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Novartis Research and Development

DFV890

Clinical Trial Protocol CDFV890B12201 / NCT04886258

A randomized, two-arm, placebo-controlled, participant and investigator-blinded study investigating the efficacy, safety and tolerability of DFV890 in patients with symptomatic knee osteoarthritis

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ACR	Urine Albumin to Creatinine Ratio
ADL	Activities of Daily Living
ADAMTS	Disintegrin and Metalloproteinase with Thrombospondin Motifs
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
APTT	Activated partial thromboplastin time
AR	Autoregressive
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
AV	Atrio Ventricular
AxMP	Auxiliary Medicinal Product
B	Blinded
BAS-MPsQ	BAS — Multidimensional Psychological Questionnaire
b.i.d./BID	bis in die/twice a day
BMI	Body Mass Index
BML	Bone Marrow Lesion
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CDS	Core Data Sheet
CE-MRI	Contrast Enhanced Magnetic Resonance Imaging
CFR 21	Code of federal regulation 21
CI	Confidence Interval
CK	Creatinine Kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	Maximum Drug Concentration
CMO&PS	Chief Medical Office and Patient Safety
CMP-MPsQ	CMP — Multidimensional Psychological Questionnaire
CO	Country Organization
CCI	[redacted]
COVID-19	Coronavirus Disease 2019
COX-2	Cyclooxygenase-2
CRA	Clinical Research Associate
CRO	Contract Research Organization
CSR	Clinical Study Report
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trials Information System
Ctrough	Trough Concentration

CV	Coefficient of Variation
CXCL10	C-X-C Motif Chemokine Ligand 10
CYP2C9	Cytochrome P450 2C9
CYP3A4	Cytochrome P450 3A4
DBP	Diastolic Blood Pressure
DCE-MRI	Dynamic Contrast Enhanced Magnetic Resonance Imaging
DDC	Direct Data Capture
DDE	Direct Data Entry
DDI	Drug-Drug Interaction
DIN	Drug Inducted Nephrotoxicity
dL	deciliter
DMC	Data Monitoring Committee
DNA	DeoxyriboNucleic Acid
ECG	Electrocardiogram
CCI	[redacted]
eCRF	Case Report/Record Form (paper or electronic)
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
eSAE	Electronic Serious Adverse Event
eSource	Electronic Source
EoS	End of Study
EU CTR	European Union Clinical Trials Regulation
EXP-MPsQ	EXP — Multidimensional Psychological Questionnaire
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	First in Human
FMA	Femoral Medial Anterior
FMC	Femoral Medial Central
FMP	Femoral Medial Posterior
FSH	Follicle Stimulating Hormone
g	gram
GBCA	Gadolinium-Based Contrast Agent
GCP	Good Clinical Practice
GCS	Global Clinical Supply
Gd-DOTA	gadolinium-tetraazacyclododecanetetraacetic acid
gfr	Glomerular Filtration Rate
GGT	Gamma-Glutamyl Transferase
GLP	Good Laboratory Practice
h	Hour
HA	Health Authority
HBcAg	Hepatitis B core Antigen

HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
(β) hCG	Human chorionic gonadotropin beta
HIV	Human Immunodeficiency Virus
hsCRP	high sensitivity C-Reactive Protein
i.v.	Intravenous
IACS	Intra-Articular Corticosteroids
IB	Investigator's Brochure
IC50	Inhibitory Concentration 50%
IC90	Inhibitory Concentration 90%
ICE	Inter-Current Event
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IL1RN	Interleukin 1 receptor antagonist
IL-18	Interleukin 18
IL-1β	Interleukin 1β
IL-6	Interleukin 6
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine System
JSW	Joint Space Width
KDOQI	Kidney Disease Outcomes Quality Initiative
kg	Kilogram
KIM-1	Kidney Injury Molecule-1
K&L	Kellgren-Lawrence
KOOS	Knee injury and Osteoarthritis Outcome Score
Ktrans	Volume transfer constant
L	Liter
LAAM	Levomethadyl
LC-MS	Liquid Chromatography-Mass Spectrometry
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LLOQ	Lower Limit of Quantification
LPLV	Last Patient Last Visit
LPS	Lipopolysaccharides

m	Meter
MAD	Multiple Ascending Dose
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
µg	microgram (s)
µL	microliter
µSv	microsievert
mSv	millisievert
mg	milligram(s)
MHRA	Medicines and Healthcare products Regulatory Agency
mL	milliliter(s)
mmol	milimole
MMPs	Matrix Metalloproteinases
MMRM	Mixed effects Model for Repeated Measures
MPsQ	Multi-Dimensional Psychological Questionnaire
mrem	milllirem
MRI	Magnetic Resonance Imaging
MS	Mass Spectrometry
NCI-CTCAE/v5	National Cancer Institute - Common Terminology Criteria for Adverse Events version 5
NFS	Nephrogenic Systemic Fibrosis
ng	nanogram
NGAL	Neutrophil Gelatinase-Associated Lipocalin
NIRT	Novartis Interactive Response Technology
NLRP3	NLR family pyrin domain containing protein 3
NOAEL	No Observed Adverse Effect Level
NRS	Numerical Rating Scale
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
ObsRO	Observer Reported Outcomes
OHP	Off-site Healthcare Professional
p.o.	Per Oral
PA	Posteroanterior
PC	Personal Computer
PCR	Protein-Creatinine Ratio
P.C.R.	Polymerase Chain Reaction
PD	Pharmacodynamic(s)
PER-MPsQ	PER - Multidimensional Psychological Questionnaire
PI	Principal Investigator
PK	Pharmacokinetic(s)
PoC	Proof of Concept

PRO	Patient Reported Outcomes
PSD	Premature Subject Discontinuation
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
QD	Once a day
QMS	Quality Management System
QoL	Quality of Life
QTcF	QT interval corrected by Fridericia's formula
R Value	ALT/ALP x ULN
RBC	Red Blood Cell(s)
RNA	Ribonucleic Acid
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
sCR	Serum Creatinine
SD	Standard Deviation
SDD	Spray-dried Dispersion
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	Suppressor of Cytokine Signaling
SoC	Standard of Care
SOP	Standard Operative Procedure
STD	Study Treatment Discontinuation
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1w	T1-weighted
TBL	Total Bilirubin
TFC	Tibiofemoral Compartment
Tmax	Time to reach Cmax
TNF-α	Tumor Necrosis Factor α
UI	Unblinded on Individual patient level
ULN	Upper Limit of Normal
CCI	[redacted]
UTI	Urinary Tract Infection
WBC	White Blood Cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent
WOMAC	Western Ontario and McMaster Universities Arthritis Index
WPI	Widespread Pain Index

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
Auxiliary Medicinal Product	Medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product (e.g., rescue medication, challenge agents, background treatment or medicinal products used to assess endpoints in the clinical trial). Concomitant therapy is not considered AxMP.
Background Therapy	Generally considered to be the current standard of care for a particular condition / disease, in addition to which study treatment is given
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Cohort	A specific group of participants fulfilling certain criteria and generally treated at the same time
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
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
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 (DDC)	eSource Direct Data Capture (DDC) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to 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 Product/ Investigational Medicinal product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference (such as an active comparator) in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
K&L	The Kellgren and Lawrence system is a method of classifying the severity of osteoarthritis using five grades
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
Off-site	Describes any trial activities performed with the participant at a location that is not the investigative site where the investigator will conduct the trial, but is for example the participant's home or another appropriate location
Off-site Healthcare Professional (OHP)	A qualified healthcare professional, such as a nurse, who performs certain protocol procedures for the participant at an off-site location such as a participant's home
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e., concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly diagnosed disease
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g., Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Perpetrator drug	A drug which affects the pharmacokinetics of the other drug
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Placebell©™	Methodology developed and owned by Cognivia to produce, compute and document prognostic covariate.

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
Randomization number	A unique identifier assigned to each randomized participant
Run-in Failure	A participant who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to participant's intervention or other treatment)
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Stage in cancer	The extent of cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study 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
Televisit	Procedures or communications conducted using technology such as a telephone or video-conference, whereby the participant is not at the investigative site where the investigator will conduct the trial
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Victim drug	The drug that is affected by the drug-drug interaction
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

Amendment 6 (December 2023)

This amendment is generated to implement learnings from ongoing and previous trials in OA, which are expected to facilitate the trial processes and reduce the burden to participants and sites, mainly by introducing a pre-screening procedure. Furthermore, the sponsor is taking the opportunity to make necessary changes to be prepared for the upcoming and required transition to the EU Clinical Trial Regulation - Regulation (EU) No 536/2014 (EU CTR). The main modifications are detailed in the next paragraphs.

The inclusion criterion for synovitis was updated with lower thresholds for the overall sum score. Synovitis is being assessed at screening using a sum score based on synovial thickness in 11 areas of the joint. This assessment is done using contrast enhanced MRI. During follow up, synovitis assessments rely on K-trans, which is a more sensitive measure of contrast enhancement. K-trans dynamically measures the permeability of newly formed vessels using a 2-compartment model as surrogate for active inflammatory processes. Since K-trans is only assessed at CCI [redacted] have suggested that the scores of the individual regions may be more relevant for the outcome assessment than the overall sum score. Therefore, the overall score for inclusion was lowered to include also participants with mild synovitis (sum score ≥7), provided that at least one area of the joint synovium presents with a score of 2 (i.e., maximum score). This means that in these specific cases an overall synovitis score indicative of mild synovitis (sum score of ≥7), instead of moderate or severe as required in the previous protocol, is sufficient for the identification of the target population. At the 3-months follow-up assessment, the synovitis assessment is done using K-trans, which is a more sensitive measurement for evaluation of the outcome. This assessment is performed in CCI [redacted], for changes in synovitis in the knee joint.

JSW data collection was removed in this amendment. JSW measurements for inclusion in the study were removed with Amendment 5. Therefore, pursuing this measure for potential post-hoc analysis is of limited benefit. With this change, only the weight bearing projections are needed, thereby reducing radiation exposure for participants.

The time interval from previous surgery has been shortened. This change was considered acceptable as long as participants are contralaterally oligosymptomatic, in which cases the identification of the target knee is possible. Furthermore, it allows for the identification of osteoarthritis as the most likely cause for persistent pain.

The period assessed for the stability of the pain level before screening has been prolonged from one week to two weeks. Furthermore, the requirement for compliance with the pain diary has been adapted from 5/7 days to 6/7 days. These changes were implemented to align CCI [redacted]

The possibility for an CCI [redacted] was introduced based on investigators' feedback. Pre-screening consists of laboratory tests, X-rays (standard long leg or knee centered weight bearing, per imaging protocol) and clinical assessments as per study requirements, to be performed and evaluated locally. Data collected during the pre-screening will only be kept in the source documents and no data will be entered into the CRF. Transition to full screening will require repeat blood sampling for central laboratory assessments. The X-ray will remain valid for 6 months (if performed per protocol requirements). The outcome of the clinical assessment

will be valid for 2 weeks, as long as the patient does not report relevant changes in symptomatology. This pre-screening allows for an early detection of the non-visible, most frequent causes of screening failure, and the exclusion of unsuitable potential participants. Thus, saving resources and limiting burden on potential participants.

This amendment removes the exclusion criterion for CYP2C9 *3/*3 genotype. Therefore, the associated CYP2C9 genotyping test was also removed from the screening assessments. The removal of this criterion is possible because safety margins at the employed doses are sufficiently large under the study specific restrictions for concomitant medication. Based on mean PK data in healthy participants (population of normal and intermediate CYP2C9 metabolizers), the safety margins for 25 mg b.i.d. are at least CCI when compared with the NOAEL exposure from the recently completed 26-week rat and 46-week monkey studies, respectively. Patients with decreased CYP2C9 activity may have up to [redacted]-fold higher AUC of DFV890 compared to normal CYP2C9 metabolizers resulting in respectively lower safety margins. Considering sufficient safety margins derived from long-lasting animal GLP studies, all patients irrespective of CYP2C9 genotype can be included in this study. To mitigate for the CCI with strong or moderate CYP3A4 inhibitors, the exclusion criterion of patients who are taking concomitant medications known to be strong or moderate inhibitors of CYP3A has been added. Participants, who were genotyped for CYP2C9 at screening and admitted to the study based on the protocol version 05, can continue to follow the concomitant medication restrictions as described in the protocol version 05.

Due to adequate safety margins the amendment lowers restriction for concomitant medications, which are strong CYP2C9 inhibitors. The CYP2C9 inhibitors are now allowed to be used with caution.

The time window when the study treatment should be taken in association with food intake has been modified. Participants are now instructed to take their study tablets with their meal or shortly after eating, instead of having to wait to take the study tablets within 5 minutes after the meal as per previous protocol versions.

Further to the modifications above, some elements which are required for compliance with EU CTR have been added:

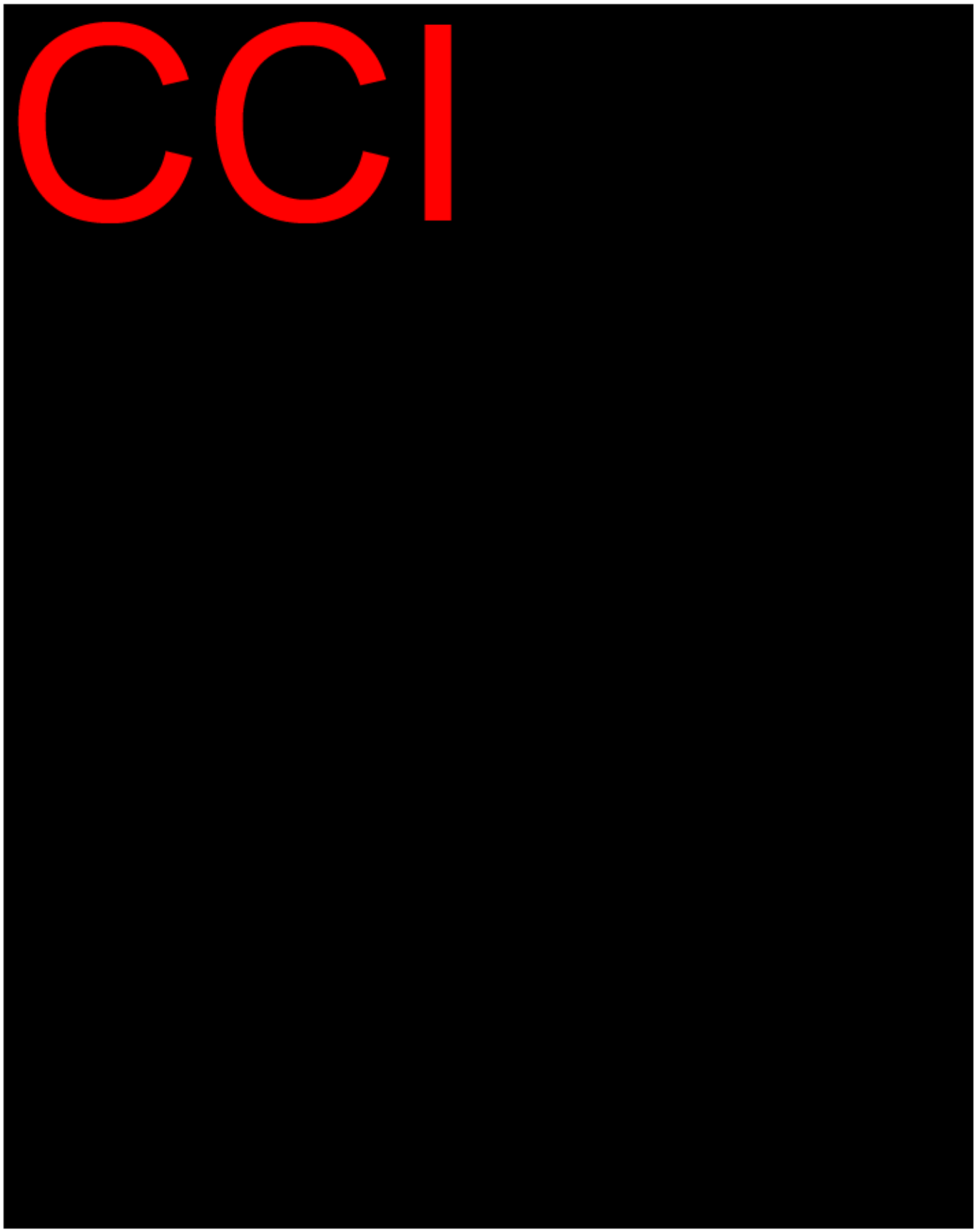
- Sponsor information on the cover page
- Definition and safety reporting of Auxiliary Medicinal Products (AxMPs)

The safety reporting requirements for Auxiliary Medicinal Products (AxMPs) will apply once the trial has transitioned under the EU CTR.

Minor editorial changes are also made throughout the protocol for increased clarity and consistency.

At the time of amendment, the study is actively recruiting. The first participant was screened on 21-September-2021. As of November 6, 2023, [redacted] participants have commenced or completed study treatment.

Screening should continue at a site under the protocol version 05 until applicable approvals have been obtained for the amendment, and all required documents and material have been provided to the site.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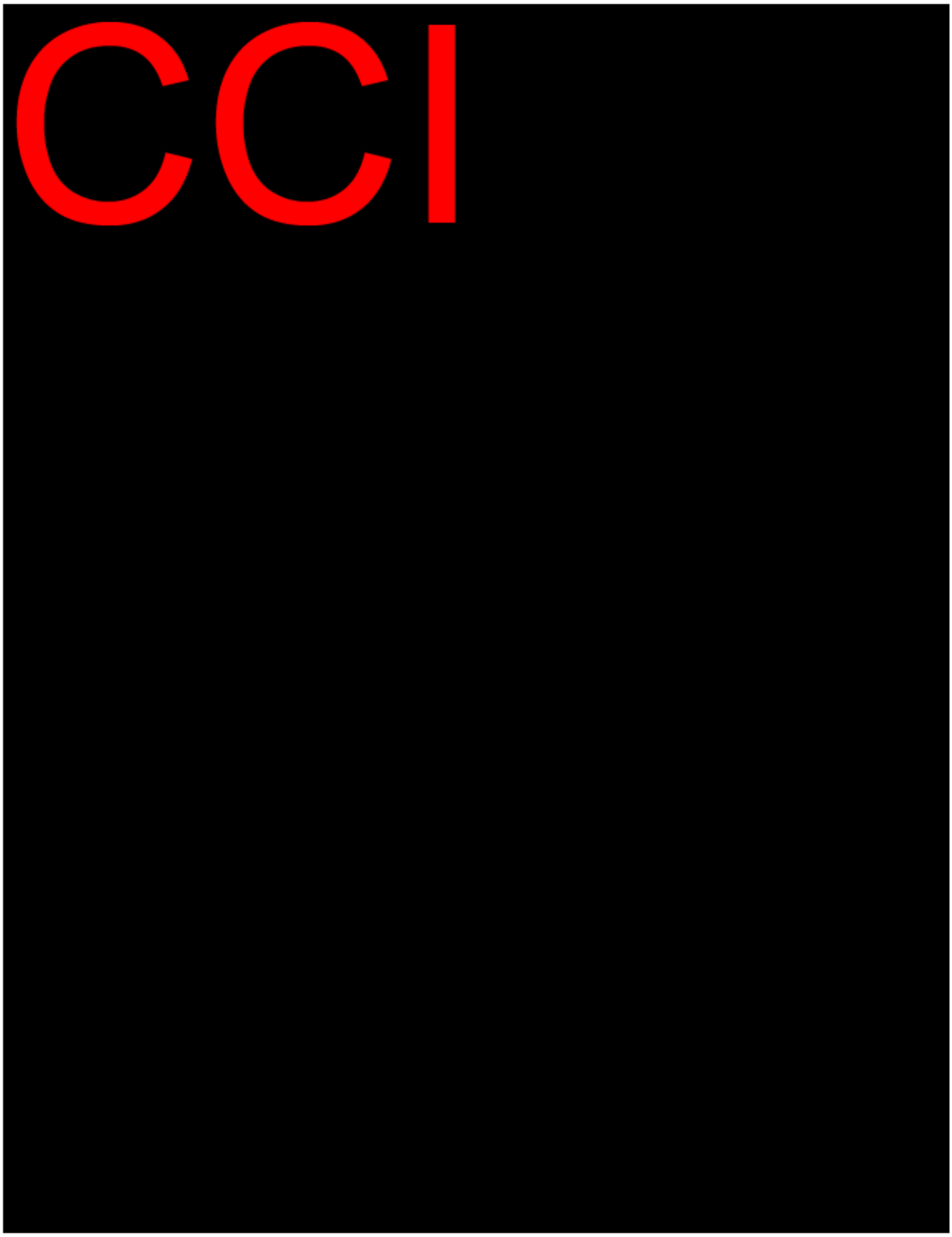
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IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes herein affect the Informed Consent. Investigational sites are required to update and submit a revised Informed Consent that takes into account the changes described in this protocol amendment.

Amendment 5 (May 2022)

Amendment rationale

The primary purpose of this protocol amendment is to reduce patient and site burden of the study conduct. Revisions to the inclusion and exclusion criteria are being made to broaden patient eligibility without compromising safety or data integrity.

Removal of joint space width (JSW) as an inclusion criterion is being done based on the primary goal of this study, which is to evaluate the safety and tolerability of DFV890 in participants with symptomatic knee OA, and to determine the efficacy of DFV890 in reducing knee pain. Structural change is not a key focus of this study given the short duration of dosing (during which structural change would not be expected), and structural requirements for inclusion have led to the exclusion of approximately 1/3 of patients screened. Moreover, JSW is sensitive to measurement error, further reducing the value of using this parameter for inclusion.

The threshold for hsCRP is also being reduced, from 2 mg/L to 1.8 mg/L. While this is a relatively minor change, the 1.8 mg/L level is based on the median value observed in the CCI study, suggesting that we will still be targeting a population with inflammatory arthritis, while allowing more patients to potentially be eligible for inclusion.

Additional changes are included to provide further clarification (i.e., regarding use of concomitant pain medications), improve wording, and update both preclinical and clinical data, where more recent results are now available.


