitoring, clinical assessments and complete other trial related procedures.

* Mild (hypothermia I) – 35.0-32.0 °C, clear consciousness with shivering, as defined by International Commission for Mountain Emergency Medicine (Durrer et al 2003).

Discontinuation of study treatment

Discontinuation of study treatment for a participant occurs when study treatment is permanently stopped for any reason prior to the protocol planned completion of study treatment administration. Discontinuation of study treatment can be initiated by either the participant or the investigator.

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

Discontinuation from study treatment is required under the following circumstances:

- Participant decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section (see Section 6.2.2)
- Any situation in which continued study participation might result in a safety risk to the participant
- Emergence of at least one of the following AEs:
  - A life-threatening adverse event (corresponding to a CTCAE Grade 4 or higher) unless clearly unrelated to DFV890 and/or the cold challenge
  - An adverse event of severe intensity (corresponding to a CTCAE Grade 3 or higher) unless clearly unrelated to DFV890 and/or the cold challenge
  - Skin rash, other than related to FCAS, greater than mild (covering >10% of the body surface area, corresponding to CTCAE grade 2 or higher), unless clearly unrelated to DFV890
- If an abnormal renal event is confirmed, and other causes are excluded, the study drug will be discontinued in the case of:

- Serum creatinine increase of 50% (i.e. acute kidney injury)
- New onset dipstick proteinuria ≥3+
- Protein-creatinine ratio (PCR, gCr) ≥1 g/g
- New evidence of clinically significant crystals on microscopy

Please refer to Section 10.2.2 (Renal safety monitoring) and Section 16.2, Table 16-4 and Table 16-5 for further instructions and monitoring.

- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the participant's overall status, prevents the participant from continuing participation in the study
- If a liver event occurs, follow guidelines outlined in Section 16.1 regarding discontinuation of study treatment

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant's premature discontinuation of study treatment and record this information.

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 9.1.2 'Withdrawal of Informed Consent' section). **Where possible, they should return for the assessments indicated** in the Assessment Schedule (Table 8-1). If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section (see Section 9.1.3). This contact should preferably be done according to the study visit schedule.

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 study treatment discontinuation, 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

9.1.1.1 Replacement policy

Replacements are not planned. Approximately 6 participants, but not more than 10, will be enrolled in order for 6 participants to complete the cold challenge included in the treatment period.

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

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

- Explicitly requests to stop use of their data

and

- No longer wishes to receive study treatment

and

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

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

Withdrawal of consent impacts the ability to further contact the participant, collect follow-up data (e.g. to respond to data queries) and potentially other country-specific restrictions. It is therefore 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 the assessment table (Table 8-1).

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

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation.

9.1.3 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.

9.1.4 Study stopping rules

Overall study stopping rules

The study will be stopped, and no further dosing and/or new recruitment will occur, pending full safety review by the sponsor and the investigator, if any of the following criteria are met:

- Any death or life-threatening event (corresponding to CTCAE grade 4 or higher) unless clearly unrelated to DFV890 and/or the cold challenge
- Any SAE (other than death or life-threatening event, corresponding to CTCAE grade 3 or higher) unless clearly unrelated to DFV890 and/or the cold challenge
- Two (2) or more participants are discontinued due to a renal event as defined in Section 16.2
- Two (2) participants experience an AE of similar type which is assessed as severe in intensity (corresponding to CTCAE grade 3 or higher) unless clearly unrelated to DFV890
- Number and/or severity of AEs, abnormal safety monitoring tests, or abnormal laboratory findings justify putting the study on hold

The safety review will be conducted jointly between medically qualified representatives of the sponsor and the investigators. The study may resume following the safety review, if the investigator and sponsor agree it is safe to proceed and necessary approvals have been obtained from authorities.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible (instructions for contacting the participant, when the participant should stop taking drug, when the participant should come in for a final visit, will be provided at that time) and treated as a prematurely withdrawn participant. 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 sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their Study completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision. Each participant will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them.

