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Novartis Research and Development

DFV890

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 Statistical Analysis Plan (SAP)

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Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse Event
AUC	Area Under the Curve
CRF	Case Report Form
CSR	Clinical Study Report
DCE	Dynamic Contrast Enhanced
DMS	Document Management System
dSPP	Development Safety Profiling Plan
ECG	Electrocardiogram
EoS	End of Study
FAS	Full Analysis Set
IA	Interim Analyses
KOOS	Knee injury and Osteoarthritis Outcome Score
LLOQ	Lower Limit of Quantification
MAR	Missing at Random
MedDRA	Medical Dictionary for Drug Regulatory Affairs
MMRM	Mixed effect Model for Repeated Measures
MRI	Magnetic Resonance Imaging
NRS	Numeric Rating Scale
PD	Pharmacodynamics
OA	Osteoarthritis
PK	Pharmacokinetics
PoC	Proof-of-Concept
RAP	Reporting & Analysis Process
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOC	Standard of Care
SSP	Safety Surveillance Plan

1 Introduction

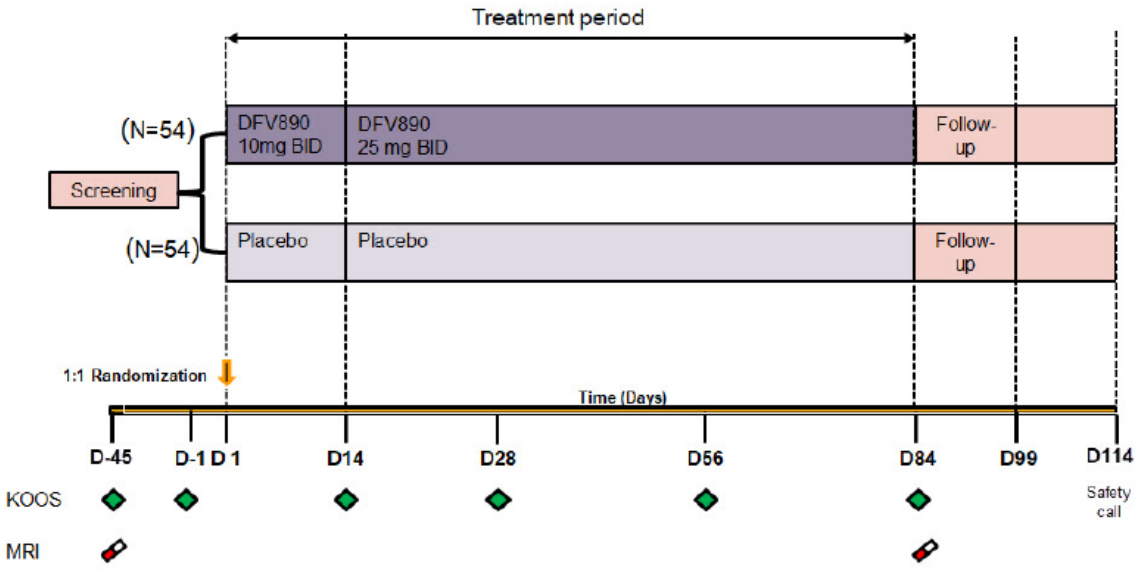
The Reporting and analysis plan (RAP) documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial "CDFV890B12201". The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

1.1 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 (randomized in a 1:1 ratio) 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. 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, followed by a 10-week treatment period where they 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).

Figure 1-1 Study design



1.2 Study objectives, endpoints and estimands

Study objectives and endpoints are listed in Table 1-1 below.

Table 1-1 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 Ktrans 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) 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, AUC last, 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 sub-scale 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)**
CCI	

Objective(s)	Endpoint(s)
CCI	

1.2.1 Primary estimand(s)

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 inflammatory knee OA?

The justification for the primary estimand is that it will capture the effect of the study drug, and the effect of both additional basic pain medication and the use of rescue medication as per protocol. The primary estimand is described by the following attributes:

1. Population: participants with mild to moderate, symptomatic knee OA (KL grade 2-3), clinical signs of inflammation, elevated hsCRP (≥1.8 mg/L) and confirmation of active synovitis by MRI.
2. Endpoint: change from baseline to week 12 of the KOOS pain sub-scale.
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 of remaining intercurrent events (ICEs): 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. 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 sub-scale score from baseline to week 12.