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

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Amendment 4 (March 2022)

Amendment rationale

This amendment aims at addressing a request from a Health Authority (HA).

Amendment 3 (December 2021)

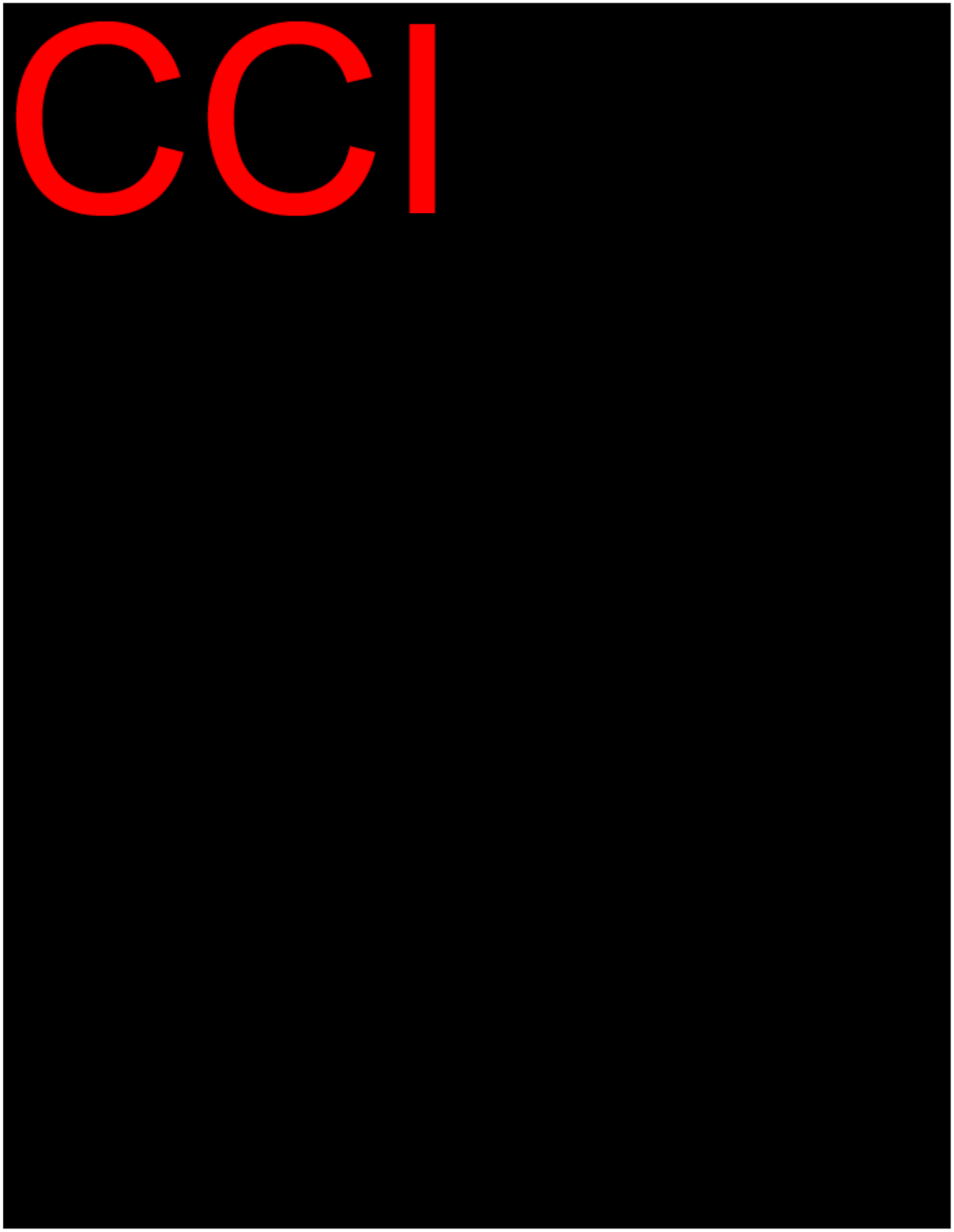
Amendment rationale

The main purpose of this global protocol amendment is two-fold: 1) to refine the estimand strategy; and 2) to introduce a decentralized trial model.

A decentralized trial model offers participants the flexibility to have some visits safely performed at an off-site location. Close consideration of the assessments and endpoints, together with data integrity and participant safety were essential in identifying visits that may be reliably conducted off-site.

This protocol amendment is also an opportunity to integrate the latest available clinical, non-clinical and pharmacokinetic data in order to provide investigators with the most current information, and to update the section related to SAE handling in order to align with local regulations.

Finally, this protocol amendment also corrects inconsistencies in the previous version and clarifies potential sources of confusion.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Amendment 2 (August 2021)

Amendment rationale

The purpose of this amendment is to address comments and requests from Health Authorities. The amendment clarifies wording related to decentralized trial activities, particularly those envisaged during the COVID-19 pandemic, and in a general manner, ensures alignment with local regulations.

At the time of this amendment no participant has been enrolled yet in the study.

Amendment 1 (April 2021)

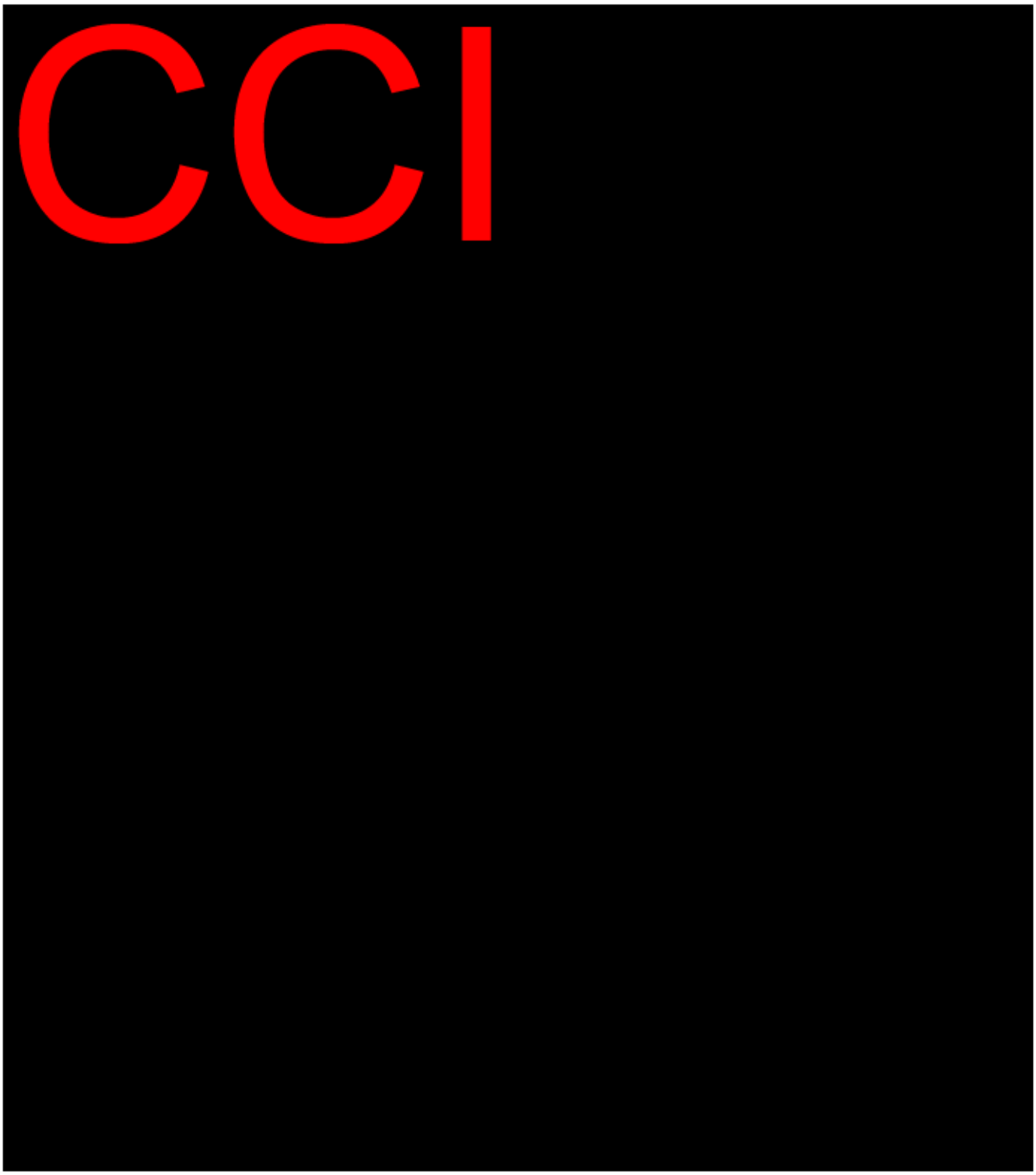
Amendment rationale

The main purpose of this global protocol amendment is to align with other studies using the same investigational drug, DFV890, in response to health authority comments, in order to ensure a consistent compound-related approach to some eligibility criteria, study stopping rules and individual treatment discontinuation.

This protocol amendment also corrects inconsistencies in the original version and clarifies potential sources of confusion.

Additionally, this study incorporates a planned decentralized trial strategy to more effectively support the trial during the Covid-19 pandemic. For that reason, standard protocol language related to pandemic mitigation measures was removed to eliminate any duplication which may cause confusion.

This amendment is issued before the study start and the original protocol v00 has not been submitted to any Regulatory Authorities.



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

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

Protocol summary

Protocol number	DFV890B12201
Full Title	A randomized, two-arm, placebo-controlled, participant and investigator-blinded study investigating the efficacy, safety and tolerability of DFV890 in patients with symptomatic knee osteoarthritis
Brief title	Study of efficacy, safety and tolerability of DFV890 in patients with knee osteoarthritis
Sponsor and Clinical Phase	Novartis, Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this Phase 2a proof of concept study is to evaluate the safety and tolerability of DFV890 in participants with symptomatic knee OA, and to determine the efficacy of DFV890 in reducing knee pain as evidenced by change in KOOS (knee injury and osteoarthritis outcome score).
Primary Objective(s)	The primary objective is to determine the efficacy of DFV890 versus placebo in participants with knee Osteoarthritis (OA) for relieving pain, based on change from baseline to week 12 in the knee injury and osteoarthritis outcome score (KOOS) pain sub-scale. The primary clinical question of interest is: What is the effect of DFV890 versus placebo on the reduction in knee pain assessed by KOOS at week 12 in participants with symptomatic knee OA?
Secondary Objectives	• To assess the efficacy of treatment with DFV890 versus placebo in participants with knee OA on inflammatory joint structure features based on change from baseline in synovitis activity level measured by Volume transfer constant (K-trans) by Magnetic Resonance Imaging (MRI) at week 12. • To evaluate the safety and tolerability of DFV890 compared to placebo over the course of the study based on systemic and local adverse events and serious adverse events; electrocardiograms; vital signs; hematology, blood chemistry and urinalysis. • To evaluate the change in systemic inflammatory markers (serum high sensitivity C-reactive protein level and absolute neutrophil count), when treated with DFV890 compared to placebo after 2, 4, 8 and 12 weeks of treatment. • To evaluate the plasma pharmacokinetics of DFV890 after 2 and 12 weeks of treatment. • To evaluate changes in knee symptoms and associated parameters, when treated with DFV890 compared to placebo after 2, 4, 8 and 12 weeks of treatment based on KOOS sub-scales including other symptoms, function in daily living, function in sport and recreation, knee-related quality of life. • To evaluate the efficacy of DFV890 compared to placebo in relieving OA pain over time based on change in KOOS pain subscale from baseline to weeks 2, 4, 8 and 12 weeks, and on change in Numeric Rating Scale (NRS) for pain from baseline to weeks 2, 4, 8 and 12.

Study design	This study is a randomized participant and investigator blinded trial with 2 parallel arms comparing oral DFV890 treatment vs placebo. After an up to 45 days screening period (including magnetic resonance imaging and X-ray), participants will be randomized into one of two groups: one treated with oral DFV890 twice per day; the other treated with placebo. The treatment period is comprised of two parts: during the first two weeks, participants will be treated with 10 mg DFV890 or placebo twice per day, followed by 10 weeks of treatment with 25 mg DFV890 or placebo twice per day. This period will include safety and efficacy assessments. After the treatment period, the participants will enter a 5-week follow-up period including an end of study visit and a safety call.
Study population	The study population will consist of approximately 108 male and female adults between 50 and 80 years of age with mild to moderate, symptomatic knee OA (Kellgren and Lawrence (K&L) score grade 2-3), clinical signs of inflammation, elevated high sensitivity C-reactive protein level ≥1.8 mg/L and confirmation of active synovitis by magnetic resonance imaging.
Key Inclusion criteria	• Male and female participants ≥ 50 and ≤ 80 years old on the day of Informed Consent signature. • Participants must weigh at least 50 kg to participate in the study, and must have a body mass index (BMI) within the range of 18 - 35 kg/m^2 at screening. BMI = Body weight (kg) / [Height (m)]^2 • High sensitivity C-reactive protein (hsCRP) ≥1.8 mg/L at screening • Symptomatic OA with pain (Numeric Rating Scale [NRS] 5-9, inclusive) in the target knee for the majority of days in the last 3 months prior to screening • KOOS pain sub-scale score ≤ 60 in index knee at screening and baseline • Radiographic disease: K&L grade 2 or 3 knee osteoarthritis in the target knee • Active synovial inflammation at screening (defined as a summary score of ≥7 with at least one region scoring 2) on contrast enhanced MRI (CE-MRI) of the whole knee for synovitis detection from 11 sites

Key Exclusion criteria	• Total WBC count < 3,000/µL, absolute peripheral blood neutrophil count (ANC) < 1,000/µL, hemoglobin < 8.5 g/dL (85 g/L) or platelet count < 100,000/µL at Screening • Known autoimmune disease with inflammatory arthritides (including but not limited to rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus), crystal-induced arthritides (gout, pseudogout associated arthritis), active acute or chronic infection or past infection of the knee joint, Lyme disease involving the knee, reactive arthritis, systemic cartilage disorders, moderate to severe fibromyalgia (widespread pain index, WPI, >4 out of 19), or a known systemic connective tissue disease • Any known active infections, including skin or knee infections or infections that may compromise the immune system, such as HIV or chronic hepatitis B or C infection COVID-19 specific: Polymerase Chain Reaction (P.C.R.) or antigen test against COVID-19 is mandatory where required by the local Health Authority and/or by local regulation, e.g. in Germany. • Use of prohibited medications: any local i.a. treatment into the knee, including but not restricted to viscosupplementation and corticosteroids within 12 weeks prior to Day 1; long-term treatment (>14 days) with oral corticosteroids >5 mg/day within 4 weeks prior to Day 1; oral glucosamine, chondroitin sulfate, or any nutraceutical with potential activity on cartilage repairfrom screening 1; systemic Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), selective Cyclooxygenase-2 (COX-2) inhibitors or other non-opioid analgesics not defined as basic pain medication within 5 half-lives from PRO assessments; any other immunomodulatory drugs or treatment which cannot be discontinued or switched to a different medication within 28 days or 5 half-lives of screening (whichever is longer if required by local regulations), or until the expected PD effect has returned to baseline. • Moderate to severe pain in the contralateral knee for the majority of days in the last 3 months prior to Screening, as per patient judgment • Severe malalignment greater than 7.5 degrees in the target knee (either varus or valgus), measured using x-ray at Screening
Study treatment	DFV890 (10 mg tablet twice per day for 2 weeks and 25 mg tablet twice per day for 10 weeks), or matching placebo. In addition, it is imperative to harmonize and document participants' pain medication as it can potentially confound results. Therefore, only the use of paracetamol/acetaminophen, up to 3000 mg/day, alone or in combination with low dose codeine, e.g., co-codamol, is allowed as basic (non-rescue) medication for pain control regardless of the origin of the pain, up until Day 84. This medication is referred to as "basic pain medication" and the investigator will either be supplied with the basic pain medication or source it locally and be reimbursed by the sponsor for its cost, depending on the country. The "basic pain medication" and the Gadolinium contrast agent used for contrast-enhanced MRI are defined as AxMPs.
Treatment of interest	The randomized treatment (the investigational treatment DFV890 or control treatment).

Efficacy assessments	• KOOS questionnaire • Contrast-enhanced Magnetic Resonance Imaging • Numerical Rating Scale • High sensitivity C-reactive protein • Absolute Neutrophil Count
Pharmacodynamic assessments	Change from baseline in serum high sensitivity C-reactive protein level and absolute neutrophil counts at week 2, 4, 8 and 12
Key safety assessments	• Adverse event and serious adverse event monitoring • Physical examinations, • Vital signs • Monitoring of laboratory markers in blood and urine • ECG parameters
Other assessments	CCI
Data analysis	The change from baseline in Knee injury and KOOS pain subscale will be analyzed using a mixed effects model for repeated measures (MMRM). The model will include baseline, treatment, time point, baseline * time points and treatment * time points as fixed effect A statistically significant difference (p-value < 0.05) between active drug and placebo at Week 12 will be considered as a positive result.
Key words	Osteoarthritis, inflammation, DFV890, NLRP3 inhibitor, inflammasome inhibition

1 Introduction

1.1 Background

Osteoarthritis (OA), a slowly progressive disease with a multifactorial pathophysiology, is one of the most common chronic health conditions, and a leading cause of pain and disability among adults (Safiri et al 2020). The knee joint is the most commonly affected weight bearing joint. Currently, there are few effective and/or tolerated symptomatic therapies other than analgesics and joint replacement surgery only is a last resort, while no structure-modifying drugs are available to date (Lohmander, Järvinen 2019). Therefore, there is a high need for both disease modifying, cartilage anabolic agents, as well as a need to address the inflammatory aspect of the disease. Inflammation is present in 30-50% of OA participants with moderate-severe disease in acute flare phases of cartilage degradation and/or as chronic low-grade inflammation. Especially in later stages of OA, intra-articular inflammation is common, but the current standard of care (intra-articular corticosteroids [IACS]) for this inflammation may have long-term detrimental effects on articular cartilage, accelerating disease progression (Wijn et al 2020).

Pro-inflammatory cytokines such as interleukin-1β (IL-1β) are critical mediators of the disturbed joint metabolism and enhanced catabolism of joint tissue involved in OA (Fraenkel et al 1998), making anti-inflammatory therapy an attractive strategy to counteract OA. These inflammatory mediators induce downregulation of anabolic events, i.e., cartilage matrix production by chondrocytes and production of degrading enzymes (MMPs, ADAMTS) by chondrocytes and synovial cells, which cause the breakdown and loss of the cartilage matrix (van den Bosch 2019). Clinical trials targeting inflammation in OA have had mixed results, but post-hoc analyses of two studies with the anti-IL-1β antibody canakinumab - the CCI trial and the CCI trial - showed positive results on reduction of joint replacement and/or effects on pain and function for canakinumab vs. placebo (Schieker et al 2020).

Through the production of IL-1β and IL-18, the NLRP3 inflammasome has been implicated as a major driver of inflammation associated with chronic inflammatory diseases. Mechanistically, NLRP3 senses a diverse range of danger signals, and reacts by forming an inflammasome protein complex that drives an ensuing inflammatory response. DFV890 is a potent small molecule inhibitor of the NLRP3 inflammasome pathway. DFV890 blocks IL-1β secretion, IL-18 secretion and pyroptotic cell death in response to a wide variety of NLRP3-dependent danger signals *in vitro* and in mechanistic mouse models *in vivo*, suggesting that NLRP3 inhibition could have improved efficacy over canakinumab in diseases where IL-1β and IL-18 both drive pathology.

It is not known whether NLRP3 inhibition results in the same clinical benefits as IL-1β inhibition in participants with symptomatic, inflammatory knee OA. There is clear need to develop a best-in-class oral OA drug to reduce pain, slow joint damage, and improve function in adults with symptomatic OA by addressing the inflammatory aspect of the disease and delaying/preventing progression to end-stage OA. CCI

CCI

[redacted]

1.1.1 Non-clinical data

DFV890 was evaluated in completed repeat-dose Good Laboratory Practice (GLP) toxicity studies up to 26 weeks duration in rats (Study 1970455) and up to 46 weeks in monkeys (Study 1970456). In addition, safety pharmacology studies and full *in vitro* and *in vivo* test batteries to assess genotoxicity and phototoxicity potential were performed. No significant effects of DFV890 were apparent during safety pharmacology assessments of central nervous system, respiratory and cardiovascular function. DFV890 did not demonstrate any genotoxic potential *in vitro* or *in vivo,* or phototoxicity potential *in vitro*.

There were no findings following DFV890 repeated oral dosing in spray-dried dispersion (SDD) in rats up to 4-weeks and in monkeys up to 13-weeks up to maximum feasible doses of 238 mg/kg/day and 150 mg/kg/day, respectively. The NOAEL in the 13-week monkey study was 150 mg/kg/day. The doses in these studies were the maximum feasible doses due to formulation limitation in both species.

Findings in the kidney and female reproductive organs occurred in13-week and 26-week toxicity studies in rats. These included changes consistent with retrograde nephropathy due to intra-tubular precipitates in the kidney at doses ≥100 mg/kg/day that correlated with clinical pathology parameter changes, including creatinine and blood urea nitrogen. Additional data suggest this kidney finding is rather a rat-specific effect and may not translate to humans (refer to the DFV890 Investigator's Brochure for further details). Changes at doses of 300 mg/kg/day for 13 weeks and at 100 mg/kg/day for 26-weeks in female reproductive tissues (ovaries, vagina, and mammary glands) and increased pituitary weights (without histologic correlate), were consistent with persistent estrus phase of reproductive senescence normally observed in Sprague Dawley rats. The findings in the kidney and female reproductive organs were partially reversible after a 4-week recovery period. Based on these observations, the no observed adverse effect level (NOAEL) in the 13-week and in the 26-week rat studies was 30 mg/kg/day.