All treated participants should have a safety follow-up call conducted 30 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the participant should be recorded in the source documentation.

Continuing care should be provided by the investigator and/or referring physician. No further study treatment will be provided.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (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 10.1.2):

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 if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. Whether it constitutes a SAE (see Section 10.1.2 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/withdrawn
6. Its outcome (i.e. recovery status or whether it was fatal)

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 until the end of the study visit.

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent (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, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease.

10.1.2 Serious adverse events

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

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- 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 and the malignant neoplasm is not a disease progression of the study indication.

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

All reports of intentional misuse and abuse of the product are also considered SAE irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 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.

For Screen Failures (e.g. a participant who is screened but is not treated or randomized), SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.

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 Chief Medical Office and 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 Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30-day period following the last administration of study treatment should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her 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 the 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 and pregnancy outcome. Any SAE experienced during pregnancy must be reported.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Pregnancy outcomes will be followed-up at the following times:

- 1 month after the estimated date of delivery
- 3 months after the estimated date of delivery (for a live birth only), and
- 12 months after the estimate date of delivery (for a live birth only).

10.1.5 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 (European Medical Association 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 eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. 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.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

Please see Section 10.1.1 and Section 10.1.2 for more information on definition and reporting requirements of AE and SAE, respectively.

10.2 Additional Safety Monitoring

10.2.1 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 16-1 in Section 16.1 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 16-1 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 16-2 and Table 16-3.

- Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation. These liver chemistry repeats should be performed using the local laboratory used by the site. Repeated laboratory test results must be reported as appropriate
- 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, Section 9.1.1), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event. 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 eCRF.

10.2.2 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, urinary tract infection, extreme exercise, or trauma), OR
  - New evidence of clinically significant crystals on microscopy

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, as defined in Table 16-4, should be monitored and followed up by the investigator or designated trial staff as summarized in Table 16-5.

11 Data Collection and Database management

11.1 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 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.

11.2 Database management and quality control

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

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

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource Direct Data Entry (DDE) or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. 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.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original ICF signed by the participant (a signed copy is given to the participant).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according

to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

The analysis will be conducted on all participant data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

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

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

12.2 Participant demographics and other baseline characteristics

The Safety set will be used for the analyses described in this section. Demographic and other baseline data including disease characteristics and smoking status will be summarized descriptively.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation (SD), median, minimum, and maximum will be presented.

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

12.3 Treatments

The Safety set will be used for the analyses described in this section. 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 frequency of DFV890 doses will be displayed for each participant.

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

12.4 Analysis of the primary endpoint(s)/estimand(s)

The primary aim of the study is to assess the efficacy of DFV890 to reduce cold-induced inflammation in participants with FCAS. The fold change in the highest value of total WCC following exposure to a cold challenge vs. pre-challenge levels will be compared between treatment and screening periods. Lower induction of total WCC is considered a favorable outcome. The PD set will be used for the analyses described in this section.

12.4.1 Definition of primary endpoint(s)/estimand(s)

The primary estimand, including the primary endpoint is defined in Section 2.1 of this protocol and is based on the fold change of WCC.

12.4.2 Statistical model, hypothesis, and method of analysis

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

1. statistically significant ($p < 0.10$) and
2. less than 80%.

12.4.3 Handling of remaining intercurrent events of primary estimand

Interruption of study treatment for any reason will be ignored.

12.4.4 Handling of missing values not related to intercurrent event

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

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12.5 Analysis of secondary endpoints/estimands

12.5.1 Safety endpoints

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

Adverse events

All information obtained on adverse events will be displayed by period and participant.

Vital signs

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

ECG

PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each participant during the study. ECG data will be read and interpreted locally. All ECG data will be listed by period, participant and time, abnormalities will be flagged. Summary statistics will be provided by period and time.

Clinical laboratory evaluations

All laboratory data will be listed by period, participant, and time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by period and time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

12.5.2 Efficacy and/or Pharmacodynamic endpoint(s)

The secondary efficacy objective is to assess the effect of DFV890 on clinical outcomes in participants with FCAS. For the following analyses, the PD set will be used.