Table 1-2 Overview on intercurrent events for the primary estimand

Intercurrent event[a]		**Handling of event**
Missed treatment doses	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, for more than three days in the seven days prior to the visit/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 intraarticular injection; systemic corticosteroids) as specified in the protocol	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 as specified in the protocol (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.		

1.2.2 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 Ktrans by DCE-MRI at Week 12 in participants with symptomatic knee OA.

The justification for the key secondary estimand(i.e. the population, treatment of interest, 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 Ktrans at Week 12.

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

2 Statistical methods

2.1 Data analysis

The analysis to address the primary objective will be conducted at the end of the treatment period. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

Unless specified otherwise, the on-treatment period will be split into 10mg for 14 days from the start of treatment and 25mg thereafter, where the morning dose + 12h on the 14th day of 10mg dosing will be considered as the start date/time of the dose change from 10mg to 25mg.

The analysis will be performed using SAS software, Version 9.4 or higher.

2.1.1 General definitions

The term study drug or investigational treatment refers to DFV890 or Placebo, while the term investigational drug refers exclusively to DFV890.

Date of first administration of investigational treatment

The date of first administration of investigational treatment is defined as the first date when a nonzero dose of investigational treatment is administered and recorded on the Dosage Administration Record (e)CRF.

Date of last administration of investigational treatment

The date of last administration of investigational treatment is defined as the last date when a nonzero dose of investigational treatment is administered and recorded on dose administration (e)CRF. The date of last administration of investigational drug will also be referred as end of investigational drug or end of investigational treatment.

Study day

Study day 1 for all assessments is taken to be the start of investigational treatment.

The study day for all assessments will be calculated as follows:

1. If date of assessment occurred on or after the start of investigational treatment, then
   Study day = Date of assessment - Start of investigational treatment + 1.
2. If date of assessment occurred before the start of investigational treatment, then
   Study day = Date of assessment - Start of investigational treatment.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

Baseline

For safety and efficacy evaluations, the last available assessment on or before the date of start of investigational treatment is taken as the ‘‘baseline” assessment. In case time of assessment and time of treatment start is captured, the last available assessment before the treatment start date/time is used for baseline. For NRS diary pain score, baseline will be considered as the same

date as the KOOS baseline assessment. Additionally, for NRS diary pain score, the baseline will be considered as the average score for all values collected for the last 7 days prior to the baseline assessment and the baseline day.

For safety parameters (e.g. ECGs), where the study requires multiple replicates per time point, the average of these measurements would be calculated (if not already available in the database) before determining baseline.

In rare cases where multiple measurements meet the baseline definition, with no further flag or label that can identify the chronological order, then the following rule should be applied: If values are from central and local laboratories, the value from central assessment should be considered as baseline. If multiple values are from the same laboratory (local or central) or collected for ECGs or vital signs, then the last value should be considered as baseline, if chronological order is known.

If participants have no value as defined above, the baseline result will be missing.

For safety parameters other than ECG, scheduled pre-dose collections as well as unscheduled collections on Day 1 for which no time is available will be considered as pre-dose.

For ECG, study baseline scheduled and/or pre-dose ECGs will be considered to have been obtained prior to start of investigational treatment if dosing time or ECG time is missing and used in the calculation of the baseline value. If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be treated and analyzed similar to an unscheduled post-dose measurement.

Regarding MRI, baseline is defined as the scan performed at screening days -45 to -2.

On-treatment assessment/event

The overall observation period will be divided into three mutually exclusive segments:

- ***pre-treatment period***: from day of participant's informed consent to before date of first administration of investigational treatment
- ***on-treatment period***: from date of first administration of investigational treatment to end of study assessments (eos)
- ***post-treatment period***: any data collected after eos

Note: If dates are incomplete in a way that clear assignment to pre-, on-, post-treatment period cannot be made, then the respective data will be assigned to the on-treatment period.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (***treatment-emergent*** AEs).

However, all safety data (including those from the post-treatment period) will be listed and those collected during the post-treatment period will be flagged.