In a 46-week GLP toxicology study in cynomolgus monkeys, moribundity was reported in four of thirteen animals receiving the highest dose of DFV890 (150 followed by 100 mg/kg/day). Two of the animals were euthanized due to injuries not related to DFV890. In the other two monkeys, adverse clinical findings and evidence of joint inflammation (consistent with a post-infectious reactive arthritis) were observed. The cause of moribundity has not been determined, and a possible relation to DFV890 cannot be excluded. These findings were not seen in a previous 13-week toxicology monkey study, which had higher systemic exposures. The risk for patients in currently ongoing trials is considered low based on safety margins and/or short treatment duration. No other findings were observed in the surviving animals at any dose during the rest of the study. The dose of 100 mg/kg/day in monkey, where no findings were observed, represented the NOAEL in the 46-week monkey study.

1.1.2 Human safety and tolerability

As of 24-Mar-2022, approximately 264 healthy subjects and patients have been enrolled in the DFV890 clinical development program, of which 164 participants/patients have received DFV890 at various doses and 100 received placebo or standard of care (SoC). CDFV890A02101 FIH (IFM2427001) and CDFV890D12201 (Covid-19) studies have been completed and the clinical study reports have been finalized.

In the FIH study (CDFV890A02101 or IFM2427001), DFV890 or placebo was administered to 122 healthy volunteers, of whom 94 participants received DFV890. DFV890 was generally well tolerated at all single and multiple dose levels. The highest daily DFV890 dose evaluated in healthy subjects in the study was 600 mg in the single ascending dose (SAD) phase, and 200 mg once-daily (QD) for 14 days in the multiple ascending dose (MAD) phase. CCI [redacted]

A Phase 2 study, CDFV890D12201, has been completed 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 received 50 mg b.i.d. oral DFV890 for 14 days. DFV890 was generally well tolerated with drug exposures as expected from the FIH study (CDFV890A02101 or IFM2427001). The overall incidences of reported AEs and SAEs were similar between the DFV890 and SoC groups, with no unexpected or new safety findings in the 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 the hospitalized COVID-19 population. There was a higher incidence of mild to moderate rash events observed in participants who received DFV890. Maculopapular/pruritic skin rashes were reported as related to DFV890 in 7 participants (approximately 10%) of whom 2 participants discontinued the study treatment. These events were of mild and moderate severity, started 5 to 15 days after initiation of DFV890 treatment, and resolved within 5 to 16 days after onset, requiring various treatments in the majority of affected participants. In summary, there were no unexpected events for the disease indication and patient population. The safety findings are consistent with the early clinical safety profile and in combination with the observed pharmacodynamic effects confirming clinically relevant reduction of NLRP3-related inflammatory markers.

The overall non-clinical pharmacology, pharmacokinetics, toxicokinetics and toxicological and clinical, safety and laboratory assessments are considered adequate to justify the continued clinical development of DFV890.

1.1.3 Human Pharmacokinetics

DFV890 is a highly permeable compound with solubility-limited absorption of crystalline formulations at high doses. In healthy participants, DFV890 as 100 mg crystalline tablet showed a positive food effect with peak concentration (Cmax) and area under the curve (AUClast) increased by 2.05 (90% CI 1.78 to 2.35) and 1.49-fold (90% CI 1.21 to 1.83) in the fed vs fasted state, respectively. Median Tmax for 100 mg tablet was 5 h, while shorter Tmax values (0.76 – 3.0 h) were reported for suspensions. In line with animal PK, DFV890 has a very low oral clearance (CLss/F ~1.03 L/h), which relates to ≤ 2% of human liver blood flow and low volume of distribution (Vss/F) of ~12.6 to 23.3 L. Slight drug accumulation of about 1.2-fold was observed in reaching steady state after daily dosing, consistent with an effective half-life of approximately 10 hours (formulation and dose dependent). CCI was the major circulating component in plasma and the CCI, were the most abundant metabolites based on semi-quantitative analysis. Both metabolites were detected in excess in plasma from rat and/or monkey in 13-week toxicology studies at the respective NOAEL doses. Five other metabolites in human plasma were detected as traces. Only ≤ 0.8% of dose as DFV890 was eliminated via urine, indicating a minor contribution of renal clearance to the total clearance pathway. Metabolism by cytochrome P450 2C9 (CYP2C9) and cytochrome P450 3A4 (CYP3A4) is considered to be the major clearance mechanism for DFV890 with fractional hepatic contributions of CCI respectively. CYP2C9 is a polymorphic enzyme. In the FIH study ~70% of evaluated participants had homozygous wild-type CYP2C9*1*1 genotype (so called normal CYP2C9 metabolizers). The population PK analysis from this study indicated that identified subjects with heterozygous CYP2C9 genotypes *1*2 (n=16), *1*3 (n=9), *1*5 (n=1), *1*11 (n=1), *2*3 (n=1) had increased AUC by a factor of CCI and CCI versus *1*1 (n=65), respectively. Based on *in vitro* results and physiology-based PK prediction, the systemic DFV890 exposure in participants who are poor CYP2C9 metabolizers (*3*3) is likely to be approximately [redacted]-fold higher compared to normal (extensive) metabolizers (*1*1).

Specific studies to investigate drug-drug interactions (DDI) have not yet been conducted with DFV890. For normal and intermediate CYP2C9 metabolizers, CCI effects are expected with concomitant administration of strong and moderate CYP2C9 and CYP3A4 inhibitors. CCI with strong or moderate CYP3A4 inhibitors is expected for poor CYP2C9 metabolizers. When dosed with a strong CYP3A4 inducer or a strong or moderate dual CYP3A4/CYP2C9 inducer, moderate DFV890 exposure reduction by CCI-fold is predicted for normal CYP2C9 metabolizers. CCI effect of inducers is expected in patients with decreased activity of CYP2C9. As a perpetrator, DFV890 has CCI potential to induce CYP3A4 and therefore may reduce AUC of sensitive CYP3A4 substrates by up to CCI-fold (refer to the Investigator's Brochure for further details).

1.2 Purpose

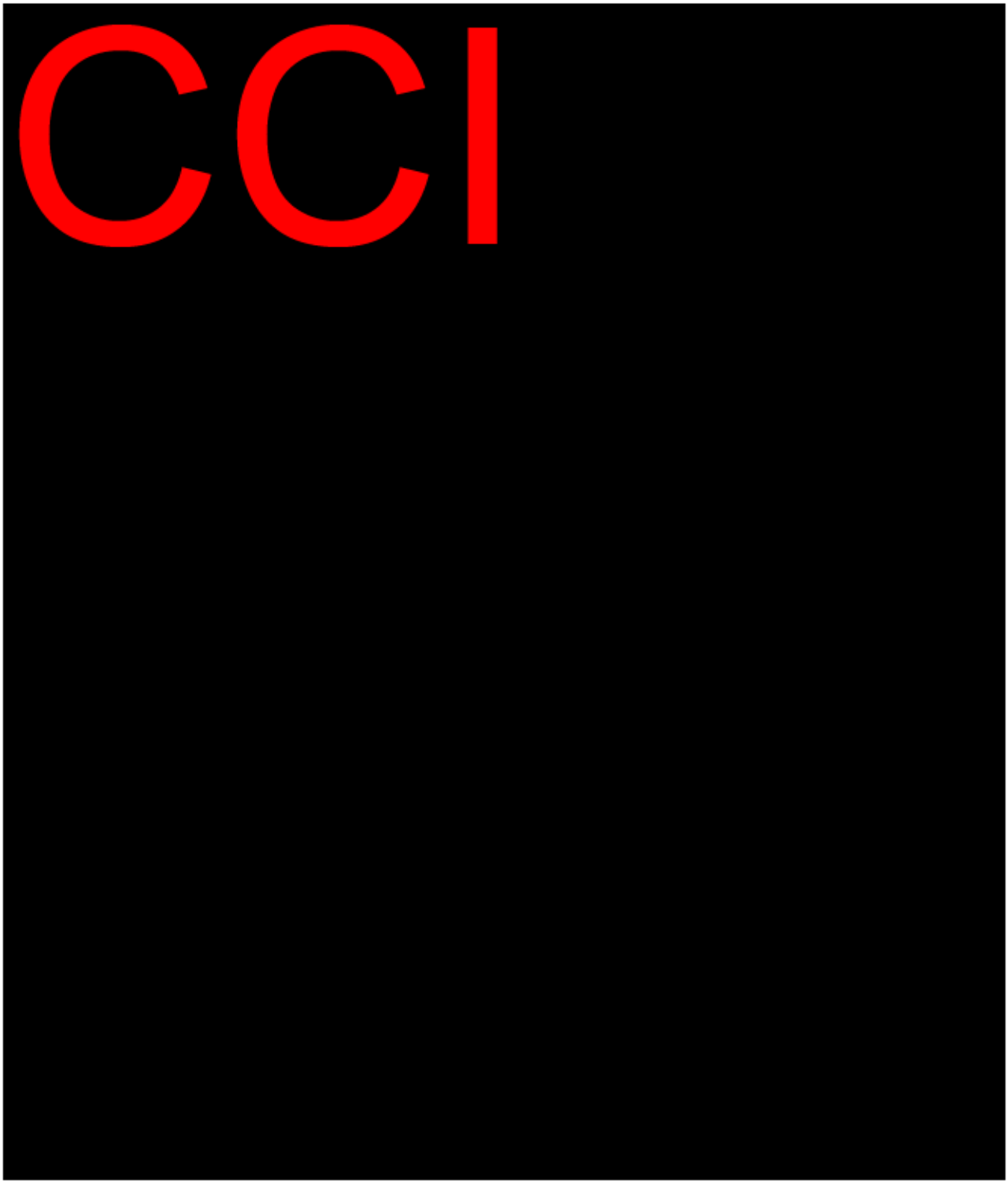
The purpose of this Phase 2a proof of concept study is to evaluate the safety and tolerability of DFV890 in participants with symptomatic knee OA and to determine the efficacy of DFV890 in reducing knee pain as evidenced by KOOS (knee injury and osteoarthritis outcome score).

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 determine the efficacy of oral DFV890 vs. placebo in participants with knee OA for relieving OA pain	• Change from baseline in Knee injury and Osteoarthritis Outcome Score (KOOS) pain sub-scale at Week 12
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the efficacy of DFV890 vs. placebo in participants with knee OA on inflammatory joint structure features	• Change from baseline in synovitis activity level measured from K-trans by DCE-MRI at Week 12
• To assess the safety and tolerability of DFV890 vs. placebo	• Systemic and local Adverse Events and Serious Adverse Events Electrocardiograms (ECGs) parameters Vital signs Hematology, blood chemistry and urinalysis
• To assess the effect of DFV890 compared to placebo on systemic inflammatory status	• Change from baseline in serum high sensitivity C-reactive protein level and absolute neutrophil counts at Week 2, 4, 8 and 12
• To assess pharmacokinetics of DFV890 in plasma	• Plasma samples to quantify concentrations of DFV890 at various time points (Week 2 and Week 12) and to derive PK parameters in plasma (including but not limited to Cmax, AUClast, AUC0-12h, and Ctrough)
• To assess the efficacy of DFV890 vs. placebo in improving participants' report of knee symptoms and associated problems over time	• Change from baseline in KOOS sub-scales (other symptoms, function in daily living, function in sport and recreation, knee-related quality of life) at weeks 2, 4, 8, and 12
• To assess the efficacy of DFV890 vs placebo in relieving OA pain over time	• Change in KOOS pain subscale from baseline to weeks 2, 4, 8 and 12 • Change in numeric rating scale (NRS) for pain from baseline to weeks 2, 4, 8 and 12
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
[redacted]	

CCI



2.1 Primary estimands

The primary clinical question of interest is: What is the effect of DFV890 versus placebo on the reduction in knee pain assessed by KOOS at Week 12 in participants with symptomatic knee OA?

The justification for the primary estimand is that it will capture the effect of the study drug under research conditions (assuming compliance to the prescribed regimen) versus placebo within the context of the protocol-specified guidelines for the use of additional basic pain medication and rescue medication.

The primary estimand is described by the following attributes:

1. Population: participants with mild to moderate, symptomatic knee OA (K&L grade 2-3), clinical signs of inflammation, elevated hsCRP (≥1.8 mg/L) and confirmation of active synovitis by MRI. Further details about the population are provided in Section 5.
2. Endpoint: change from baseline in KOOS pain sub-scale at Week 12.
3. Treatment of interest: the randomized treatment (the investigational treatment DFV890 or placebo), plus, if needed, the allowed basic pain medication and the use of rescue medication outside of the 48-hour window prior to a study visit.
4. Identification and handling of intercurrent events (ICEs):

Table 2-2 Overview of intercurrent events for the primary estimand

Intercurrent event		Handling of event
Missed treatment doses [a]	At least 1 missed dose within 48 hours prior to an assessment	Only assessment immediately following this ICE will be excluded for the purposes of this estimand
	At least 12 missed doses within 4 weeks prior to assessment	Data collected after this ICE will not be evaluated for the purposes of this estimand
	At least 36 missed doses	Data collected after this ICE will not be evaluated for the purposes of this estimand
Rescue medication	Unforeseen use of rescue medication within 48 hours prior to an assessment or exceeding the guidelines specified in the protocol for use of rescue medication	Only assessment immediately following this ICE will be excluded for the purposes of this estimand
Prohibited medication	Unforeseen use of any medication expected to have a sustained effect on the primary endpoint (i.e., any intra-articular injection; systemic corticosteroids)	Data collected after this ICE, which would require permanent discontinuation, will not be evaluated for the purposes of this estimand
	Unforeseen use of medication expected to have a limited effect on the primary endpoint (i.e., any other prohibited medications)	Only assessment immediately following this ICE will be excluded for the purposes of this estimand

[a] refers to doses missed for any reason, including, but not limited to permanent discontinuation of the study drug

All ICEs will be handled by a hypothetical strategy to impute what the treatment effect would have been at Week 12 if participants had adhered to the initially randomized treatment up until that time point, i.e. any affected data will be excluded from the primary analysis and (implicitly) imputed under the assumption that the outcome in the affected participants would be no different than in the remaining population (see Section 12.4.3 for implementation details). Although data post-ICEs are not required for the primary estimand, these assessments will be collected for evaluation of supportive estimands.

5. Summary measure: difference between treatment groups in mean change in KOOS pain subscale score from baseline to Week 12.

2.2 Secondary estimands

The key secondary clinical question of interest is: What is the effect of DFV890 versus placebo on the synovitis activity level, assessed by K-trans by DCE-MRI at Week 12 in participants with symptomatic knee OA.

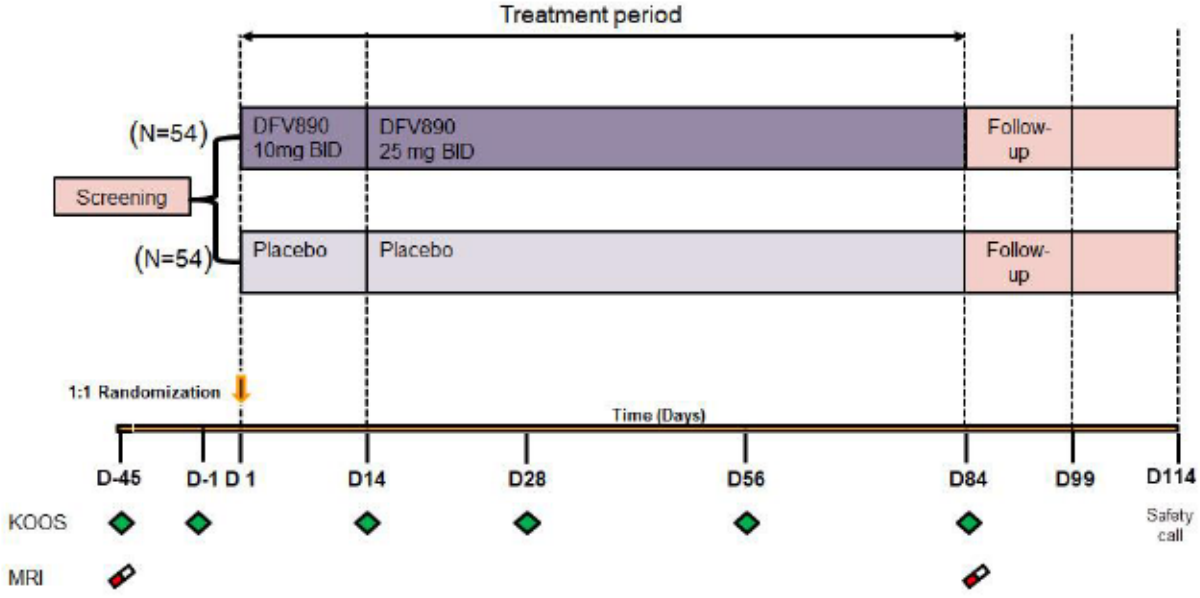
The justification for the key secondary estimand, as well as the population, treatment of interest and handling of ICEs apply in the same way as for the primary estimand. In addition, the attributes of the key secondary estimand are:

Endpoint: Change from baseline in K-trans at Week 12

Summary measure: difference between treatment groups in mean change in K-trans from baseline to Week 12.

3 Study design

Figure 3-1 Study design



This study uses a randomized, 2 treatment arm, parallel-group, participant and investigator-blinded, placebo-controlled design with the purpose of evaluating the safety and tolerability of oral DFV890 in approximately 108 participants with symptomatic, inflammatory knee OA, and determining efficacy of DFV890 as evidenced by reduction in knee pain by KOOS (knee injury and osteoarthritis outcome score) after 12 weeks of treatment.

The study consists of a screening period of up to 45 days, used to assess eligibility and to taper participants off disallowed medications. At Day 1 visit, eligible participants will be randomized to one of the treatment arms. Eligible participants will enter the treatment period, which will begin with a 2-week titration period where they will receive DFV890 10 mg b.i.d. or placebo orally for 14 days. The last 10 mg dose will be taken in the morning of Visit Day 14 at the site after the pre-dose PK samples are collected. The first 25 mg dose will be taken on Day 14 in the evening. Treatment with the 25 mg dose will continue for a 10 week treatment period (until Day 84 in the morning only). During this period participants will receive DFV890 25 mg b.i.d. or placebo orally. An end of study visit will occur 15 days after the last dose and a post study safety contact will occur 30 days after last dose. The total study duration from screening until end of study is expected to be a maximum of 21 weeks.

The assessment to address the primary objective will be performed at the end of the treatment period (Week 12).

Screening period

The screening period consists of 2 visits, a screening visit and a baseline visit.

Screening visit: Following their informed consent, participants will undergo assessments to confirm study eligibility. The required assessments may be conducted over several days if it is in the best interest of the participant, or for logistical reasons. **MRI should only be arranged if the participant qualifies based on all other assessments.** The order of assessments that should be followed to minimize participant burden is described in Section 8.1. Participants treated with prohibited medications (see Table 6-6) at screening will initiate washout at the screening visit.

An CCI [redacted] (according to protocol imaging criteria, i.e., standard weight bearing long leg or knee focused projection), local laboratory analysis (e.g., hsCRP), as well as a knee physical examination is possible, after the trial and the procedures of pre-screening have been explained to participants and they have signed the pre-screening informed consent. In case of actual screening, laboratory analyses will have to be repeated centrally, the X-ray will remain valid for 6 months and the outcome of the clinical assessment will be valid for 2 weeks, as long as the patient does not report relevant changes in symptomatology.Baseline visit: The baseline visit will include assessments listed in the Assessment Schedule (Table 8-1).

Treatment period

The treatment period will consist of 5 visits:

- Treatment initiation visit (Day 1): Participants who meet all inclusion and no exclusion criteria, will be enrolled and will begin taking a total daily dose of 20 mg (10 mg b.i.d.) of DFV890 or matching placebo tablets b.i.d. for 14 days (last dose on Day 14, morning dose). The first dose, either DFV890 10 mg or placebo, will be administered and study treatment will be dispensed to the participant for continued treatment at home. Participants may be domiciled the evening prior to a scheduled visit for their convenience and logistical aspects, at the discretion of the participant and investigator.
- Participants will be evaluated on Day 14 as outlined in the assessment schedule. Provided the treatment was well tolerated based on the Investigator's judgement and guidance provided in Section 6.5.1, they will start taking a total daily dose of 50 mg (25 mg b.i.d.) of DFV890 or matching placebo tablets b.i.d. starting on Day 14 (evening dose only) for 10 weeks. The last dose will be administered on Day 84 (morning dose only).
- Participants will have assessments on Day 28, Day 56, and Day 84. The site staff will perform phone calls at least once between two monthly visits to remind participants to take their study treatment.

During the treatment period, participants will undergo the efficacy, PK and PD assessments as outlined in the Assessment Schedule (Table 8-1)

Follow-up period

Participants will be followed-up for an end of study evaluation at the End of study visit, approximately 15 days after last dose (Day 99). A safety follow-up call will be performed approximately 30 days after the last dosing (Day 114) to record any potential safety event. For assessments, see Assessment Schedule (Table 8-1).

Unscheduled visit

Participants will be instructed to contact the investigator if they develop rash or pruritus between visits from Day 1 to the End of Study visit, and an unscheduled visit should be arranged and related assessments performed (Table 8-1).

3.1 Off-site procedures

At the investigator's discretion and based on benefit-risk considerations of the participant's clinical condition, qualifying participants may be offered the option to have certain clinical trial procedures performed at an off-site location, as defined in Section 8. A hybrid model is planned for this study incorporating both onsite and off-site visits. The off-site procedures will be utilized in certain countries and sites as determined by protocol needs and based on national and local/site regulations. Patients have the option of participating in one or more off-site visits, based on their preference and the investigator's discretion.