Physician global assessment of autoinflammatory disease activity

Summary statistics will be provided for physician global assessment of autoinflammatory disease activity by period and time.

Physician's severity assessment of autoinflammatory disease signs and symptoms

Summary statistics will be provided for physician's severity assessment of autoinflammatory disease signs and symptoms by period and time.

Patient's global assessment of disease activity

Summary statistics will be provided for patient's global assessment of disease activity by period and time.

12.5.3 Patient reported outcomes

Please refer to Section 12.5.2 for detailed information on the patients global assessment of disease activity.

12.6 Analysis of exploratory endpoints

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12.7 Interim analyses

No interim analysis is planned for this trial.

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

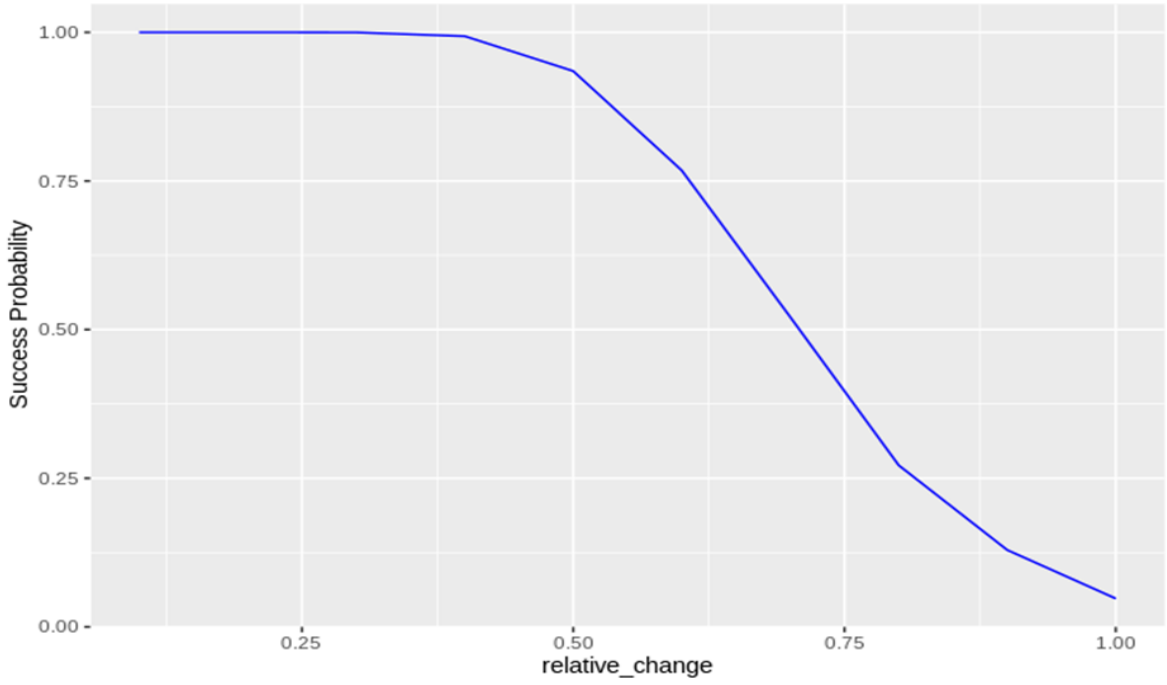
12.8 Sample size calculation

12.8.1 Primary endpoint(s)

Previous results of a cross-over cold challenge design were reported with a maximum mean treatment effect of approximately -8x10^9/L in WCC and a standard deviation of the difference of approximately 3x10^9/L (Hoffman et al 2004). In the relative scale, the ratio of fold changes from pre-challenge to highest post challenge WCC between treatment and screening period is found to be a minimum of approximately 25%. Thus, assuming that with a treatment ratio (treatment *vs* screening period) in the geometric mean of fold changes in WCC of at most 50% and a corresponding standard deviation of the logarithmic fold change to be 0.5, 6 participants provide at least 90% probability to fulfill the combined success criterion described in Section 12.4.2.