One or more of the following elements may be implemented to support off-site visits where allowed by national and local regulations:

- Telemedicine

- Off-site healthcare professionals (OHP)
- Direct-to-patient shipment of study supplies
- Direct-to-patient shipment of study treatment (refer to Section 6)
- Electronic Source (eSource) Direct Data Capture (DDC)

3.1.1 Responsibility of Investigators

Procedures that are performed off-site remain under the oversight of the investigator, who retains accountability for the conduct of all safety and efficacy assessments delegated to an OHP, and will ensure the rights, safety and wellbeing of participants. This includes the following (including, but not limited to):

- the identification, management and reporting of AEs and SAEs are performed in accordance with the protocol and applicable regulations
- OHPs have appropriate qualifications, training, and experience to successfully conduct off-site procedures
- source data collected off-site are reviewed and evaluated in a timely manner
- the investigator or delegate is available to be contacted by the OHP if any issues or concerns are noted during an off-site visit
- where relevant, the investigator or delegate will be present via telemedicine for a portion of the off-site visit to support the physical examination

3.1.2 Responsibility of OHPs

OHPs must have the required qualifications, training, and experience to conduct off-site assessments. OHPs are responsible to conduct delegated assessments and collect relevant data at off-site visits in accordance with the clinical trial protocol, International Conference for Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and national and local regulations and guidelines.

The OHPs will be provided by a third-party vendor sourced by Novartis. Where a site wishes to use OHPs that are not provided by Novartis this must be agreed with Novartis before use.

Any issues or safety concerns identified by the OHP will be promptly communicated to the investigator or delegate according to a pre-defined communication plan.

3.1.3 Telemedicine

The sponsor has qualified and contracted a third-party vendor to provide telemedicine platform technology for this study. The selected platform is a validated system complying with relevant ICH E6 GCP guidelines. Trial participants can interact with site personnel using online communication tools built into the platform, enabling the following capabilities:

- Secure videoconferencing which allows the patient, OHP and site personnel to be connected
- Reminders to be automatically sent to participants (e.g. visit or dosing reminders)
- eSource DDC (see Section 3.1.4)

3.1.4 Data flow

The OHPs will enter data at off-site visits into electronic source documentation forms contained in an eSource DDC platform, which has been validated for use in clinical research. Where paper source documentation exists, images of documentation will be uploaded electronically into the same platform as certified copies, and the original documentation will then be sent to the trial site.

Data contained in the platform are available to site and sponsor staff based on role-based access and permissions and will be stored in a robust and secure cloud-based back-end environment. Only sponsor staff who are responsible for field monitoring activities will have access to the source data, which may include some personally identifiable information, consistent with the access that is provided to a field monitor in a traditional onsite clinical trial model.

Relevant data in the eSource DDC platform may be manually transcribed by site staff into the study EDC system. Alternatively, the platform allows for configuration that enables data to be automatically exported into the study EDC system.

Certified copies of data in the eSource DDC platform will be provided to investigator and/or site personnel, and promptly and regularly uploaded into the participant's medical records, according to local guidelines.

Investigators will have continuous, near real time access to this study and all participant records within this study in the eSource DDC platform, with the ability to add, edit, review and sign forms within participant records.

The platform maintains a secure, GCP-compliant audit trail and uses measures such as encryption and access controls to ensure that data privacy and security is maintained. Additional details will be contained in a separate manual.

SARS-CoV-2

If an epidemic or pandemic (e.g., COVID-19 pandemic) limits or prevents on-site study visits, additional off-site assessments (as defined in Table 8-1) may be implemented where allowed by national and local regulations, and as agreed by the investigator and participant. To mitigate potential SARS-CoV-2 and other infections among participants, and because an NLRP3 inhibitor has the potential to be immunosuppressive, guidance and requirements provided by the local regulatory authorities or local site-specific SOPs will be followed (e.g., participants may be screened for SARS-CoV-2 by P.C.R. or comparable approved methodology prior to admission at the study/hospital site for any overnight stays following local site-specific SOPs).

4 Rationale

4.1 Rationale for study design

The design of this study addresses the primary objective of determining the efficacy of daily oral DFV890 vs. placebo in participants with symptomatic, inflamed knee OA for relieving OA pain. This study takes into account: 1) the unmet clinical need, 2) clinical and pre-clinical data on DFV890, and 3) the burden on participants with symptomatic, inflamed knee OA. The combination of MRI measurement of synovitis, as well as potentially cartilage volume in the index region and the whole femur, bone marrow lesion and effusion volume, and well-established Patient Reported Outcomes (PROs) such as KOOS (Bekkers et al 2009), will ensure appropriate evaluation of the effects of DFV890 in an inflamed joint.

Participants will be randomized in a 1:1 ratio to either DFV890 or matching placebo to decrease the chance of an imbalance in participant characteristics between groups, thereby facilitating unbiased assessments of the study endpoints.

This study has been designed as participant and investigator blinded in order to ensure that both investigators and participants remain agnostic, and a putative difference between treatment and control groups can be appropriately interpreted as an effect of study treatment. Given that the primary endpoint (KOOS pain) is a subjective assessment and therefore potentially influenced by the placebo effect (more so than other objective endpoints such as cartilage volume, for example), specific assessments and analytic measures are incorporated to allow for adjustment based on vulnerability to placebo effects.

Based on findings from prior pharmacotherapy studies (Dakin et al 2019), 12 weeks of dosing is considered to be adequate for detecting a change in the primary endpoint, KOOS pain; participants will therefore be dosed for 12 weeks. An initial dose of 10 mg b.i.d. is planned to mitigate the risk of rash prior to advancing to 25 mg b.i.d.

The Screening visit will be used to confirm that the study inclusion and exclusion criteria are met, and for obtaining clinical assessments and biological sampling. Participants who have been treated with prohibited medications may be screened if they are willing to discontinue the prohibited medication as described in Table 6-6.

Inclusion criteria (e.g., elevated hsCRP $\geq$1.8 mg/L, K&L Grade as measured by X-ray, age 50-80, increased baseline pain, signs of synovitis based on MRI) have been selected to enrich for participants with inflamed knee OA and ensure homogeneity in a relatively small number of participants. Moreover, this population is being selected in order to minimize bias caused by pain from the contralateral knee affecting the reporting of pain from the index knee as well as knee function. The exclusion of participants with Widespread Pain Index (WPI) > 4 is to minimize bias potentially affecting the reporting of pain and function by the presence of generalized pain (Yazici et al 2020).

4.1.1 Rationale for choice of background therapy

It is necessary to harmonize and document participants' pain medication as it can potentially confound study results; this is particularly important since the primary endpoint in the study is based on a pain assessment. Therefore, only the use of paracetamol/acetaminophen, up to 3000 mg/day, alone or in combination with low-dose codeine (e.g., co-codamol) is allowed as basic (non-rescue) medication for pain control until the EoS visit.

4.2 Rationale for dose/regimen and duration of treatment

The starting dose for DFV890 for participants enrolled in this trial is set at 10 mg p.o. twice daily (b.i.d.) for two weeks to assess tolerability, followed by a single-step dose escalation to 25 mg p.o. b.i.d. for 10 weeks, for a total treatment period of 12 weeks. The initial dose level was selected based primarily on data from the FIH study CDFV890A02101 (IFM-2427-001), in which skin rashes have been observed in some participants dosed once daily with 30, 100, and 200 mg or twice daily with 50 mg DFV890. No rashes were observed in participants in the 25 mg b.i.d. dose cohort. The mechanism of the skin rash is likely CCI [redacted]. In addition to assessing the tolerability of DFV890, the two-week run-in period at a lower dose of 10 mg b.i.d. will also inform about the extent of peripheral PD marker inhibition.

There is no established occupancy marker for NLRP3. An *ex vivo* whole blood assay of lipopolysaccharides (LPS)-stimulated IL-1β secretion in healthy participants has been used as a pharmacodynamic readout to estimate efficacious dose. Based on the results of this assay, the mean total DFV890 plasma trough concentration required to inhibit 90% of stimulated IL-1β release (IC_{90}) in healthy participants is on average CCI [redacted]
For participants with OA, the binding mode of DFV890 to NLRP3 is expected to be similar to healthy participants. Assuming plasma levels above IC_{90} for a 24-hour period are needed to maintain complete target occupancy, a DFV890 dose of 25 mg b.i.d. when given as a crystalline tablet has been predicted to meet this criterion. The initial dose of 10 mg b.i.d. will provide plasma trough concentrations which are above IC_{50} of IL-1β release. Similar unbound DFV890 concentrations are expected in plasma and synovial fluid already after the first dose based on the preliminary results from the rat PK study.

Pathway PD markers for IL-1β inhibition have been established in canakinumab trials, and include high sensitivity C-reactive protein (hsCRP) and absolute neutrophil count (ANC). In the CCI [redacted] trial, reduction in these markers plateaued at higher canakinumab doses (Ridker et al 2017), suggesting saturation of PD effects.

ANC and hsCRP have been monitored in the FIH study CDFV890A02101 (IFM-2427-001). Similar to the reduction seen upon canakinumab dosing in a wide range of trials, a rapid drop of ~12-22% in ANC was observed in all MAD cohorts. There was no observed dose response in ANC decrease, though the data was limited to 8 participants per cohort (6 on DFV890 and 2 on placebo). Analysis of hsCRP data in healthy participants indicates reduction in the 30 mg MAD cohort, but with higher variability and less consistency than seen with neutrophil data. No effect on hsCRP was seen in other MAD cohorts, but healthy volunteers enrolled in these cohorts did not have elevated hsCRP at baseline. The ANC and hsCRP changes suggest that

DFV890 could inhibit PD response at doses lower than those predicted by the *ex vivo* LPS challenge assay, but more data will be needed to build these relationships.

In this study, DFV890 will be administered with a meal or shortly after completion of a meal and all doses should be taken approximately 12 h apart (+/- 2h). A positive food effect on PK (2.05-fold increase in Cmax and 1.49-fold increase in AUClast) was demonstrated with 100 mg crystalline tablet in FIH study CDFV890A02101 (IFM-2427-001), but a lower effect, especially on Cmax, is expected for the 25 mg dose due to a better solubility at lower dose. The apparent terminal elimination half-life of DFV890 tablet under fed conditions is approximately 10 hours, thus after multiple doses, the steady state is anticipated by Day 4.

Based on FIH study CDFV890A02101 (IFM-2427-001), the mean (%CV) steady-state plasma exposure to DFV890 for 25 mg b.i.d. was 27.5 µg*h/mL (17.2%) for AUCtau, 3.50 µg/mL (13.1%) for Cmax and 1.40 µg/mL (31.0%) for Ctrough. These parameters were derived from healthy participants, who were normal (n=3) or intermediate CYP2C9 metabolizers (n=2 with *1*2 and n=1 with *1*3 diplotypes).

The safety of the treatment period is supported by completed 13-week GLP toxicology studies in rats and cynomolgus monkeys and by the 26-week study in rats and the 46-week GLP study in monkeys. Based on the observed mean AUC0-24h at steady-state in healthy participants, the safety margins for 25 mg b.i.d. are at least CCI [redacted] when compared with the NOAEL exposure from the chronic toxicology studies. For unbound exposure (corrected for plasma protein binding) safety margins to be multiplied by CCI [redacted] (Table 4-1). Patients with decreased CYP2C9 activity may have up to [redacted]-fold higher exposure of DFV890 compared to normal CYP2C9 metabolizers resulting in respectively lower safety margins. Considering sufficient safety margins all patients irrespective of CYP2C9 diplotype are allowed in this study.

Table 4-1 Safety margins for DFV890 dosed at 25 mg b.i.d. based on GLP toxicology studies

Human Dose	Mean human PK [b]		Exposure multiples based on total NOAEL exposure					
			Rat 13-week		Monkey 13-week		Rat 26-week		Monkey 46-week	
	Cmax (µg/mL)	AUC0-24h (µg*h/mL)	Cmax	AUC	Cmax	AUC	Cmax	AUC	Cmax	AUC
25 mg b.i.d./ crystalline tablet with food	CCI [redacted]									

a: NOAEL Cmax and AUC0-24h on day last from tox studies averaged for females and males in rat (13-week and 26-week study, 30 mg/kg) and monkey (13-week study, 150 mg/kg; 46-week study, 100 mg/kg). For unbound exposure (corrected for plasma protein binding) safety margins to be multiplied by CCI [redacted]; b: measured mean human plasma exposure at steady state for 25 mg b.i.d, AUC0-24h corresponds to 2 x AUCtau (CDFV890A02101 (IFM-2427-001)).

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

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

4.4 Purpose and timing of interim analyses

No formal interim analysis is planned. 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. Additional information is presented in the interim analysis section.

4.5 Risks and benefits

4.5.1 Compound risks

It is not known whether there will be a benefit for participants with symptomatic, inflamed knee OA participating in this study. No disease modifying therapy exists as standard of care for participants with knee OA. Therefore, no such therapies are potentially withheld for study participants.

Appropriate eligibility criteria and specific dose-limiting toxicity definitions, as well as specific dose modification and stopping rules, are included in this protocol. Recommended guidelines for prophylactic or supportive management of study-drug induced adverse events are provided.

The risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring, and study stopping rules. Please refer to the Investigator's Brochure.

4.5.1.1 Potential risk and recommended management of skin rash

In the FIH (CDFV890A02101 or IFM-2427-001) and Phase 2 COVID-19 (CDFV890D12201) studies, DFV890 was generally well-tolerated at single and multiple dose levels. In the CDFV890A02101 (IFM-2427-001) FIH study, CCI [redacted]

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

Decision-making criteria for managing a rash, as well as monitoring procedures, are included in this protocol (Section 6.6.2).

To reduce the potential risks of the development of maculopapular and/or pruritic rashes, for early participant 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. In addition, the dose and duration of DFV890 administered in this study will be limited to a maximum of 25 mg b.i.d. for 12 weeks.

Investigators should be vigilant for symptoms of pruritus and signs of rash (e.g., maculopapular on upper trunk, spreading centripetally and usually associated with pruritus) and should instruct participants to contact the investigator if they develop rash or pruritus to ensure a rapid clinical assessment. See Section 6.6.2 for recommended management of maculopapular/pruritic rashes.

4.5.1.2 Potential risk of renal abnormalities and recommended monitoring

In non-clinical studies, analysis of the data from the ≥ 13-week GLP repeat-dose study in rats showed unexpected adverse effects in kidneys consistent with obstructive nephropathy at doses ≥ 100 mg/kg/day accompanied by changes in kidney-specific urinary and blood parameters. In the non-clinical monkey studies, up to 46 weeks (4-, 13- and 46-week GLP studies at doses up to 150, 150 and 150/100 mg/kg/day) no adverse effects on kidneys or renal function were observed. The absence of the renal finding in monkeys with kidney physiology and urine concentration more similar to humans, and the higher concentrations of DFV890 metabolite in rat urine than in humans, are suggestive of a rat-specific species effect and that there is a low potential risk to humans.

Clinically, in the CDFV890A02101 (IFM-2427-001) FIH and CDFV890D12201 COVID-19 studies, based on available clinical safety data from both studies, there has been no evidence of adverse effects on kidneys or renal function related to DFV890 administration in COVID-19 participants and healthy participants.

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

4.5.1.3 Potential risk and recommended monitoring of hematological parameters

Transient asymptomatic decreases in ANC and WBC were observed in the CDFV890A02101 (IFM-2427-001) FIH and CDFV890D12201 COVID-19 studies. These transient self-limiting decreases in ANC and WBC were not associated with an increased risk of infection which could be consistent with a PD effect of DFV890 resulting from inhibition of IL-1β signaling

downstream of NLRP3 (NLRP3 blockade, similar to known effects of canakinumab). To reduce the risk of developing clinically relevant 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).

4.5.1.4 Potential risk and recommended treatment of infection

As with any immune-modulating compound, there is a theoretical risk of immune system impairment, which might increase risk of infection in treated participants. However, DFV890 is not expected to elicit broad immune suppression. Moreover, the target NLRP3 is not essential for health (NLRP3 deficient mice are generally healthy). In a 46-week GLP toxicology study in cynomolgus monkeys, moribundity was reported in four of thirteen animals receiving the highest dose of DFV890 (150 followed by 100 mg/kg/day). Two of the animals were euthanized due to injuries (not related to DFV890). In the other two monkeys, adverse clinical findings were seen with evidence of joint inflammation (consistent with a post-infectious reactive arthritis). The cause has not been determined, and a possible relation to DFV890 cannot be excluded. These findings were not seen in a previous 13-week toxicology monkey study, which had higher systemic exposures. The risk for patients in currently ongoing trials is considered low based on safety margins and/or short treatment duration. To mitigate potential risks of immune suppression and infection in this study, exclusion criteria include other immune suppressive treatments administered 28 days or 5 half-lives, whichever is longer, prior to screening. Participants 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.

4.5.1.5 Potential risk and guidance on vaccinations

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

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

4.5.1.6 Other potential compound risks

At this stage of development, DFV890 has not yet been studied in reproductive toxicology studies, and women of child-bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. Oral hormonal contraception is not allowed until a drug-drug interaction study is performed, as DFV890, based on the *in vitro* data, may induce CYP3A4 enzyme in the intestine, where it is involved in the metabolism of some hormonal contraceptives. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

A DDI risk exists for DFV890 as a victim when dosed with CYP2C9 and/or CYP3A inhibitors and inducers. More than [redacted]-fold higher DFV890 plasma exposure is expected in participants who are poor CYP2C9 metabolizers (approximately 2-4% of the population) upon co-administration of strong or moderate inhibitors of CYP3A. Up to [redacted]-fold lower plasma exposure is expected with inducers of CYP2C9 and/or CYP3A posing an increased DDI risk. To mitigate these risks, strong or moderate inhibitors of CYP3A, strong/moderate inducers of CYP2C9 and strong inducers of CYP3A will be excluded until a DDI study is performed.

4.5.2 Procedural risks

Invasive, study-specific, procedures include synovial fluid aspiration. Sterile technique will be used. Potential adverse effects may include local reactions at the site of aspiration, such as local pain, swelling or inflammation, or joint infection (risk 1/30,000 procedures, Fink et al 2008). Potential adverse events will be monitored clinically.

4.5.3 Imaging risks

This clinical study involves exposure to radiation from the X-ray assessment. For screening purposes, a standing long leg view of the lower limb (target knee) is required. These are often performed during the routine evaluation of participants with knee pain, but not always. Consequently, in some participants this assessment will be obtained only for research purposes. The total amount of radiation exposure per participant from this X-ray will be about 60 µSv (6 mrem), which is equivalent to approximately 7 days of exposure to natural background radiation (normal exposure is approx. 0.3 µSv per hour at sea level for the average person in the United States). For effective radiation doses under 3 mSv (300 mrem), the risk is considered to be "minimal". Therefore, the radiation exposure in this study involves minimal risk and is necessary to ensure eligibility of participants.

Magnetic resonance imaging (MRI) will be used in this study both for participant selection and follow-up purposes. MRI is a non-invasive radiology technique that does not involve X-ray radiation exposure. Thus, in principle, MRI scans can be repeated in the same participant as often as necessary. The MRI scanning equipment may cause a feeling of claustrophobia in susceptible persons. The presence of metal in the body may also be a safety hazard or affect the MR image quality. For more information, see exclusion criterion 16.

In addition, for synovitis assessments, a gadolinium-based contrast agent (GBCA, ATC Code: V08CA) will be administered as an i.v. bolus during each DCE-MRI session. Risks of i.v. infusion include infection, pain or thrombosis. There is recent evidence of gadolinium deposition in brain tissues following use of GBCAs. Although no symptoms or diseases linked to gadolinium accumulation in the brain have been identified, health authorities took a precautionary approach (e.g., EMA recommendations on GBCAs, EMA 2017), noting that data on the long-term effects in the brain are limited. This led to the suspension of several linear GBCAs and the recommendation that another class of GBCAs known as macrocyclic agents be used as an alternative solution, as they are deemed more stable and have a lower propensity to release gadolinium than linear agents. Although this is highly debated, the current belief is that such agents, especially the linear gadolinium agents, may also increase the risk of a rare but serious disease called nephrogenic systemic fibrosis (NFS). To prevent this risk and in accordance with health authority guidance (e.g., Medicines and Healthcare products Regulatory Agency Drug Safety Update on GBCAs (MHRA 2017), Food and Drug Administration Drug Safety Communications on GBCAs (FDA 2017a, FDA 2017b)), participants with previous severe allergic/anaphylactoid reaction to a gadolinium-based contrast agent; participants with severe renal disease (eGFR <60 mL/min/1.73 m^2), or acutely deteriorating renal function, who would be at risk of nephrogenic systemic fibrosis must be excluded from participating in this study.

4.5.4 Risks associated with off-site visits

Participants are not anticipated to be exposed to greater risks when participating in off-site assessments. OHPs will perform assessments according to the same processes and instructions defined in the protocol and study manuals for onsite visits, thus data integrity is also expected to be comparable to onsite assessments. Safety management in an off-site setting will adhere to the same quality standards as for the traditional onsite model and remains under the responsibility of the investigator (refer to Section 3.1).

4.5.5 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected over a period of 19 weeks, from each participant as part of the study. The approximate volumes are mentioned in the Informed Consent Form (ICF). Additional samples may be required for safety monitoring. Risks of collecting blood may include fainting, pain and/or bleeding and/or bruising at the site of needle puncture.

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

A summary blood log is provided in the laboratory manual. Instructions for sample collection, processing, storage and shipment information are also available in the laboratory manual.

See Section 8.5.3.7 on the potential use of residual samples.

4.5.6 SARS-CoV-2 risks

The current SARS-CoV-2 pandemic may pose a challenge to integrity of the trials, protection of participants' rights, safety and wellbeing, as well as the safety of study staff. Therefore, risk mitigation strategies have been established and will be evaluated on an ongoing basis for the duration of the study, in line with health and governmental authority guidance.

4.5.7 Overall risk benefit

Based on the clinical experience with DFV890 in the CDFV890A02101 (IFM-2427-001) FIH study, the CDFV890D12201 phase II study in COVID-19, relevant nonclinical findings, the biological understanding of the pathways and their relevance to OA, the overall risk-benefit of DFV890 is, to date, considered favorable. The available clinical, safety and laboratory assessments from the FIH study and the COVID-19 study show that DFV890 is generally well tolerated and has a manageable safety profile. Based on the available non-clinical and clinical data the potential risks to be considered for DFV890 include renal abnormalities and changes in female reproductive tissues, which were observed in the rat, and self-limiting skin rashes observed in the clinical studies. In addition to the risks noted above, there may be risks to DFV890 that are serious and unforeseen. Therefore, the risks to OA participants in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, frequent follow up, minimal duration of the study and stopping rules.

4.6 Rationale for public health emergency mitigation procedures

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

4.7 Rationale for planned off-site procedures

Off-site procedures are planned in this study to minimize burden on participants, and offer them increased flexibility to participate in the study from an off-site location (as described in Section 3 and defined in Section 8). This has the potential to broaden access to clinical trials for both participants and investigators. The hybrid approach will allow participants to maintain contact with investigator, both in person during clinic visits at site and through the telemedicine platform during off-site participation.

The scope of off-site procedures was determined based on thorough operational feasibility assessments to assure comparability with onsite assessments, together with consideration of patient safety, investigator, and patient feedback.

5 Study Population

The study population will consist of approximately 108 male and female adult participants with mild to moderate, symptomatic knee OA (K&L grade 2-3), clinical signs of inflammation and confirmation of active synovitis by MRI. To match the population to the one evaluated and having benefited according to the post-hoc analysis of the [redacted] study (Schieker et al 2020) participants will also be selected based on elevated hsCRP (≥1.8 mg/L).

The investigator must ensure that a participant meets all of the inclusion and none of the exclusion criteria before enrolling him/her into the trial. No additional criteria should be applied by the investigator when considering a participant's eligibility. In the case where a safety laboratory assessment at screening meets any of the exclusion criteria but the condition is expected to be transient and resolved prior to first dose, the assessment may be repeated once prior to randomization. If the repeat value remains abnormal and clinically significant, then the participant will be excluded from the study.

5.1 Inclusion criteria

Please note that the term "Screening" throughout this section refers to the first screening visit.

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

1. Written informed consent must be obtained before any assessment is performed.
2. Able to communicate well with the investigator, to understand and comply with the requirements of the study.
3. Male and female participants ≥50 and ≤ 80 years old on the day of Informed Consent signature.
4. Participants must weigh at least 50 kg to participate in the study, and must have a body mass index (BMI) within the range of 18 - 35 kg/m^2 at screening. BMI = Body weight (kg) / [Height (m)]^2

5a. High sensitivity C-reactive protein (hsCRP) ≥1.8 mg/L at screening

6b. Symptomatic OA with pain (corresponding to Numeric Rating Scale [NRS] 5-9, inclusive) in the target knee for the majority of days in the last 3 months prior to screening, as per participant's judgement. At Screening, the patient will be given a diary to record pain and use of analgesic medications. The participant must be compliant with filling in the diary at least 6 out of 7 days prior to Baseline, and have diary NRS Pain ≥5 to ≤9 for each of the two weeks prior to baseline at least 6 days out of 7 days AND have PRO reported NRS pain ≥5 to ≤9 at Screening and Baseline

7. Primary source of pain is due to OA in target knee based on widespread pain index (WPI) score ≤4 at screening
8. KOOS pain sub-scale score ≤60 in index knee at screening and baseline

9a. Radiographic disease: K&L grade 2 or 3 knee osteoarthritis in the target knee, confirmed by X-ray at screening.

10a. Active synovial inflammation at screening (defined as at least mild synovitis (sum score ≥7) and at least one individual area with a score of 2/2; appearance of synovitis atypical for OA will be exclusionary based on the central readers judgment) based on contrast enhanced MRI (CE-MRI) of the whole knee for synovitis detection from 11 sites (Guermazi et al 2011).

11. Diagnosis of primary tibiofemoral knee OA by standard *American College of Rheumatology* clinical and radiographic criteria at Screening

12a. Current use of analgesic therapy for control of local pain in the target knee:

- Patients taking paracetamol/acetaminophen, including combination drugs containing low dose opioids, can continue using this as per the package insert/doctor's instruction.
- Patients taking any other analgesic medication, including NSAIDs and selective COX-2 inhibitors or central analgesic or pain-modulatory medication but excluding topical NSAIDs or topical steroids, for any pain indication including knee pain, must be willing to switch at Screening to paracetamol/acetaminophen, including combination drugs containing low dose opioids, as per the package insert/doctor's instruction. NSAIDs or other non-opioid analgesics (excluding centrally acting substances) are allowed only as rescue medication as indicated based on the patient profile (background medication), but must not be used within 48 hours or five half-lives, whichever is longer, prior to any PRO assessment.
- Patients taking glucosamine or chondroitin must be willing to discontinue these from Screening.

5.2 Exclusion criteria

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

1. Total WBC count < 3,000/μL, absolute peripheral blood neutrophil count (ANC) < 1,000/μL, hemoglobin < 8.5 g/dL (85 g/L) or platelet count < 100,000/μL at screening
2. Known autoimmune disease with inflammatory arthritides (including but not limited to rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus), crystal-induced arthritides (gout, pseudogout associated arthritis), active acute or chronic infection or past infection of the knee joint, Lyme disease involving the knee, reactive arthritis, systemic cartilage disorders, moderate to severe fibromyalgia (widespread pain index, WPI, >4 out of 19), or a known systemic connective tissue disease
4. Metabolic or genetically-based abnormalities associated with arthropathy

5a. Participant has an unstable target knee joint or insufficiently reconstructed ligaments based on medical history and physical examination by the Investigator at screening

6. Participant has symptomatic, isolated patellofemoral pain in the index knee as per the Investigator's examination at screening
7. Use of electrotherapy, acupuncture, and/or chiropractic treatments for knee OA within 4 weeks prior to screening

8. Any known active infections, including skin or knee infections or infections that may compromise the immune system, such as HIV or chronic hepatitis B or C infection.

   COVID-19 specific: P.C.R. or antigen test against COVID-19 is mandatory where required by the local Health Authority and/or by local regulation, e.g. in Germany. Note that some countries may require P.C.R. testing only, e.g. Czech Republic. It is highly recommended that P.C.R. or antigen testing for COVID-19 be completed within 1 week prior to first dosing. If testing is performed, negative test results are required prior to enrolment into the study. Additional testing may occur at the discretion of the investigating physician. COVID-19 testing should be completed via nasal or throat swabs. If testing is not performed, the investigator must document their discussion with the participant regarding testing, and the rationale for not testing, in the source documentation. This requirement may be ignored if the pandemic is declared ended by the country where the site is located, and resumed if the pandemic recurs.

9a. Any diagnosed psychiatric condition that includes, but is not limited to, a history of mania, bipolar disorder, psychotic disorder, schizophrenia, or schizoaffective disorder, depression or anxiety disorder.

10. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within 5 years of screening (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the 3 months prior to screening, or carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed)

11a. Symptomatic hip OA or hip prosthesis recently implanted ($\geq$6 months prior to screening, if fully recovered after $\geq$ 6 months inclusion is acceptable) or foreseen within the study period (either side)

12. Other pathologies affecting the knee, including subchondral insufficiency fractures, bone fracture (acute or subacute in less than 6 months prior to screening) or bone bruise, osteonecrosis, osteochondral lesion, malignant bone marrow infiltration, solid tumors, meniscus extrusion greater than 50% and/or macerated meniscus and/or patellofemoral dysplasia based on clinical or imaging assessments

14a. Use of prohibited medications including but not limited to:

   a. any local i.a. treatment into the knee, including but not limited to viscosupplementation and corticosteroids within 12 weeks prior to Day 1 (steroid injections into other joints are prohibited from Screening);
   b. long-term treatment (>14 days) with oral corticosteroids >5 mg/day within 4 weeks prior to Day 1;
   c. oral glucosamine, chondroitin sulfate, or any nutraceutical with potential activity on cartilage repair within 2 weeks prior to screening;
   d. systemic Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) or selective COX-2 inhibitors or other non-opioid analgesics within 48 hours or five half-lives, whichever is longer, from PRO assessments;

e. any other immunomodulatory drugs or treatment which cannot be discontinued or switched to a different medication within 28 days or 5 half-lives of screening(whichever is longer if required by local regulations), or until the expected PD effect has returned to baseline.

f. See also Table 6-6

15. Severe malalignment greater than 7.5 degrees in the target knee (either varus or valgus), measured using X-ray at Screening

16a. Participant unable or unwilling to undergo MRI or having contraindications to MRI (e.g., MRI-incompatible metallic implants, metallic foreign bodies, pacemaker, defibrillator) or to the use of gadolinium-based agents, e.g., patients with previous severe allergic/anaphylactoid reaction to a gadolinium-based contrast agent; patients with severe renal disease (eGFR < 60 mL/min calculated using the CKD-EPI formula [https://www.kidney.org/professionals/KDOQI/gfr_calculator] or >= 2+ protein on urine dipstick testing at screening), or acutely deteriorating renal function.

17a. Moderate to severe pain in the contralateral knee for the majority of days in the last 3 months prior to Screening, as per patient judgment

18a. History of, or plans for the following surgical interventions;

a. Knee replacement (partial or total) in the target knee;
b. Knee replacement partial or total in the contralateral knee with residual pain or within 6 months prior to screening
c. Arthroscopy or lavage in either knee, within 3 months prior to Screening or planned during the study
d. Mosaicplasty, microfracture or other cartilage repair surgery, meniscectomy >50% in the target knee.
e. Any other previous surgical intervention in the either knee, or within 6 months prior to Screening 1 (12 months for osteotomies) or planned during the study. If in doubt, please contact the Sponsor.

19a. 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 15 days after stopping of investigational drug.

Highly effective contraception methods include:

- Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the 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 bilateral 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 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.
- Due to its in vitro CCI CYP3A4 induction potential, DFV890 can potentially decrease systemic exposure of sensitive CYP3A4 substrates by approximately [redacted]-fold or some oral hormonal contraceptives which are CYP3A4 substrates (e.g., ethinylestradiol), by CCI . Therefore, oral hormone-based contraceptives may not be considered as a highly effective contraception method.

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 ICF.

Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms). Women are considered not of child-bearing potential if they are post-menopausal 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).

20. Pregnant or nursing (lactating) women.
21. History or current diagnosis of ECG abnormalities indicating significant safety risk for participants participating in the study such as:
    - Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
    - History of familial long QT syndrome or known family history of Torsades de Pointes
22. History of drug abuse or unhealthy alcohol use within the 12 months prior to expected first dose, or evidence of such abuse as indicated by the laboratory assays conducted at screening visit.

    Unhealthy alcohol use is defined as a history of, or current, alcohol misuse/abuse or "Five or more drinks on the same occasion on each of 5 or more days in the past 30 days."
23. History of hypersensitivity to any of the study treatments or excipients or to drugs of similar chemical classes.
24. Use of other investigational drugs within 5 half-lives of enrollment, or until the expected pharmacodynamic effect has returned to baseline, whichever is longer.
25. If, in addition to primary knee osteoarthritis, spine/hand/shoulder/hip/foot/other primary osteoarthritis is present, it should have been present for at least 3 months prior to screening and should be documented with a diagnosis and symptoms as by investigator's judgements.

26. Secondary osteoarthritis with history or any evidence in the potential target joint of the following diseases: septic arthritis, inflammatory joint disease, gout, recurrent episodes of pseudogout, Paget's disease of bone, articular fracture, ochronosis, acromegaly, hemochromatosis, Wilson's disease, primary osteochondromatosis, heritable disorders, collagen gene mutations.

27a. Participants receiving concomitant medications that are known to be strong or moderate inducers of cytochrome CYP2C9 enzyme and/or strong/moderate dual inhibitors of CYP2C9/CYP3A, strong or moderate inhibitors of CYP3A and/or strong inducers of CYP3A (see list of prohibited drugs: Section 6.2.2) and the treatment cannot be discontinued or switched to a different medication within 5 half-lives or 1 week (whichever is longer) prior to Day 1 and for duration of the study.

28. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests (as defined below) including but not limited to SGOT (AST), SGPT (ALT), alkaline phosphatase, serum bilirubin, albumin and prothrombin time. The Investigator should be guided by the following criteria:
    - Any single parameter may not exceed 2 x upper limit of normal (ULN).

31. Live vaccines within 4 weeks of Day 1 (i.e. first dose of DFV890).

32. Known history of renal disease including nephrolithiasis.

33. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the patient in case of participation in the study. The investigator should make this determination in consideration of the patient's medical history and/or clinical or laboratory assessments, in consultation with the Sponsor when necessary.

6 Study treatment(s) and concomitant therapy

6.1 Description of Study treatments and treatment arms

6.1.1 Investigational and control drugs

The investigational drug DFV890 will be prepared by the sponsor as 10 and 25 mg tablets. Investigational drug will be supplied to the investigator as double-blind participant-specific kits. DFV890 will be administered orally with food or shortly after meal twice per day approximately 12 hours apart (morning and evening).

Table 6-1 Investigational and control drug

Treatment Title	DFV890	DFV890	DFV890 matching placebo	DFV890 matching placebo
Treatment Description	Tablet, 10 mg, BID	Tablet, 25mg, BID	Tablet, 10mg, DFV890 matching placebo, BID	Tablet, 25mg, DFV890 matching placebo, BID
Type	Drug	Drug	Drug	Drug
Dose Formulation	Tablet	Tablet	Tablet	Tablet
Unit Dose Strength(s)	10 mg	25 mg	10 mg matching placebo	25 mg matching placebo
Dosage Level(s)	10 mg BID	25 mg BID	10 mg matching placebo BID	25 mg matching placebo BID
Route of Administration	Oral	Oral	Oral	Oral
Use	experimental	experimental	placebo	placebo
IMP	Yes	Yes	Yes	Yes
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study treatment will be provided in container. Supply type is double blinded patient specific kits. Each container will be labeled as required per country requirement.	Study treatment will be provided in container. Supply type is double blinded patient specific kits. Each container will be labeled as required per country requirement.	Study treatment will be provided in container. Supply type is double blinded patient specific kits. Each container will be labeled as required per country requirement.	Study treatment will be provided in container. Supply type is double blinded patient specific kits. Each container will be labeled as required per country requirement.

6.1.2 Additional study treatments

It is imperative to harmonize and document participants' pain medication as it can potentially confound results. Therefore, only the use of paracetamol/acetaminophen, up to 3000 mg/day, alone or in combination with low dose codeine, e.g., co-codamol, is allowed as basic (nonrescue) medication for pain control, regardless of the origin of the pain, up until Week 12. This medication is herein referred to as "basic pain medication". The basic pain medication is considered to be AxMP as per EU CTR Regulation (EU) No 536/2014.

The investigator will either be supplied with the basic pain medication or source it locally and be reimbursed by the sponsor for its cost, depending on the country.

At each study visit (Visit 1- Week 12), participants will be provided with a quantity of the basic pain medication, either the paracetamol/acetaminophen or the paracetamol/acetaminophen plus codeine combination product, that is estimated to be sufficient until the next planned study visit. The investigator will dispense a known quantity of basic pain medication at each visit and will follow up with a count of the returned pills at each subsequent visit (starting at Visit 2), recording the number of pills taken on the appropriate case record form. The investigator and participant can agree to switch from one to the other type of basic pain medication, for example from single compound paracetamol/acetaminophen to the codeine combination product or vice versa, if deemed necessary and provided both types are available to the investigator.

Participants who use other pain medications must be willing to switch to the basic pain medication at Screening (inclusion criterion).

The participant should only use the basic pain medication provided by the investigator, even if he/she typically uses or purchases the same generic compound privately.

The basic pain medication can be taken at any point in the study, also within 48 hours of a study visit. To the extent possible, no other pain medication should be used up until Week 12, see Section 6.2.3 (rescue medication i.e. concomitant drugs that are allowed by protocol, e.g., NSAIDs or other non-opioid analgesics, is not to be taken within 48h or 5 half-lives, whichever is longer, of PRO assessments). See Section 6.2.3 for information on how to proceed in case mentioned medications were taken within 48 hours from the visit.

Participants will be provided with a diary in which they will document their daily pain (via Numeric Rating Scale) and the use of (any) pain medication from screening up to Week 12, see Section 8.3.1.The investigator or delegate should review the pain diary at each visit to ensure the number of returned basic pain medication tablets is reasonable compared to the documented use in the pain diary.

The use of basic pain medication should be documented in the concomitant medication page (including AxMPs) of the CRF, including for which indication the medication is taken (e.g., target knee pain, headache, back pain).

6.1.2.1 Supply of additional study treatments

Table 6-2 Basic pain medication

Medication (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Supplier Sponsor (global or local)
Paracetamol/acetaminophen 500 mg	Tablet	Oral use	Open label bulk supply	Sponsor (local) or site
Paracetamol/acetaminophen in combination with low dose codeine 500/30 mg	Tablet	Oral use	Open label bulk supply	Sponsor (local) or site

Tablet strengths can be different, depending on the country. Only one or both of the alternatives may be supplied to the investigator site, depending on the country.

Table 6-3 Additional study treatment

Treatment Title	Paracetamol/acetaminophen 500 mg	Paracetamol/acetaminophen in combination with low dose codeine 500/30 mg	V08CA Paramagnetic contrast media (Gadolinium based contrast agent)
Treatment Description	500 mg Tablet, up to 3000mg per day, as needed	500/30 mg paracetamol/codeine tablet, up to 3000mg/180mg paracetamol/codeine as needed	IV contrast agent for single injection at 3ml/sec
Type	drug	drug	drug
Dose Formulation	Tablet	Tablet	Solution for injection
Unit Dose Strength(s)	500 mg	500mg (paracetamol/ 30 mg codeine	Multiple, in line with local marketing authorization.
Dosage Level(s)	up to 3000 mg/day	up to 3000 mg/day alone or in combination with low dose codeine	multiple, as per local guidelines and clinical practice, in line with the marketing authorization of the diagnostic drug
Route of Administration	oral	oral	IV Injection
Use	Background intervention	background intervention	diagnostic
Authorization status of the AxMP in EEA	Yes	Yes	Yes
Sourcing	locally by the study site	locally by the study site	Locally by the study site/imaging facility
Packaging and Labeling	Original packaging. Supplied locally and will be labeled as per country requirement.	Original packaging. Supplied locally and will be labeled as per country requirement.	Original packaging, compounds sourced by study site/imaging facility per local practice

No other treatment beyond investigational drugs, control drug and additional study treatment (as auxiliary medicinal products) are provided in this trial. The choice of the gadolinium-based contrast agent is left to the study site/imaging facility based on local practice, in line with local marketing authorization and included as part of the imaging procedure.

6.1.3 Treatment arms/group

Participants will be assigned at the Day 1 visit to one of the following 2 treatment groups in a ratio of 1:1.

Table 6-4 Treatment Arm(s)

Arm Title	DFV890 10 mg	DFV890 25 mg	Placebo
Arm Type	Investigational drug	Investigational drug	placebo
Arm Description	DFV890 10 mg BID from Day 1 until Day 14 (morning dose only)	DFV890 25 mg BID from Day 14 (evening dose) until Day 85 (morning dose only)	Matching placebo BID from Day 1 until Day 85 (morning dose only)

6.2 Other treatment(s)

DDI with DFV890 as a victim

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

- for patients who are CYP2C9 normal metabolizers (genotypes *1*1, majority of population), chronic dosing with dual CYP2C9/CYP3A4 inducers is expected to induce both enzymes, thereby may reduce DFV890 drug exposure by approximately CCI -fold to sub-therapeutic levels. CCI effects are foreseen for patients, who are poor or intermediate metabolizers of CYP2C9.
- co-administration of DFV890 with strong inhibitors of CYP2C9 is expected to reduce enzymatic metabolic capacity, thereby may increase DFV890 drug exposure by approximately CCI -fold.
- when CYP2C9 normal metabolizers are dosed with strong/moderate CYP3A inhibitors or dual moderate inhibitors of CYP2C9/CYP3A (e.g fluconazole), the DFV890 AUC is expected to increase on average by approximately CCI -fold, respectively. Higher DDI risk with CYP inhibitors is likely for patients, who are poor (CCI -fold) or intermediate (CCI -fold) CYP2C9 metabolizers.

DDI with DFV890 as perpetrator

Due to its in vitro CCI CYP3A4 induction potential, DFV890 can potentially decrease systemic exposure of sensitive CYP3A4 substrates by approximately CCI -fold or some oral hormonal contraceptives (e.g., ethinylestradiol) by CCI .

Considering DDI risk, certain concomitant medications when dosed with DFV890 are required to be used with caution or they are prohibited. List of concomitant medications to be used with caution is presented in Table 6-5 and prohibited drugs are listed in Table 6-7 (please note that the lists may not be comprehensive). In case of doubt, please contact the sponsor.

6.2.1 Concomitant therapy

NSAIDs or other non-opioid analgesics are recommended as rescue medication (see Section 6.2.3) but are not permitted for basic pain medication. Participants will be asked to record pain and analgesic use in a diary from screening and throughout the 12 weeks treatment period.

The investigator must instruct the participant to notify the study site about any new medications he/she takes after the participant was enrolled into the study.

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapyand blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

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 randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Novartis to determine if the participant should continue participation in the study.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Topical NSAIDs and topical steroids are allowed during the study.

Clinical studies to investigate DDIs with Cytochrome P450 (CYP) substrates/modulators and DFV890 have not been performed yet. Evaluation and recommendations are based on in vitro / preclinical data and physiology-based PK simulations, and there are no clinical data confirming whether such interactions will occur in participants, although very likely.

Investigators at their discretion may administer concomitant medications known to be metabolized by CYP3A. 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 6-5).

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

Table 6-5 Concomitant medications to be used with caution

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, , 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
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
Strong inhibitors of CYP2C9	miconazole, sulfaphenazole, tasisulam
Moderate inhibitors of CYP2C9	amiodarone, ataciguat, azapropazone, bucolome, benzbromarone, milk thistle (silymarin, silibinin)[1], nitisinone, oxandrolone, phenylbutazone, piperine[2], tienilic acid

[1] Herbal product

[2] Food product

6.2.2 Prohibited medication

Use of the treatments displayed in the below table are not allowed for the duration indicated.