Figure 12-1 shows the probability of success for a sample size of 6 participants with varying ratios (from 0.25 to 1) and SD equal to 0.5.

Figure 12-1 Probability of success with 6 participants, varying ratio of fold changes, SD=0.5



13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the trial protocol, written ICF, consent form updates, participant recruitment procedures (e.g. advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign 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. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (*defined as last patient last visit*) 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, EudraCT 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 Last Participant Last Visit (LPLV) date, since multinational studies are locked and reported based upon the global LPLV.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System that includes all activities involved in quality assurance and quality control, to ensure compliance with written SOPs as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

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.

14.1 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

15 References

References are available upon request

Coll RC, Robertson AA, Chae JJ, et al (2015) A small-molecule inhibitor of the NLRP3 inflammasome for the treatment of inflammatory diseases. Nat. Med; 21(3):248-55.

Dinarello CA (2011) A clinical perspective of IL-1β as the gatekeeper of inflammation. Eur J Immunol; 41(5):1203-17.

Dow J, Giesbrecht GG, Danzl DF, et al (2019) Wilderness Medical Society Clinical Practice Guidelines for the Out-of-Hospital Evaluation and Treatment of Accidental Hypothermia: 2019 Update. Wilderness Environ Med; 30(4S):S47-S69.

Durrer B, Brugger H, Syme D (2003) The medical on-site treatment of hypothermia: ICAR-MEDCOM recommendation. High Alt Med Biol; 4(1):99-103.

Evavold CL, Kagan JC (2018) How Inflammasomes Inform Adaptive Immunity. J. Mol. Biol; 430(2):217-237.

Hoffman HM, Kuemmerle-Deschner JB, Goldbach-Mansky R (2019) Cryopyrin-Associated Periodic Syndromes (CAPS). In: Hashkes P, Laxer R, Simon A (eds). Textbook of Autoinflammation. Springer, Cham. p. 347-365.

Hoffman HM, Rosengren S, Boyle DL, et al (2004) Prevention of cold-associated acute inflammation in familial cold autoinflammatory syndrome by interleukin-1 receptor antagonist. Lancet; 364(9447):1779-85.

Hoffman HM, Throne ML, Amar NJ, et al (2008) Efficacy and safety of rilonacept (interleukin-1 Trap) in patients with cryopyrin-associated periodic syndromes: results from two sequential placebo-controlled studies. Arthritis Rheum; 58(8):2443-52.

Hoffman HM, Wanderer AA, Broide DH (2001) Familial cold autoinflammatory syndrome: Phenotype and genotype of an autosomal dominant periodic fever. J Allergy Clin Immunol; 108(4):615-620.

Johnstone RF, Dolen WK, Hoffman HM (2003) A large kindred with familial cold autoinflammatory syndrome. Ann Allergy Asthma Immunol; 90:233-237.

Mangan MSJ, Olhava EJ, Roush WR, et al (2018) Targeting the NLRP3 inflammasome in inflammatory diseases. Nat Rev Drug Discov; 17(8):588-606.

Ridker PM, Everett BM, Thuren T, et al (2017a) Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N. Engl. J. Med; 377(12):1119-1131.

Ridker PM, Libby P, MacFadyen JG, et al (2018) Modulation of the interleukin-6 signalling pathway and incidence rates of atherosclerotic events and all-cause mortality: analyses from the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS). Eur. Heart J; 39(38):3499-3507.

Ridker PM, MacFadyen JG, Thuren T, et al (2017b) Effect of interleukin-1β inhibition with canakinumab on incident lung cancer in patients with atherosclerosis: exploratory results from a randomised, double-blind, placebo-controlled trial. Lancet; 390(10105):1833-1842.

Ross JB, Finlayson LA, Klotz PJ, et al (2008) Use of anakinra (Kineret) in the treatment of familial cold autoinflammatory syndrome with a 16-month follow-up. J Cutan Med Surg; 12(1):8-16.