Table 6-6 Prohibited medication

Medication	Prohibition period	Action taken
Local i.a. treatment into the knee, including but not limited to hyaloronic acid, viscosupplementation and corticosteroids (steroid injections into other joints are prohibited from Screening)	12 weeks prior to Day 1 to week 12 visit (inclusive)	Discontinue study treatment and report protocol deviation
Oral corticosteroids > 5 mg/day for more than 14 consecutive days	4 weeks prior to Day 1 to Week 12 visit (inclusive)	Discontinue study treatment and report protocol deviation
Oral glucosamine, chondroitin sulfate, or any nutraceutical with potential activity on cartilage repair	From screening to Week 12 visit (inclusive)	Must be recorded on Concomitant medications/Significant non-drug therapies section of eCRF Report protocol deviation
Diacerein/diacetylrhein of the class anthraquinone	12 weeks prior to Screening visit to Week 12 visit (inclusive)	Discontinue study treatment and report protocol deviation
Indomethacin	2 weeks prior to Screening visit to Week 12 visit (inclusive)	Discontinue study treatment and report protocol deviation
Acetylsalicylic acid >325 mg/day or any systemic NSAID, selective COX-2 inhibitor or other non-opioid anagesic including combination drugs with codeine or caffeine other than the trial rescue medication (See Section 6.2.3). Topical NSAIDs is permitted	From Screening to Week 12 visit (inclusive)	Must be recorded on the Concomitant medications/Significant non-drug therapies section of eCRF Report protocol deviation and reschedule pain-related assessments if taken within the last 48 hours or five half-life (whichever is longer *
Paracetamol/acetaminophen >300 0 mg per day (See Section 6.2.3)	From Screening visit to EoS	Must be recorded on the Concomitant medications/Significant non-drug therapies section of eCRF Report protocol deviation and reschedule pain-related assessments if taken within the last 48 hours*
Opioids, either oral (i.e., tramadol) or transdermal (i.e., fentanyl patches) formulations except oral low dose codeine combination drugs	From Screening visit to Week 12 visit (inclusive)	Must be recorded on the Concomitant medications/Significant non-drug therapies section of eCRF Report protocol deviation and reschedule pain-related assessments if taken within the last 48 hours or five half-life (whichever is longer *
Any biologic drug interfering with immune pathways, osteoarthritis processes/cartilage or pain	26 weeks prior to Day 1 until Week 12 visit (inclusive)	Discontinue study treatment and report protocol deviation

Medication	Prohibition period	Action taken
Centrally acting analgesics (e.g., duloxetine, medical marijuana and CBD oil, neuroleptics or other psychoactive medication (unless prescribed for insomnia and dosed accordingly) Tolperison as centrally acting muscle relaxant is allowed, for other substances please discuss with the sponsor to ensure no distinct impact on pain processing.	12 weeks prior to Day 1 until Week 12 visit (inclusive)	Must be recorded on the Concomitant medications/Significant non-drug therapies section of eCRF Report protocol deviation and reschedule pain-related assessments if taken within the last 48 hours*
Inhibitors and inducers of CYP3A or inducers of CYP2C9 according to Table 6-7	1 week or at least 5 times the half-life of the medication (whichever is longer) prior to Day 1 until Week 12 visit (inclusive)	Discontinue study treatment and report protocol deviation

*Pain-related assessments that should be rescheduled if prohibited medications were taken within 48 hours of the visit refer to NRS Pain and KOOS. The assessments should be rescheduled to the first possible time point outside the 48-hour limit (after last intake), even if this pushes the completion to outside the visit window specified in Table 8-1. The rescheduled assessments may be done as a remote contact, in which case the site personnel must remember to provide the related PROs to the participant at the current visit. Before the pain assessments are completed at the rescheduled time point, the responsible site staff member should ensure any of the relevant prohibited medications were not again taken within 48 hours of the contact.

Table 6-7 Prohibited drugs due to DDI (CYP3A and CYP2C9 modulators)

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

[1] Herbal product

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

[3] combination therapy

Due to DDI risk, modulators (strong or moderate inducers) of CYP2C9 and/or dual strong/moderate inhibitors of CYP2C9/CYP3A, strong or moderate inhibitors of CYP3A and/or strong inducers of CYP3A and oral hormone-based contraceptives are prohibited (for detailed list see Table 6-7).

Note that if prohibited medications were taken within 48 hours or five half-lives (whichever is longer) of Screening or Baseline visit then the entire visit will have to be rescheduled with a washout period of a minimum of 48h or five half-lives (whichever is longer) for the above-mentioned prohibited medications.

Except for medication that may be required to treat adverse events and standard of care medication in line with inclusion and exclusion criteria, no medication other than study drug will be allowed from Screening visit or dosing on Day 1 until EoS.

Considering DDI risk, should a participant have an incidental and limited need for a prohibited medication (Table 6-6, Table 6-7) to be taken within the restricted timeframe, investigators should discuss the case with the sponsor. The administration of any prohibited concomitant medication may require the participant to be withdrawn or DFV890 treatment to be put on hold.

No live vaccinations are permitted within 4 weeks prior to 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

If adequate pain control is not achieved with basic pain medication (paracetamol/acetaminophen alone or in combination with low-dose codeine as described above in Section 6.1.2), then NSAIDs or other non-opioid analgesics will be permitted as rescue medication for up to three out of seven consecutive days, but must not be taken within 48 hours or five half-lives, whichever is longer, prior to any pain related assessments (NRS Pain or KOOS). In the event that NSAIDs are taken within 48 hours of a study visit, please refer to Section 6.2.2.

Rescue medication will not be provided by the Sponsor.

Decisions regarding specific NSAIDs or other non-opioid medication to be used as rescue medication should be made by the site Principal Investigator (PI), based on local practice and individual participant needs. The maximum dose should not exceed the approved dose in each country.

Allowable treatment for skin rash is described in Section 6.6.2.

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

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.

Any non-drug treatments (i.e., physiotherapy) must be reported in the Concomitant medications/Significant non-drug therapies eCRF.

6.2.4.1 Dietary restrictions and smoking

1. No cigarettes/use of nicotine products are allowed during the stay at the investigational site.
2. A maximum of 2 units (20 mL) pure alcohol per day is allowed in the last 48 hours prior to each study visit (e.g. 330 mL of beer (5% alcohol content) is equivalent to approx. 1.7 units)
3. Grapefruit or grapefruit juice should be avoided between Baseline and EoS.
4. Study treatment will be taken twice daily 12 h apart with the meal or shortly after completion of the meal in the morning e.g., at 7 a.m. and in the evening e.g., at 7 p.m. (with/after breakfast and dinner)

6.2.4.2 Other restrictions

- No unusual strenuous activities causing heavy loading or rapid movements/rotations of the knee are allowed from 48 hours prior to first dosing until after EoS.
- 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.

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 informed consent form, 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

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

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the NIRT provider using a validated system that automates the random assignment of participant numbers to randomization

numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

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

6.4 Treatment blinding

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

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

Site staff

With the exception of any unblinded site staff identified below, all site staff (including study investigator, study nurse and OHPs) will be blinded to study treatment throughout the study.

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

Sponsor staff or delegate

The following unblinded sponsor roles are required for this study

- Unblinded sample analyst(s) (PK, PD)

The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team under blinded conditions unless otherwise allowed.

The study statistician will be able to access the randomization list for interim analyses and is allowed to share unblinded information with the rest of the clinical team as appropriate for internal decision purposes, as outlined in Table 6-8. For example, unblinded summaries and unblinded individual data can be shared with the team for interim analyses.

Study programmers and other personnel involved in study data analysis (e.g., biomarker expert) are allowed to access treatment assignment information for the purpose of conducting interim analyses.

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

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

Following final database lock all roles may be considered unblinded.

Table 6-8 Blinding levels

Role	Time or Event			
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)	Interim Analysis & dose escalation
Participants	B	B	UI	B
Site staff (including OHP)	B	B	UI	B
Drug Supply and Randomization Office	UI	UI	UI	UI
Statistician/statistical programmer/data analysts	B	B	UI	UI
Unblinded sponsor staff (see text for details)	B	UI	UI	UI
All other sponsor staff not identified above	B	B	UI	UI

B Remains blinded

UI Allowed to be unblinded on individual patient level

6.5 Dose escalation and dose modification

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

6.5.1 Dose escalation guidelines

Participants randomized to the DFV890 treatment arm will receive 10 mg oral DFV890 twice daily from Day 1 to Day 14 (morning dose only). Provided the treatment was well tolerated and based on the Investigator's judgement, they will start taking a total daily dose of 50 mg (25 mg b.i.d.) of DFV890 on Day 14 (evening dose) for 10 weeks (on Day 84 only the morning dose will be taken).

6.5.1.1 Starting dose

The starting dose for DFV890 will be 10 mg b.i.d. for 2 weeks (14 days). Note that on Day 14 the 10 mg dose will only be taken in the morning.

6.5.1.2 Provisional dose levels

Table 6-9 describes the starting dose and the dose levels that may be evaluated during this trial.

Table 6-9 Provisional dose levels

Dose level	Proposed daily dose	Increment from previous dose
1.	20 mg (as 10 mg b.i.d.)	Starting dose
2.	50 mg (as 25 mg b.i.d.)	250%

Participants will be randomized in a 1:1 ratio to receive DFV890 or placebo for 12 weeks.

Participants randomized to the DFV890 arm will receive:

10 mg oral DFV890 twice daily for 2 weeks (from Day 1 to Day 14 morning dose), followed by 25 mg oral DFV890 twice daily for 10 weeks (from Day 14 evening dose to Day 84). Note that on Day 84 only the morning dose will be taken.

On Day 1, after the first dose intake, the participant must stay onsite for observation as per local practice and investigator decision but for a minimal duration of 1 hour.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all participants treated with DFV890, as detailed in the pharmacokinetics Section 8.5.2. The investigator must promote compliance by instructing the participant to take the study treatment exactly as prescribed and by stating that compliance is necessary for the participant's safety and the validity of the study. The participant must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the participant. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

Off-site treatment administration compliance will be assessed by the OHP and information provided to the Investigator and/or study personnel.

6.6.2 Recommended treatment of adverse events

Treatment and management of skin rash:

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

Depending on severity, investigators can consider as per medical judgment early treatment of mild rashes (maculopapular rash covering <10% body surface area with or without symptoms, e.g., pruritus, burning) with symptomatic treatment (e.g., topical steroids) and 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 participant 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

Emergency code breaks must only be undertaken when it is required to in order to treat the participant safely. Blinding codes may also be broken after a participant discontinues treatment due to disease progression if deemed essential to allow the investigator to select the participant's next treatment regimen, and after discussion and agreement with the sponsor. Most often, study treatment discontinuation (STD) and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT/NIRT. When the investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

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

- protocol number
- name
- participant number

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

In the event of an emergency breaking of assigned treatment code, participant should be permanently discontinued of study treatment.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT/NIRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

For off-site visits by OHPs, where delivery of study medication directly to a participant's secure off-site location (e.g., home) is permitted by national and local governing regulations, then dispatch of study medication directly to the participant may be performed under the accountability of the Investigator. The dispatch of Investigational Medicinal Product (IMP) from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 1-month supply. In this case, regular phone calls or virtual contacts will occur between the site and the participant for instructional purposes, safety monitoring, investigation of any adverse events, and discussion of the participant's health status.
In addition to IMP, a sufficient quantity of Basic Pain Medication will be supplied to last until the next visit, as described in Section 6.1.2.

The treatment for off-site administration will be handled and shipped in line with the pharmacy manual and required procedures and conditions for shipping.

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 study treatment must be stored according to the instructions specified on the labels or in the Investigator's Brochure.

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

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

The investigator or designated site staff must maintain an accurate record of the shipment and dispensing of study 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 study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

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

6.7.1.2 Handling of additional treatment

The following additional treatment has to be monitored specifically:

- Paracetamol/acetaminophen - allowed per instructions in Table 6-2
- Codeine - allowed per instructions in Table 6-2
- Paramagnetic contrast media (Gadolinium based contrast agent, ATC code V08CA)

Detailed guidance is provided in Section 6.1.2.

6.7.2 Instruction for prescribing and taking study treatment

Table 6-10 Dose and treatment schedule

Investigational / Control Drug (Name and Strength)	Daily Dose	Frequency and/or Regimen
DFV890 10 mg or matching placebo	20 mg (10 mg in the morning and 10 mg in the evening)	Twice daily with food or shortly after meal (from Day 1 to Day 14 included) N.B. last dose to be taken on Day 14 in the morning only.
DFV890 25 mg or matching placebo	50 mg (25 mg in the morning and 25 mg in the evening)	Twice daily with food or shortly after meal (from Day 14 in the evening to Day 84 included) N.B. last dose to be taken on Day 84 in the morning only.

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

- Participants should take DFV890 or placebo twice daily at approximately the same time each day in the morning and evening approximately 12 h (+/-2 h) apart. On days that PK samples are obtained, the participant should take DFV890 or placebo visit after the pre-dose PK samples and prior to post-dose PK samples, when instructed by the study staff.
- From Day 1 to Day 14 (morning dose only), participants will take 1 tablet of 10 mg strength DFV890 or matching placebo in the morning and 1 tablet of 10 mg strength DFV890 or matching placebo in the evening. The last dose will be taken on Days 14 in the morning only.
- From Day 14 (evening dose only) to Day 84 participants will take 1 tablet of 25 mg strength DFV890 or matching placebo in the morning and 1 tablet of 25 mg strength DFV890 or matching placebo in the evening. The last dose will be taken on Day 84 in the morning only.
- On Day 84 participants will take their last study drug administration in the morning i.e., 1 tablet of 25 mg strength DFV890 or matching placebo.
- Participants should take DFV890 or placebo with food. Each dose should be taken with a glass of water with the meal or shortly after completion of their meal. On Day 14 and Day 84 when serial PK samples are collected, the morning dose should be taken within 5 min after completion of a breakfast, which should not take longer than 30 min.
- Participants should be instructed to swallow whole tablets and not to chew or break them.

- If vomiting occurs during the course of treatment, participants should not take the study treatment DFV890 or placebo again before the next scheduled dose.
- Participants should be instructed not to make up missed doses. A missed dose is defined as a case when the full dose is not taken within 8 hours after the approximate time of the usually daily dosing. That day's dose should be omitted, and the participant should continue treatment with the next scheduled dose.
- Participants will be provided with individual diary to record each administration of study treatment as well as use of basic pain and rescue medication, and NRS pain, as described in Section 8.3.1. These will be checked regularly by site staff.

For pharmacokinetic assessment days, blood collection will be done in relation to the morning dose.

The basic pain medication should be taken according to the package insert and investigator instructions.

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.

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

Prior to screening, CCI [redacted] may be carried out, including X-ray (read locally), specific local laboratory analyses (e.g., hsCRP) as well as a knee physical examination, to assess participants potential eligibility based on these criteria. Prior to the conduct of any study specific assessments, a pre-screening informed consent form must be signed by the participant. If an X-ray is taken during pre-screening according to the protocol imaging criteria (requiring standard weight bearing long leg or knee focused projection), it will not need to be repeated during the actual screening if submitted within 6 months of the X-ray acquisition if there is no change in symptoms. It will then have to undergo a central read. The outcome of the clinical assessment will remain valid for 2 weeks as long as the patient does not report a change in symptomatology. An evaluation of laboratory markers at the central laboratory will be necessary before inclusion in the study requiring repeat sampling.

A full informed consent must be obtained before conducting any additional study-specific procedures (e.g., screening tests or any other 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 E6 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 treatment can be found in the Investigator's Brochure (IB) and CDS for marketed drugs. 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 or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

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

The following informed consents are included in this study:

- Main study consent, which also included:
  - CCI [redacted]
  - CCI [redacted]
- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the female partners of any male participants who took study treatment
- CCI [redacted]

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.

CCI [redacted]

CCI [redacted]

This study includes the option for the participant to have certain study procedures performed off-site by an OHP instead of at the study site, for which a separate signature is required if the participant agrees. It is required as part of this protocol that the Investigator presents this option to the participant in countries where this service is being offered, 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.

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

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g., telephone, videoconference) if allowable by a local Health Authority. Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g., the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

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 discontinue from study treatment are to return for the end of treatment visit as soon as possible, and attend the follow-up visits as indicated in the Assessment Schedule.

Participants who discontinue from study or withdraw their consent/oppose the use of their data/biological samples should be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications not previously reported must be recorded on the eCRF.

Table 8-1 Assessment Schedule

Epoch	Screening		Treatment													Follow-Up	
Visit Name	Screening	Baseline	Week 1	Week 2 [3]					Week 4 [3]	Week 8 [3]	Week 12					EoS [3]	Post-Study Safety Contact
Visit Numbers[1]	1	2	101	102					103	104	105					201	
Days	-45 to -2	-1	1	14					28 ±3	56 ±3	84 ±3					99 ±3	114 ±5
Time (post-dose)	-	-	-	pre-dose[2]	1h	3h	5h	8h	pre-dose[2]	pre-dose[2]	pre-dose[2]	1h	3h	5h	8h	-	-
Informed consents	X																
Inclusion / Exclusion criteria	X																
CCI																	
Medical history/current medical conditions	X																
Hepatitis screen	S																
HIV screen	S																
Alcohol Test and Drug Screen	S	S							S	S							
Smoking history	X			X					X	X	X						
Body Height	X																
Body Weight	X	X							X							X	

Epoch	Screening		Treatment													Follow-Up	
Visit Name	Screening	Baseline	Week 1	Week 2 [3]					Week 4 [3]	Week 8 [3]	Week 12					EoS [3]	Post-Study Safety Contact
Visit Numbers[1]	1	2	101	102					103	104	105					201	
Days	-45 to -2	-1	1	14					28 ±3	56 ±3	84 ±3					99 ±3	114 ±5
Time (post-dose)	-	-	-	pre-dose[2]	1h	3h	5h	8h	pre-dose[2]	pre-dose[2]	pre-dose[2]	1h	3h	5h	8h	-	-
Vital Signs [13]	X	X	X	X					X	X	X					X	
Body Temperature	X	X	X	X					X	X	X					X	
Physical Examination	S	S		S					S	S	S					S	
Electrocardiogram (ECG)	X	X	X				X[4]		X	X				X[4]		X	
Hematology	X	X		X					X	X	X					X	
Coagulation Panel	X																
Clinical Chemistry	X	X		X					X	X	X					X	
hsCRP[3]	X	X		X					X	X	X					X	
CCI																	
Urinalysis	X	X		X					X	X	X					X	
Pregnancy and assessments of fertility[5]	X	X		X					X	X	X					X	
WPI	X																
NRS Pain	X	X		X					X	X	X						
KOOS	X	X		X					X	X	X						
CCI																	

Epoch	Screening		Treatment													Follow-Up	
Visit Name	Screening	Baseline	Week 1	Week 2 [3]					Week 4 [3]	Week 8 [3]	Week 12					EoS [3]	Post-Study Safety Contact
Visit Numbers[1]	1	2	101	102					103	104	105					201	
Days	-45 to -2	-1	1	14					28 ±3	56 ±3	84 ±3					99 ±3	114 ±5
				[2]					[2]	[2]	[2]						
CCI																	
X-ray (target knee)	X																
MRI (target knee)	X[6]										X						
DCE-MRI (target knee)	X[6]										X						
Patient diary (pain)	X																
Patient diary (study treatment)			X														
Randomization			X														
Drug dispensation			S	S					S	S							
Study drug administration			X														
PK blood collection[7]				X[8]	X	X	X	X	X[8]	X[8]	X[8]	X	X	X	X	X	
Meal record				X					X	X	X						
CCI																	

Epoch	Screening		Treatment													Follow-Up	
Visit Name	Screening	Baseline	Week 1	Week 2 [3]					Week 4 [3]	Week 8 [3]	Week 12					EoS [3]	Post-Study Safety Contact
Visit Numbers[1]	1	2	101	102					103	104	105					201	
Days	-45 to -2	-1	1	14					28 ±3	56 ±3	84 ±3					99 ±3	114 ±5
Time (post-dose)	-	-	-	pre-dose[2]	1h	3h	5h	8h	pre-dose[2]	pre-dose[2]	pre-dose[2]	1h	3h	5h	8h	-	-
Blood collection for protein profiling (plasma)		X		X							X						
CCI																	
Concomitant medications / non-drug therapies	X																
Adverse Events	X																
Study completion information																X	
Safety Follow up Call																	S

[X] Assessment to be recorded in the clinical database or received electronically from a vendor
[S] Assessment to be recorded in the source documentation only
[1] Visit structure given for internal programming purpose only
[2] Refers to morning dose
[3] Based on national and local regulations and capabilities, these visits may be performed at an off-site location. Screening, Baseline and week 12 assessments will be performed onsite. If any skin rash is reported prior to the Day 14 visit, then this visit have to be completed at the site. If the pandemic (e.g. COVID-19) limits or prevents onsite study visits, the mandatory onsite visits (Screening, Baseline, week 12 and potentially Day 14 in the event of a rash) may be performed off-site depending on national and local regulations and capabilities, and as agreed by the investigator and patient.
[4] To be performed around Tmax, i.e. 5h after the first administration
[5] Serum pregnancy test at Screening and EoS visit, urine pregnancy test at all other visits.
[6] MRI/DCE-MRI at Screening visit should only be completed after all other eligibility criteria have been confirmed.
[7] In case needed (e.g. skin rash), an unscheduled sample should be collected to assess PK relationship as near as possible to the event.
[8] Taken at 0h prior to morning dose and 12h after the evening dose the day before.
[9] [redacted]
[13] Including blood pressure and pulse rate
[CC] [redacted]

8.1 Screening

It is permissible to re-screen a participant if s/he fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis, a new Screening number assigned, and a new written informed consent signed by the participant and investigator.

In the case where a safety laboratory (including hsCRP if ≥1.5 mg/L) assessment at screening and/or initial baseline is outside of the range specified in the eligibility criteria, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the participant must be excluded from the study.