Schieker M, Conaghan PG, Mindeholm L, et al (2020) Effects of Interleukin-1β Inhibition on Incident Hip and Knee Replacement : Exploratory Analyses From a Randomized, Double-Blind, Placebo-Controlled Trial. Ann Intern Med; 173(7):509-515.

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Shpall RL, Jeffes EWB, Hoffman HM (2004) A case of familial cold autoinflammatory syndrome confirmed by the presence of a CIAS1 mutation. Br J Dermatol; 150(5):1029-31.

Wanderer AA, Hoffman HM (2004) The spectrum of acquired and familial cold-induced urticaria/urticaria-like syndromes. Immunol Allergy Clin North Am; 24(2):259-86.

Vande Walle L, Stowe IB, Šácha P, et al (2019) MCC950/CRID3 potently targets the NACHT domain of wild-type NLRP3 but not disease-associated mutants for inflammasome inhibition. PLoS Biol; 17(9):e3000354.

16 Appendices

16.1 Appendix 1: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-1 Liver event and laboratory trigger definitions

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

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; non-infectious hepatitis; benign, malignant, and unspecified liver neoplasms
ULN: upper limit of normal

Table 16-2 Follow up requirements for liver laboratory triggers with liver symptoms

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

Table 16-3 Follow up requirements for liver laboratory triggers

Criteria	Actions required	Follow-up monitoring
Total Bilirubin (isolated)		
>1.5 – 3.0 ULN	• Maintain treatment • Repeat liver function tests (LFTs) within 48-72 hours	Monitor LFTs weekly until resolution[a] 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 eCRF	Monitor LFTs weekly until resolution[a] to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
>10 x ULN	• Discontinue the study treatment immediately • Hospitalize the participant • Establish causality • Record the AE and contributing factors(e.g. conmeds, med hx, lab) in the appropriate eCRF	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution[a] (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 eCRF	Investigator discretion

[a]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; non-infectious hepatitis; benign, malignant and unspecified liver neoplasms ULN: upper limit of normal

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.

16.2 Appendix 2: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-4 Specific Renal Alert Criteria and Actions

Renal Event	Actions
Confirmed serum creatinine increase 25 – 49%	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase 50% +	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider participant hospitalization and specialized treatment
New onset dipstick proteinuria ≥3+ OR Protein-creatinine ratio (PCR) ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)	• Consider causes and possible interventions • Assess serum albumin & serum total protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria ≥3+ on urine dipstick	Assess & document • Repeat assessment to confirm • Distinguish hemoglobinuria from hematuria • Urine sediment microscopy • Assess sCr • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder
New evidence of clinically significant crystals on microscopy	Assess & document • Repeat assessment to confirm • Assess serum creatine, urea and electrolytes • Consider causes and possible interventions • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected

+ Corresponds to KDIGO criteria for Acute Kidney Injury

Additional specialized assessments are available to assess renal function or renal pathology.

(Note: In exceptional cases, when a nephrologist considers a renal biopsy, it is recommended to make slide specimen available for evaluation by the RSG to potentially identify project-wide patterns of nephrotoxicity.)

Whenever a renal event is identified, a detailed patient history and examination are indicated to identify and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5-minute rest, with an appropriate cuff size)
- Signs and symptoms like fever, headache, shortness of breath, back or abdominal pain, dysuria or hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other diseases or causes, e.g. dehydration due to delirium, tumor lysis

Table 16-5 Renal Event Follow up

Assess, document and record in eCRF • Urine dipstick and sediment microscopy evidence of DIN: crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells • Blood pressure and body weight • Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output
Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the eCRF.
Monitor patient regularly (frequency at investigator's discretion) 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 protein:creatinine ratio stabilization at a new level with ±50% variability over last 6 months. • Analysis of urine markers in samples collected over the course of the DIN event