Table 8-2 Rescreening

If reason for screen failure is:	Then	Actions	Rationale
Unrelated to knee X-ray	Re-screening is permitted.	Participant will not require a repeat knee X-ray IF re-screening occurs within 6 months of original X-ray date. Please refer to Section 8.1.1.3 for details	Avoids additional radiation exposure, given that meaningful radiologic changes are unlikely to occur during re-screening period
Related to knee X-ray;	Re-screening is permitted.	Participant will not require a repeat knee X-ray IF re-screening occurs within 6 months of original X-ray date. Please refer to Section 8.1.1.3 for details Participant will require all other assessments to be repeated unless re-screening is done within 7 days of original assessment.	Avoids additional radiation exposure, given that meaningful radiologic changes are unlikely to occur during re-screening period Repeat of laboratory assessments and PROs needed due to variable nature of these assessments

8.1.1 Eligibility screening

This section describes assessments which are performed at screening in order to evaluate a participant's eligibility. Eligibility assessments which are performed at screening to describe the population or also later during the study to evaluate efficacy, safety or other outcomes, are described in separate sections.

The screening assessments should be completed as per assessment schedule (Table 8-1), starting with informed consents. The assessments should be performed from the less invasive/burdensome to the more invasive/burdensome assessments for the participant.

The screening MRI will only be completed upon confirmation that all other inclusion/exclusion criteria are fulfilled.

During screening, the investigator should detect any active infections that would disqualify the participant for this study (exclusion criterion). The decision to locally test the participant for active SARS-Cov-2 infection in order to evaluate the exclusion criterion is at the investigator's discretion and should be in adherence to local policies or regulations. However, it is highly recommended that P.C.R. or antigen testing for COVID-19 be completed within 1 week prior to first dosing. If testing is performed, negative test results are required prior to enrolment into the study. P.C.R. or antigen test against COVID-19 is mandatory where required by the local Health Authority and/or by local regulation, e.g. in Germany. Additional testing throughout the study may occur at the discretion of the investigating physician. COVID-19 testing should be completed via nasal or throat swabs. If testing is not performed, the investigator must document their discussion with the participant regarding testing, and the rationale for not testing, in the source documentation. This requirement may be ignored if the pandemic is declared ended by the country where the site is located, and resumed if the pandemic recurs.

8.1.1.1 Hepatitis screen, HIV screen

All participants will be screened for Hepatitis B surface antigen (HBsAg). Additional standard local practices could apply. Screening for Hepatitis C will be based on 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.

8.1.1.2 Alcohol test, Drug screen, Urine cotinine

Participants will be tested for substances of abuse (e.g., alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine and opiates).

Cotinine in urine will not be analyzed at screening but the investigator should clarify tobacco use habits for participants who use tobacco products to ensure it is realistic that the participant can comply with the restriction described in Section 6.2.4.1. Nicotine replacement therapies are allowed.

8.1.1.3 Knee X-ray

A long leg or knee centered weight bearing X-ray will be performed only at Screening to evaluate the K&L grade eligibility criteria, using a non-fluoro, standardized and quality-controlled method, as described in the Imaging charter. A central reader will analyze the images as described in the Imaging charter.

If a patient has been screened for a similar trial with the same conventional X-ray projection, the image acquired during screening can be used within 6 months of the X-ray date.

8.1.1.4 Pain

Widespread Pain Index (WPI) (Wolfe et al 2016) is assessed at screening only, to exclude participants with substantial pain originating from other regions than the target knee, such as fibromyalgia or other undiagnosed diseases.

Other pain PROs are collected for screening purposes as well as for efficacy evaluation, see Section 8.3.1.

The same method of collection as for the PROs described in Section 8.3.1 will be used.

8.1.1.5 Contrast-enhanced MRI

Contrast-enhanced MRI will be acquired for screening purposes as well as for efficacy, based on synovitis evaluation. For additional details on the assessment, see Section 8.3.2

8.1.2 Information to be collected on screening failures

Participants who sign an informed consent form and are subsequently found to be ineligible prior to randomization will be considered a screen failure. All reasons for screen failure should be recorded on the appropriate Case Report Form. The visit date, demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data need to be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event or an adverse event related to AxMPs during the screening period (see SAE section for reporting details). Data and samples collected from participants prior to screen failure may still be analyzed.

Participants who are randomized and fail to start treatment, e.g., participants randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form. The IRT/NIRT must be notified within 2 days of the screen failure/early termination.

8.1.3 Pre-screening procedure

Prior to the Screening 1 visit, CCI [redacted] may be carried out, including X-ray as per study guidance but read locally (Section 8.1.1.3), individual local laboratory analyses such as hsCRP and knee physical examination (e.g., assessment of knee OA laterality or effusion) to assess participants potential eligibility based on these hard to predict features. Pre-screening tests can only be repeated in case of technical issues. Prior to any study specific assessments being carried out, the pre-screening informed consent form must be signed by the participant.

Data from the pre-screening will not be entered into the study clinical database, unless either 1) the participant experiences an SAE causally related to pre-screening study procedures or AxMPs, in which case the SAE will be collected using paper SAE from only (see Section 10.1.3), or 2) the participant signs the main consent and is screened within 6 months of the X-ray acquisition, in which case the pre-screening X-ray can replace the screening X-ray, if performed as per study requirements. The participant will be entered in IRT/NIRT only after signing the main consent. All other data related to pre-screening will only be recorded in source documents.

In case of actual screening, all laboratory tests used for screening (Table 8-1) will need to be performed by the central laboratory. Local analyses performed at pre-screening are solely informative for investigators' decision for patients to continue to full screening. In the case where a safety laboratory (including hsCRP if ≥1.5 mg/L) assessment at screening is outside of the range specified in the eligibility criteria, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the participant must be excluded from the study.

8.2 Participant demographics/other baseline characteristics

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

Participant 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: age, sex, race, predominant ethnicity (if permitted) and relevant medical history/current medical conditions (until date of signature of informed consent) will be recorded in the eCRF. Where possible, the diagnosis and not symptoms should be recorded.

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 for further details on what information must be recorded on the appropriate page of the eCRF.

8.3 Efficacy

The efficacy assessments described in this section will be evaluated in all participants in both treatment arms.

Pain (primary endpoint) will be assessed by Patient Reported Outcomes (PROs) as described in Section 8.3.1.

Pharmacodynamic samples will be collected at the time points defined in the Assessment Schedule (Table 8-1). Follow instructions outlined in the Laboratory manual regarding sample collection, numbering, processing, and shipment.

Synovitis (secondary endpoint), potentially articular cartilage volume/thickness, bone marrow lesions, and CCI [redacted] can be evaluated from MRI as described in Section 8.3.2.

Pharmacodynamic (PD) samples will be obtained and evaluated in all participants at all dose levels, including the placebo group.

8.3.1 Patient Reported Outcomes (PROs)

The participant must be given the PRO measure(s) to be completed at the scheduled visit before other clinical assessments are conducted. The questionnaires should be completed in the language most familiar to the participant. The participant should be given sufficient space and time to complete the PRO measure(s). A participant's refusal to complete all or any part of a PRO measure should be documented in the eCRF. Study staff should check the PRO measure(s) collected for completeness and ask the participant to complete any missing responses. Completed PROs, including any unsolicited comments written by the participant, must be reviewed and assessed by the investigator for responses which may include potential AEs or SAEs before any clinical study examinations are conducted. If AEs or SAEs are confirmed, then study investigators should not encourage the participant to change responses reported in the completed questionnaires. Study investigators must follow reporting instructions described in Section 10.

Knee Injury and Osteoarthritis Outcomes Score (KOOS)

Knee-related pain will be assessed as the primary endpoint by means of the Knee Injury and Osteoarthritis Outcomes Score (KOOS) measure collected at regular intervals (Roos, Davis 2012). The KOOS includes 42 items grouped into five sub-scales: Pain, Other Symptoms, Activities of Daily Living (ADL), Function in Sport and Recreation (Sport/Rec), and Knee-related Quality of Life (QoL). Each sub-scale is scored separately on a scale from 0 to 100, with a higher number indicating better condition (Collins et al 2011). The PRO KOOS score is an expanded version of the WOMAC score, which traditionally has been used in OA clinical trials (KOOS User Guide 2003). KOOS includes WOMAC OA Index LK3.0 in its complete and original format and WOMAC scores are able to be calculated. Therefore, the KOOS score provides a more comprehensive assessment as it also includes functioning in sport and recreation, as well as knee-related quality of life. KOOS requires approximately 10 minutes for participants to complete.

Numerical Rating Scale (NRS)

The Numerical Rating Scale (NRS) for Pain (Hawker et al 2011) with a recall period of 24 hours and traditionally used to assess pain in clinical trials, is assessed at regular intervals to confirm eligibility and to evaluate pain status throughout the study.

Widespread Pain Index (WPI)

Widespread Pain Index (WPI) is assessed at screening only to exclude participants with substantial pain originating from other regions than the target knee, fibromyalgia, or other undiagnosed diseases which may interfere with pain assessment.

Pain diary

A pain diary will also be completed by the participant daily during the 12-weeks study and transferred to the eCRF at each visit, beginning with Screening. This diary will be used to record basic pain medication, rescue medication and pain levels, daily. The participant may choose when, but should assess their pain intensity at approximately the same time every day.

The NRS pain assessment in the diary and the NRS pain assessment performed during study visits should be documented separately in the eCRF. At each study visit from Screening to Day 84, participants must be provided with a new pain diary that covers at least the period until the next planned visit. Prescription or use of pain medications will still need to be documented as Concomitant Medications according to Section 6.2.1.

Study treatment diary

A study treatment diary will also be completed by the participant daily during the 12-weeks study and transferred to the eCRF at each visit, beginning with Day 1. This diary will be used to record study treatment on a daily basis. At each study visit from Day 1 to Day 84, participants must be provided with a new diary that covers at least the period until the next planned visit.

PROs will be completed by the participants when attending scheduled visits (Table 8-1). If an electronic version of the questionnaires is used, data will be transferred and saved in the vendor's study database on a regular basis. Otherwise, a paper version will be provided.

8.3.2 Knee MRI

MRI will be obtained from the target knee to identify potential participants with active synovitis and to visualize the cartilage and other structures of the knee. The imaging protocol will allow a quantification of changes in synovitis, effusion volume, and bone marrow lesions and volume and thickness of cartilage in the index region as well as the whole femoral joint compartment (i.e., the region where most cartilage damage occurs in OA participants with K&L 2-3) during treatment. The index region is defined as the union of the femoral medial anterior (FMA), central (FMC) and posterior (FMP) cartilage sub-regions in the knee. This approach will demonstrate the effectiveness of DFV890 in reducing knee inflammation and whether this response is correlated with a decrease in pain. It will also be used to potentially quantify changes in volume and thickness of cartilage in the index region and the whole femur.

In addition, the assessment of the synovitis activity level using a dynamic-contrast-enhanced (DCE)-MRI approach will demonstrate the effectiveness of DFV890 in reducing knee inflammation and whether this response is correlated with a decrease in pain.

8.3.2.1 Image collection

The acquisition of magnetic resonance images will be performed by a trained MRI professional at each site. The MRI technologist will be blinded to the treatment received by the participant. All participants will be imaged using a clinical MRI 3T scanner after ensuring there are no contraindications for MRI (such as metallic implants, claustrophobia etc.). For each MRI session, images from the index knee will be acquired as described in the imaging protocol to assess synovitis, cartilage quantity as well as other knee features such as effusion and Bone Marrow Lesion (BML). Participant setup will ensure correct reproducible positioning of the knee as well as sufficient comfort to limit motion artifacts. The duration of the scanning sessions would be 30-40 minutes. 3D non-contrast MRI pulse sequences will be acquired for quantitative assessments. As the last acquisition in the protocol, for synovitis assessment T1weighted (T1w) DCE-MR images will be obtained before and after the injection of the gadolinium contrast agent. Macrocyclic GBCAs, which have higher stability than linear agents, should be used to mitigate the risk of gadolinium deposition. MR images will be acquired at

selected and qualified imaging site(s) and sent for independent central review by imaging specialists. The reviewers will be blinded to the treatment received by the participant.

The image analysis will be performed centrally, as defined in the imaging charter, in order to:

1. Screen for participants with active synovitis prior to the DFV890 administration. At screening, a comprehensive semi-quantitative scoring system will be performed on one of the scans obtained from the DCE-MRI series to assess whole-knee synovitis as previously described (Guermazi et al 2011). Synovitis will be assessed at 11 sites of the joint and whole-knee synovitis will be categorized as follows: 0–4 normal or equivocal synovitis; 5–8 mild synovitis; 9–12 moderate synovitis and ≥13 severe synovitis.
2. Assess changes in the activity level of synovitis, evaluated using primarily the volume transfer rate of the GBCA from the blood plasma in synovium, or K-trans (Riis et al 2017) from the DCE-MRI scans. Changes in the thickness of the synovial membrane, volume of bone marrow lesion and knee effusion will also be assessed. Other quantifiable measures may also be investigated.
3. Potentially assess changes in bone marrow lesions and effusion volume, as well as cartilagevolume, and thickness both in the index region and the rest of the joint, in 21 separate knee regions using CCI for the volumetric changes.

The coded medical images will be used primarily for analysis as described in this protocol; however, the images may also be used for the development and evaluation of new analysis methods directly related to the area of research that this study covers.

Incidental findings are beyond the scope of central imaging vendor. If an investigator/radiologist recognizes any incidental finding in the images during the course of conducting the clinical trial, the investigator should follow up as part of his/her duty of care to ensure the safety and wellbeing of the participant.

8.3.3 Appropriateness of efficacy assessments

Efficacy assessments were selected on the following basis:

- Patient Reported Outcome measures used (e.g., KOOS, NRS) are standard measurements for assessing pain in participants with OA (Guermazi et al 2011). The KOOS PRO is an expanded version of the Western Ontario and McMaster Universities Arthritis Index (WOMAC) score, which traditionally has been used in OA trials (KOOS User Guide, 2003). KOOS includes WOMAC OA index LK 3.0 in its complete and original format and WOMAC scores can be derived from the KOOS instrument. Compared to WOMAC, the KOOS score provides a more comprehensive picture because it includes additional domains, "Function in sport and recreation" and "Knee related QoL". The NRS pain score is traditionally used to assess pain.
- Imaging techniques including MRI are standard measures used for assessing joint structure in participants with OA (Hayashi et al 2019). For additional details on appropriateness of knee MRI parameters, see Section 8.3.2.

8.4 Safety/Tolerability

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section.

Table 8-3 Safety 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 knee joint examination will also be performed, including examination for bulge sign and patellar tap sign as well as for patellofemoral pain. Targeted physical examinations to elaborate self- reported symptoms, complaints, injection site reactions or post-injection flares as applicable, can be done at any visit. 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 Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs will include the collection of body temperature (recorded in °C), blood pressure (BP) and pulse measurements. The same method for measuring body temperature should be used throughout the study. After the participant has been sitting for 3 minutes, with back supported and both feet placed on the floor, SBP and DBP will be measured using an automated validated device, e.g., OMRON with an appropriately sized 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. In case of repeated vital assessments, the eCRF should contain all repeat measurements.
Height and weight	Height is obtained in centimeters (cm) and body weight is obtained in kilograms (kg) and rounded to the nearest 0.1 kg. Weight is obtained in indoor clothing, but without shoes). Height and weight will be measured as specified in Table 8-1. Body mass index (BMI) will be calculated using the following formula: • BMI = Body weight (kg) / [Height (m)]^2 Rounding should be done to nearest whole number (e.g., calculated BMI is 30.44, the BMI value can be rounded to 30 kg/m^2). The Screening Visit height measurement will be used for BMI calculations throughout the study.

8.4.1 Laboratory evaluations

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

In the case where a laboratory range is not specified by the protocol, but a value is outside the reference range for the laboratory at screening and/or initial baseline, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator (in consultation with 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 randomization.

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

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

If the COVID-19 pandemic limits or prevents the use of central laboratory services, e.g., due to transport restrictions of tissue samples, the sponsor may request essential laboratory screening and/or safety assessments to be analyzed by a local laboratory, if available. If used, relevant documentation should be obtained from the local laboratory to evaluate the validity of the data, considering potential differences in analysis assays, reference ranges, etc. between the local and central laboratories. It must be clear from the final data set which data originate from local laboratory analyses.

Urinalysis

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

Special clinical laboratory evaluations

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

Table 8-4 Laboratory evaluations

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands).
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (non-fasting)

Test Category	Test Name
	If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated. In addition, high sensitivity C-reactive Protein (hsCRP) will be measured for inclusion and for assessing systemic inflammation. Clinical chemistry samples will be used as per assessment schedule if still feasible. In case respective clinical chemistry samples have been already destroyed, CCI [redacted]
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	Prothrombin time (PT), International normalized ratio [INR]), Activated partial thromboplastin time (APTT)
Pregnancy Test	Serum / Urine pregnancy test, see Section 8.4.3

8.4.2 Electrocardiogram (ECG)

ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. In the case of a series of assessments, ECG should be first assessment obtained while 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 and Baseline visit(s) to assess eligibility according to the following formula:

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

Single 12-lead ECGs are collected and results are entered into the appropriate eCRF page. The original ECGs on non-heat-sensitive paper, appropriately signed, must be collected and archived.

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 baseline 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

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 90 days after stopping study treatment.

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

Serum pregnancy testing is required at Screening and EoS. Urine pregnancy testing is required at all other visits as specified in the Assessment Schedule (Table 8-1). Additional pregnancy testing might be performed if requested by local requirements. Local pregnancy test and associated results will not be collected on eCRF and results will be recorded in source documentation.

A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative.

If participants cannot visit the site to have serum pregnancy tests 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, urine pregnancy test kits may be used, if and where permitted by the local regulations and agreed with the local Health Authorities (in Germany only serum pregnancy tests are permitted at screening and EoS visits). 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

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, FSH testing is required of any female participant regardless of reported reproductive/menopausal status at screening/baseline.

8.4.4 Appropriateness of safety measurements

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

8.5 Additional assessments

8.5.1 CCI

CCI

[redacted]

8.5.2 Pharmacokinetics

PK samples will be collected at the visits defined in the assessment schedule. Follow instructions outlined in the Central Laboratory Manual regarding sample collection, numbering, processing and shipment. See the potential use of residual samples for more information. In case needed (e.g., skin rash), an unscheduled sample should be collected as near as possible to the event in order to assess a potential PK relationship.

Pharmacokinetic (PK) plasma samples will be obtained from all participants and evaluated only in participants exposed to DFV890 (placebo group excluded from analysis). CCI [redacted]

DFV890 and CCI [redacted], a metabolite of DFV890, in plasma will be determined by a validated LC-MS/MS method; the anticipated lower limit of quantification (LLOQ) is 1 ng/mL. DFV890 in synovial fluid will be determined by a qualified LC-MS/MS method; the anticipated lower limit of quantification (LLOQ) is 1 ng/mL.

Concentrations will be expressed in mass per volume units. Concentrations below the LLOQ will be reported as "zero" and missing data will be labeled as such in the Bioanalytical Data Report. In order to better define the PK profile, the timing of the PK sample collection may be altered based on emergent data with alteration ±5 min for time points ≤ 2 h post-dose; ±30 min for time points 2h < 12 h post-dose; ±1 h for Ctrough (before dose administration).

For standard pharmacokinetic abbreviations and definitions see the list provided at the beginning of this protocol. The following plasma pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 8): Cmax, Tmax, AUCtau (AUC0-12h), AUClast. To calculate AUCtau, the concentration at 0 h will be used also as a 12 h time point or it will be extrapolated. Calculation method will be specified in the report. Metabolite to parent ratio for AUC and Cmax will be derived. Also trough concentrations (Ctrough) in plasma and synovial fluid will be measured at the visits defined in the assessment schedule.

The linear trapezoidal rule will be used for AUC calculation.

8.5.3 Biomarkers

8.5.3.1 Soluble biomarkers

CCI [redacted]

Additional biomarker assessments in serum/synovial fluid may include biomarkers reflective CCI [redacted] or others, which are gated and may be triggered upon the overall outcome of this or other studies.

The list of biomarkers may be changed or expanded, if it is recognized that more relevant or additional biomarkers should be assessed during the conduct of the study.

In addition, hypothesis-free platforms such as SomaScan, CCI [redacted] arrays or others may be used to identify molecular participant profiles and new pharmacodynamic markers in serum and synovial fluid. Results obtained may be able to support the identification of pathways/markers that characterize the disease in addition to response to treatment with DFV890, to inform joint transmission into circulation, and to correlate markers with other clinical readouts.

NLRP3-pathway biomarkers or results generated by profiling assessments will be correlated with other readouts, such as imaging-based readouts or pain, to understand the translation of potential molecular changes into a reduction of synovitis, and subsequently, participant benefit.

8.5.3.4 Renal impairment biomarkers

CCI [redacted]

Sample(s) will be collected at the time point(s) defined in the Assessment Schedule (Table 8-1).