16.3 Appendix 3: Cold challenge description and follow up procedures

- Room:
  - Ambient temperature of 4ºC should be maintained. The temperature in the cold room should be monitored with a validated temperature monitoring device during the cold challenge. The temperature at the start and stop of the cold challenge should be documented in the eCRF. Any deviations outside 4-6ºC should be documented in the source documents
  - Forced cooled air to simulate the condition to trigger acute FCAS.
  - Prior to the cold challenge patient should remain at room temperature ideally greater than 23°C
- Total duration:
  - 45 minutes from start to finish
- Patient monitoring:
  - During the cold challenge the clinical site staff must continuously monitor the participant to ensure the patient remains alert, oriented to time, place and person and is able to mobilize
  - Vital signs should be collected at baseline and then at least every 10 minutes and at completion of the cold challenge (captured in source documentation only)
  - Cold challenges should take place at sites with immediate access to equipment and trained staff for treating participants with FCAS in the case of an adverse event.
- The cold challenge must be stopped if any of the following criteria are met:
  - The participant requests to discontinue the cold challenge
  - The participant's body temperature is 35.0°C or below on two consecutive temperature readings
  - The criteria for an overall study stopping rule are met (see Section 9.1.4)
- Participant instructions:
  - Participants should be wearing light clothing (e.g. t-shirt and shorts)
  - Participants can stand, sit or walk-around
  - Strenuous exercise is not allowed
- Passive rewarming post cold challenge:
  - Participants will be returned to an ambient temperature of approximately 23°C for at least 24 hours at the clinical site for clinical monitoring and to complete trial related procedures, this period may be extended as per medical judgement
  - The participant should be covered with blankets and other types of insulation, until normal temperature is restored, or fever develops as part of the FCAS episode

In addition, guidance and requirements provided by the local regulatory authorities or local site-specific standard operating procedures must also be followed, as applicable.

16.4 Appendix 4: Physician Global Assessment of Autoinflammatory Disease Activity

Figure 16-1 Physician Global Assessment of Autoinflammatory Disease Activity

Physician global assessment of autoinflammatory disease activity:
□ Absent □ Minimal □ Mild □ Moderate □ Severe *(tick only one)*

16.5 Appendix 5: Physician's Severity Assessment of Autoinflammatory Disease Signs and Symptoms

Figure 16-2 Physician's Severity Assessment of Autoinflammatory Disease Signs and Symptoms

1. Assessment of skin disease (urticarial skin rash):
□ Absent □ Minimal □ Mild □ Moderate □ Severe *(tick only one)*

2. Assessment of arthralgia:
□ Absent □ Minimal □ Mild □ Moderate □ Severe *(tick only one)*

3. Assessment of myalgia:
□ Absent □ Minimal □ Mild □ Moderate □ Severe *(tick only one)*

4. Assessment of headache/migraine:
□ Absent □ Minimal □ Mild □ Moderate □ Severe *(tick only one)*

5. Assessment of conjunctivitis:
□ Absent □ Minimal □ Mild □ Moderate □ Severe *(tick only one)*

6. Assessment of fatigue/malaise:
□ Absent □ Minimal □ Mild □ Moderate □ Severe *(tick only one)*

7. Assessment of other symptoms related to autoinflammatory syndrome:
Describe and assess symptoms:
_____
□ Absent □ Minimal □ Mild □ Moderate □ Severe *(tick only one)*

8. Assessment of symptoms not related to autoinflammatory syndrome:
Describe and assess symptoms:
_____
□ Absent □ Minimal □ Mild □ Moderate □ Severe *(tick only one)*

16.6 Appendix 6: Patients Global Assessment of Disease Activity

Figure 16-3 Patients Global Assessment of Disease Activity

CDFV890A12201	Site No. Subject No. Date of Assessment day month year	**Visit Name**

Time of Assessment: __/___/____

Patients Global Assessment of Disease Activity

- *Please rate your overall symptoms at this given time point (tick one only):*

☐ Absent
☐ Minimal
☐ Mild
☐ Moderate
☐ Severe