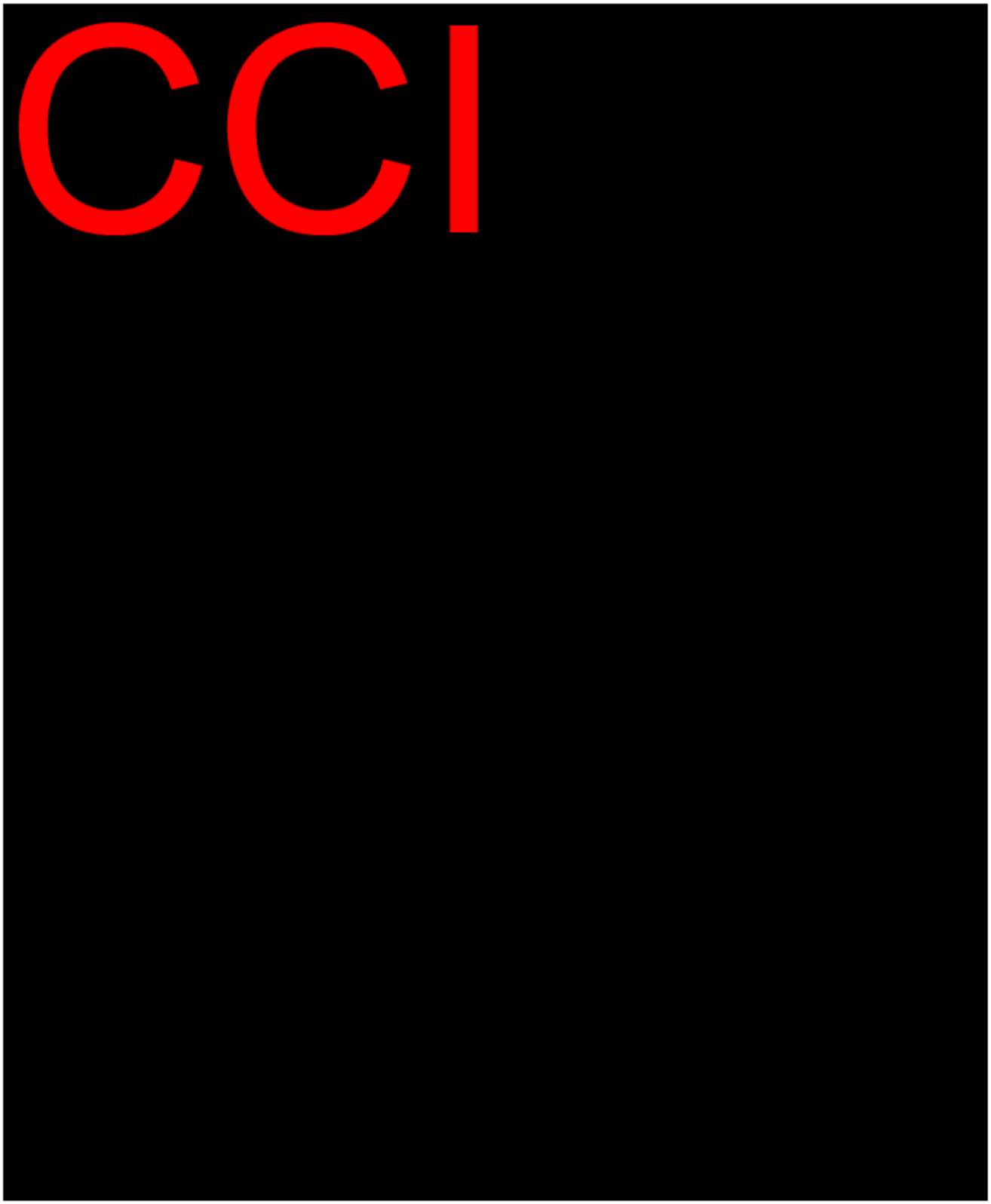
Follow instructions for sample collection, numbering, processing, and shipment provided in the laboratory manual.

8.5.3.5 DNA sampling / Pharmacogenetics

This study involves both a mandatory and an CCI [redacted].

Pharmacogenetic sample for CYP2C9 genotyping

CCI [redacted]


CCI

8.5.4 Synovial fluid collection

CCI [redacted] Collection will depend on whether or not synovial fluid is present in the knee, and on participant willingness to undergo this procedure and based on the investigator judgement. Synovial fluid samples will be collected by appropriately equipped and trained staff. For more details on the procedure, please refer to the Central Laboratory Manual.

8.5.5 Imaging

The methods for assessment and recording are specified in the Imaging charter.

The coded medical images will be used primarily for analysis as described in this protocol; however, the images may also be used for the development and evaluation of new analysis methods directly related to the area of research that this study covers.

8.5.6 Other Assessments

CCI [redacted]

8.5.6.2 Meal Record

Meal records are required for onsite meals in conjunction with study treatment intake in order to assess food intake impact on PK data. For these meals the date, start and end time of meal consumption will be captured in the eCRFs. Data will not be collected outside of study visits.

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

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 drug 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/guardian 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
- Following emergency unblinding
- Emergence of at least one of the following adverse events:
  - A life-threatening adverse event (corresponding to CTCAE Grade 4 or higher) considered related to DFV890 treatment
  - An AE of severe intensity (corresponding to CTCAE Grade 3 or higher) considered related to DFV890 treatment
  - Skin rashes greater than mild (covering > 10% of the body surface area, corresponding to CTCAE Grade 2 or higher), considered as related to DFV890
  - If an abnormal renal event is confirmed, and other causes are excluded, the study drug will be interrupted in the case of:
    - Serum creatinine increase of 50 % (i.e., acute kidney injury)
    - New onset dipstick proteinuria ≥ 3+
    - Urine Protein-creatinine ratio (PCR, gCr) ≥ 1 g/g
    - New evidence of clinically significant crystals on microscopy

  Please refer to Section 10.2.2 and Appendix 2 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 Appendix 1 regarding discontinuation of study treatment.

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

Participants who discontinue from study treatment agree to return for the end of treatment and follow-up visits indicated in the Assessment Schedule (refer to Section 8)

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

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

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

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

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section.

9.1.1.1 Replacement policy

Additional participants may be enrolled to replace discontinued participants if the drop-out rate (based on discontinuations prior to Week 12) exceeds 10%.

9.1.2 Discontinuation from study

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

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table (refer to Section 8).

9.1.3 Withdrawal of informed consent

Withdrawal of consent/opposition to use data/biological samples occurs when a participant:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use participant's data and biological samples)

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 in writing (depending on local regulations) and recorded in the source documentation.

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/opposition to use data/biological samples and record this information.

Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the participant therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their Personal Data.

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/opposition to use data/biological samples should be made as detailed in the assessment table (refers to Section 8).

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

9.1.4 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent/oppose to the use of their data/biological samples, 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.

9.1.5 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, if any of the following criteria are met:

- Any death or life-threatening event (corresponding to CTCAE Grade 4 or higher) considered to be related to DFV890 treatment
- Two (2) or more SAEs of a similar type (other than death or life-threatening event, corresponding to CTCAE Grade 3 or higher) considered to be related to DFV890 treatment
- Two (2) or more participants are discontinued due to a renal event as defined in Section 16.2
- Two (2) or more participants experience three or more AEs of similar type which are assessed as severe in intensity (corresponding to CTCAE Grade 3 or higher) and considered to be related to DFV890 treatment
- Number and/or severity of AEs, abnormal safety monitoring tests, or abnormal laboratory findings justify putting the study on hold
- Two (2) or more participants presenting DFV890 treatment related acute exacerbations of knee symptoms, as judged by the Investigator and/or the Sponsor

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.

9.1.6 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
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- 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 and treated as a participant who discontinued from study treatment: instructions for contacting the participant, when the participant should stop taking drug, and when the participant should come in for a final visit, will be provided at that time. 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 EoS 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.

For medical devices (investigational or marketed), an adverse event (AE) is any untoward medical, unintended disease or injury or untoward clinical signs, including an abnormal laboratory finding, in participants, users or other persons, in the context of a clinical investigation, whether or not related to the device. For investigational devices, this includes events related to the investigational device or the comparator and events related to the procedures involved in the clinical investigation plan.

The Investigator and any qualified designees are responsible for managing the safety of individual participants. They are also responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and for following up all AEs and SAEs.

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

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events 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 (e.g. indicated by comments in the pain diary).

Adverse events 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: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
   - moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
   - severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
2. The causality

   The investigator is obligated to assess the relationship between any treatment used in the study (study treatment, AxMP(s)) and each occurrence of each AE. The investigator will use clinical judgment to determine the relationship. A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated. For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.

   The causality assessment is one of the criteria used when determining regulatory reporting requirements.
3. Its duration (start and end dates or ongoing) and the outcome 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 study treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/ permanently discontinued

6. Its outcome
    - not recovered/not resolved;
    - recovered/resolved;
    - recovered/resolved with sequelae;
    - fatal; or unknown.

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

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

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

Once an adverse event 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 can be found in the Investigator's Brochure (IB) for the investigational drug or in the product information for marketed products.

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

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in a participant with the underlying disease.

Reporting of AEs related to AxMP(s)

All AEs related to any authorized auxiliary medicinal product used in this study must be reported to Novartis.

In assessing causality, the investigators will use the points above.

If a suspicion that medical occurrence could be related to study treatment (and/or interaction with study treatment) cannot be ruled out, the reporting rules for study treatment apply.

The AE reporting requirements for AxMPs will apply once this trial has been transitioned under EU Clinical Trial Regulation 536/2014.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [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 in-patient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in the participant's OA 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 out-patient 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

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

understand potential etiologies, the investigator must initiate a close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

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 a SAE irrespective of whether or not 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. Information about all SAEs is collected and recorded on Serious Adverse Event Report Form)eSAE with paper backup). All applicable sections of the form must be completed in order to provide a clinically thorough report.

The investigator must review and provide an assessment of causality for each SAE. There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to Novartis. However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to Novartis. The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

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).

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

Reporting of SAEs related to AxMP(s)

The SAE reporting requirements for AxMPs will apply once this trial has been transitioned under EU Clinical Trial Regulation 536/2014.

All SAEs related to any auxiliary medicinal product (whether authorized or not) used in this study must be reported to Novartis within 24 hours of the site becoming aware of it. In assessing causality, the investigators will use the points above. If a suspicion that the medical occurrence could be related to study treatment (or and interaction with study treatment) cannot be ruled out, the reporting rules for study treatment apply.

Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

If an SAE is not previously documented in the IB or product information for marketed products and is thought to be related to any study treatment, Novartis may urgently require further information from the investigator for HA reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment. SUSARs will be reported to the competent authorities and relevant ethics committees in accordance with national regulatory requirements in participating countries, including EU Clinical Trial Regulation 536/2014.

10.1.4 Pregnancy reporting

Pregnancies

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

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

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

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

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 (EMA definition).

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate 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

For more information on AE and SAE definition and reporting requirements, please see the respective Section 10.1.

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 Appendix 1 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Section 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 GGT) to confirm elevation.

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

- Initiate close observation of the participant if the initial elevation is confirmed, including consideration of treatment interruption if deemed appropriate.
- Discontinue the investigational drug (refer to the Discontinuation of study treatment Section 9.1.1), if appropriate
- Hospitalize the participant, if appropriate
- Assess causality of the liver event
- Include thorough follow-up of the liver event:
  - These investigations may 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, UTI, 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 Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, and allow modification and/or verification of the entered data by the investigator staff.

Participants will be asked to complete PROs on a paper copy. The participant's responses will be transcribed into the eCRF by the study staff. When a paper copy is used off-site, the participant should bring the completed questionnaire(s) to the next study visit at earliest convenience.

The pain / medication diaries will be paper-based and should be completed and returned by the participants at each visit up to Day 84. The diary data will be transcribed into the eCRF by the site personnel.

Completed paper questionnaires (if any) and diaries will be kept as source documentation at the investigator site and are not to be collected by the sponsor.

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 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 adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

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

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

Once all necessary actions have been completed and the database has been declared complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis/moved to restricted area to be accessed by the independent programmer and statistician. 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/delegated CRO representative will review the protocol and data capture requirements (i.e., eSource 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 Good Clinical Practice, 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/delegated CRO/CRA organization. Additionally, a central analytics organization may analyze data & identify risks and 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 informed consent form 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.

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

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

For all analysis sets, participants will be analyzed according to the study treatments received.

The full analysis set (FAS) will include all participants who received any study drug.

The safety analysis set (SAF) will include all participants who received any study drug.

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

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

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively by treatment group for the FAS.

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

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by treatment group.

12.3 Treatments

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

The duration of exposure in days to DFV890 will be summarized by means of descriptive statistics using the safety set.

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

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

The primary aim of the study is to evaluate the efficacy of DFV890 vs. placebo in participants with symptomatic, inflamed knee OA as evidenced by reduction in the index knee pain by KOOS (knee injury and osteoarthritis outcome score) at 12 weeks.

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

The definition of the primary estimand is provided in Section 2.1.

The primary efficacy endpoint of the study is the change from baseline in Knee injury and Osteoarthritis Outcome Score (KOOS), pain subscale at Week 12.

12.4.2 Statistical model, hypothesis, and method of analysis

The change from baseline in Knee injury and Osteoarthritis Outcome Score (KOOS) pain subscale will be analyzed using a mixed effects model for repeated measures (MMRM). The model will include baseline, treatment, time point, baseline * time points and treatment * time points as fixed effects. An unstructured covariance or other covariance structures will be assumed to account for within-participant variability. A two-sided 95% confidence interval for the treatment effect (i.e., DFV890 minus Placebo) at Week 12 will be reported.

12.4.3 Handling of intercurrent events of primary estimand

As described in Section 2.1, ICEs related to missed doses and unforeseen use of rescue medications or prohibited medications will be handled according to a hypothetical strategy, i.e., either the KOOS assessment at the next visit or all subsequent KOOS assessments will be excluded from the primary analysis, as detailed in Table 2-2. Data affected by the ICE will instead be considered missing and implicitly imputed by the MMRM under the missing at random (MAR) assumption (i.e. assuming that participants with missing data would have efficacy outcomes like those of similar participants in their treatment group who continue their randomized treatment).

12.4.4 Handling of missing values not related to intercurrent events

The MMRM model used for the analysis of the primary endpoint implicitly imputes missing data under a missing at random assumption.

12.4.5 Sensitivity analyses for primary endpoint/estimand

Any deviation from the imputation techniques assuming MAR and its impact on the primary estimand will be assessed via jump to reference imputation as a conservative option.

12.4.6 Supportive analyses

The change from baseline in Knee injury and Osteoarthritis Outcome Score (KOOS) pain subscale will be analyzed separately for participants with and without presence of contralateral knee OA.

Also, the average amount of concomitant (basic pain medication) and rescue medications will be presented by treatment group.

12.4.7 Supplementary analyses

Additional analyses may be carried out, e.g., in which the assessments for participants who use rescue medication within 48 hours prior to the visit and/or for at least three consecutive days would not be considered an ICE, and/or in which treatment policy strategy would be applied to all ICE (i.e., use all data as collected). These supplementary estimands will be specified in the SAP.

12.5 Analysis of secondary endpoints/estimands

The statistical analysis for secondary endpoints will be described in detail in the SAP.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

The secondary efficacy objectives are as follows:

- To assess the efficacy of DFV890 vs. placebo in participants with symptomatic, inflamed knee OA on inflammatory joint structure features. The variable associated with this objective is change from baseline in synovitis activity level measured from K-trans by DCE-MRI at Week 12, and will be analyzed using ANCOVA adjusting for baseline.
- To assess the efficacy of DFV890 vs. placebo in improving participants' report about their knee symptoms and associated problems over time. The variable associated with this objective is change in KOOS sub-scales (other symptoms, function in daily living, function in sport and recreation, knee-related quality of life) from baseline to weeks 2, 4, 8, and 12, and will be analyzed using an MMRM model.
- To assess the efficacy of DFV890 vs. placebo in relieving OA pain over time. The two variables associated with this objective are: 1.) change in KOOS pain subscale from baseline to weeks 2, 4 and 8, and 12. 2.) change in numeric rating scale (NRS) for pain from baseline to weeks 2, 4, 8 and 12. These two endpoints will be analyzed separately using an MMRM model.

The structure of the above MMRM models will be the same as the one mentioned in the analysis of the primary endpoint.

12.5.2 Safety endpoints

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

Adverse events

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

The number (and percentage) of participants with treatment emergent adverse events will be summarized by treatment, primary system organ class and preferred term, with a breakdown by treatment.

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

Vital signs

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

12-lead ECG

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

Clinical laboratory evaluations

All laboratory data will be summarized by treatment group and visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

12.5.3 Pharmacokinetics

Descriptive summary statistics of DFV890 (secondary endpoint) and CCI [redacted] plasma concentration data will be provided by visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

DFV890 concentrations below the LLOQ will also be treated as zero for the calculation of PK parameters.

Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is *Tmax* where median, minimum, and maximum will be presented.

Table 12-1 Non-compartmental pharmacokinetic parameters

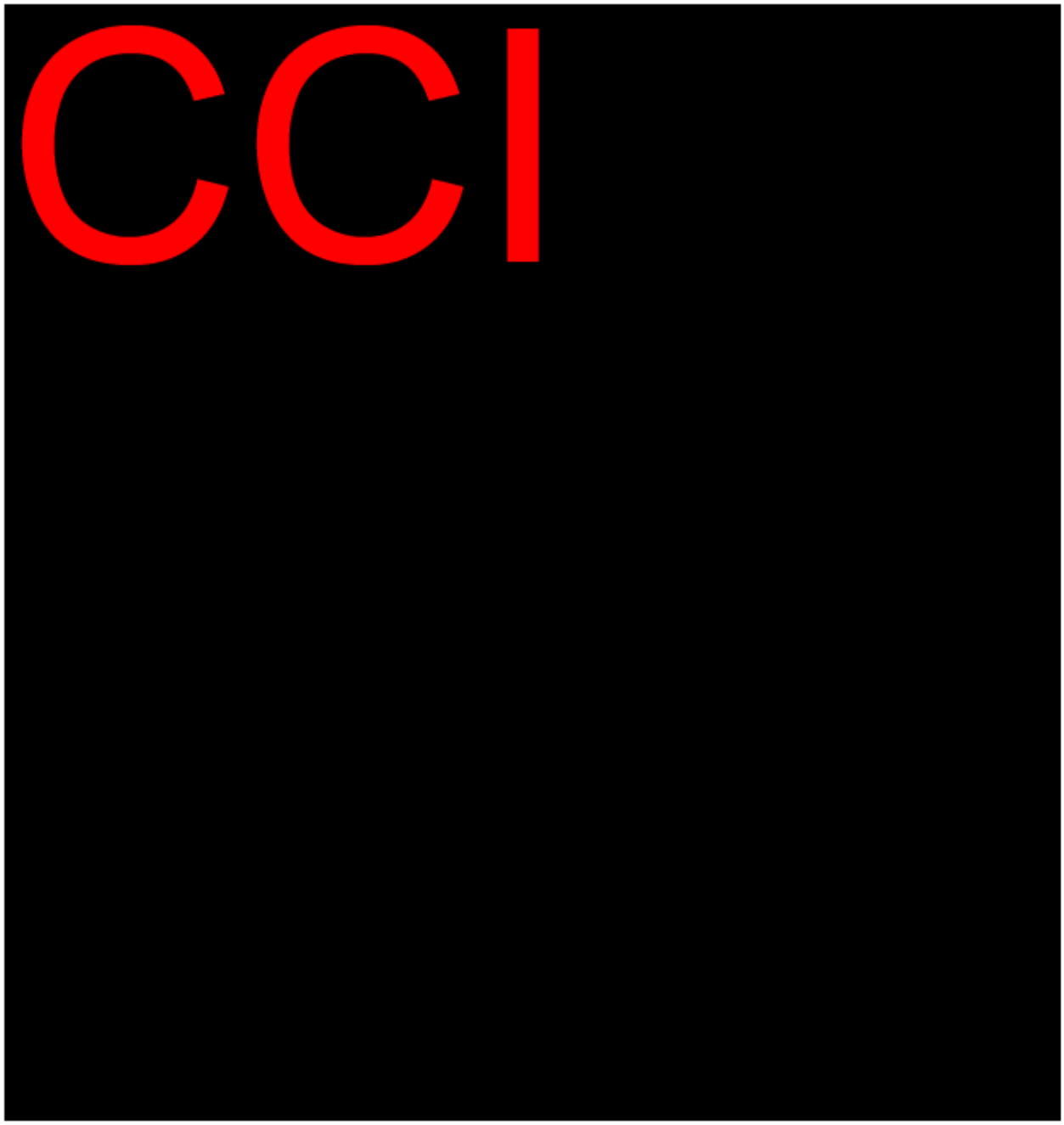
AUClast	The AUC from time zero to the last measurable concentration sampling time (tlast) (mass x time x volume-1)
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (amount x time x volume-1)
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1)
Ctrough	The concentration that is just prior to the beginning of, or at the end, of a dosing interval (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)

12.5.4 Biomarkers

CCI [redacted]

12.6 Analysis of exploratory endpoints

CCI [redacted]



12.7 Interim analyses

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)

A positive treatment effect is indicated by an increase in KOOS pain score. Assuming a true treatment difference in KOOS pain score of 12 points and a standard deviation of 19, a sample size of 108 participants provides approximately 80% power that the primary analysis will be statistically significant at the two-sided 5% significance level assuming 25% of losses to follow-up including early discontinuations because of CCI or other reasons.

12.8.2 Secondary endpoint(s)

Assuming 1:1 randomization ratio and a true treatment effect of 0.07min-1 and variability of 0.1min-1 (Hodgson et al 2008) in K-trans, a sample size of around 70 participants (including dropout rate 25%) provides 80% power to show statistical significance at one-sided 5% significance level.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and will be implemented, executed and reported in accordance with the protocol and the following:

- Consensus ethical principles derived from international guidelines including the

Declaration of Helsinki and Council for International Organizations of Medical Sciences

(CIOMS) international ethical guidelines

- Applicable ICH Tripartite Guidelines for Good Clinical Practice (GCP)
- Applicable local regulations (including European Directive 2001/20/EC or European

Clinical Trial Regulation 536/2014, US CFR 21)

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated at that specific site. Any amendments to the protocol will require IRB/IEC and Health Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, 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 Policy

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT or CTIS public website. In addition, after study completion (defined as last participant 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 or CTIS public website etc.).

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.

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

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures 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.

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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 > 3x baseline AND >5x ULN

*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 > 5 x ULN for more than two weeks OR ALT> 8 x ULN	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	• **Interrupt study drug** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin and CK, 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 elevated at baseline: ALT > 3 x baseline AND >5x ULN > for more than two weeks OR ALT ≥ 5x baseline AND ≥ 8x ULN			
ALT increase with bilirubin increase:			
If normal at baseline: ALT > 3 x ULN	TBL > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
If elevated at baseline: ALT > 2 x baseline AND >3x ULN			
If normal at baseline: ALT > 3 x ULN	Normal or elevated *	Severe fatigue, nausea, vomiting, right upper quadrant pain *	
If elevated at baseline: ALT > 2 x baseline AND >3x ULN)			

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

Table 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 LFTs within 48-72 hours	Monitor LFTs weekly until resolution[c] 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[c] 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[c] (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]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN

[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

[c]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.

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	• 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	• Repeat assessment to confirm • Assess serum creatinine, 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 participant 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

FOLLOW-UP OF RENAL EVENTS
• 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
• 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