2.2 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 treatment.

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

The PK analysis set will include all participants with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received any study 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.

The analysis sets and protocol deviation codes are related as follows:

Participants without a signed informed consent obtained prior to participation in the study (INCL01) and any data other than safety collected from the GCP non-compliance sites (OTH33) will be excluded from any analyses. All the protocol deviation codes and the details are included in Table 2-1.

Table 2-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
INCL01	Signed informed consent not obtained	Exclude subjects from all analysis sets
INCL06	NRS pain score for the last 3 months and at screening and baseline visits ranging from [5-9] inclusive	Exclude participants from the PD analysis set
INCL07	Widespread Pain Index (WPI) score ≤4 at screening	Exclude participants from the PD analysis set
INCL08	KOOS pain sub-scale score ≤60 in index knee at screening and baseline	Exclude participants from the PD analysis set
INCL12	Current use of analgesic therapy for control of local pain in the target knee	Exclude participants from the PD analysis set
EXCL02	Known autoimmune disease with inflammatory arthritides crystal-induced arthritides, 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, or a known systemic connective tissue disease	Exclude participants from the PD analysis set
EXCL05	Participant has an unstable target knee joint or insufficiently reconstructed ligaments based on medical history and physical examination by the Investigator at screening	Exclude participants from the PD analysis set
EXCL06	Participant has symptomatic, isolated patellofemoral pain in the index knee as per the Investigator's examination at screening	Exclude participants from the PD analysis set

Category Deviation code	Text description of deviation	Data exclusion
EXCL09	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	Exclude participants from the PD analysis set
EXCL12	Other pathologies affecting the knee	Exclude participants from the PD analysis set
EXCL14A-C	Use of prohibited medications	Exclude participants from the PD analysis set
EXCL18A	Knee Replacement	Exclude participants from the PD analysis set
Only Exclude from Structural Assessments (MRI)		
INCL10	Active synovial inflammation at screening	Exclude participants from the PD analysis set
EXCL02	Known autoimmune disease with inflammatory arthritides crystal-induced arthritides, 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, or a known systemic connective tissue disease	Exclude participants from the PD analysis set
EXCL12	Other pathologies affecting the knee	Exclude participants from the PD analysis set
EXCL14A-C	Use of prohibited medications	Exclude participants from the PD analysis set
OTH14	Gadolinium contrast dose administration or agent differs between timepoints or from protocol specified technique	Exclude participants from the PD analysis set

Any updates to the above table will be updated via SAP amendment prior to final DBL as required.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

A summary disposition for all screened participants will be presented for each treatment. Screened participants include those who completed screening and were randomized, those who completed screening and were not randomized, and participants who did not complete the screening (with reasons for not completing screening).

Randomized participants included in the FAS will be presented. The following summaries will be provided (with % based on the total number of FAS participants):

- Number (%) of participants who were randomized but not treated (based on DAR (e)CRF page not completed for any investigational treatment component) along with the primary reason for not being treated (based on ‘End of Treatment’ disposition page)

- Number (%) of participants who were treated (based on DAR (e)CRF page completed for any investigational treatment component)
- Number (%) of participants who completed treatment and those who discontinued the investigational treatment phase along with the primary reason for investigational treatment discontinuation (based on the 'End of Treatment' disposition page)

Participant disposition data and screened participants not randomized will be listed.

2.3.2 Demographics and other baseline characteristics

Demographic and other baseline data will be listed and summarized descriptively by treatment and participant. Summary statistics will be provided by treatment 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. For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized. A listing by system organ class (SOC)/preferred term (PT) for each participant by treatment will be reported.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

The Safety set will be used for the analyses below.

Dose administration will be listed by treatment group, date and time. The duration (in days) of exposure to DFV890 will be summarized by means of descriptive statistics.

2.4.2 Prior, concomitant and post therapies

The number and percentage of patients taking concomitant, rescue and prohibited medications, as well as significant non-drug therapies prior to and after the start of the study treatment may be tabulated according to the WHO Anatomical Therapeutic Chemical (ATC) classification system using the latest version available prior to clinical database lock, by preferred term and treatment with a flag to differentiate those who started more than 15 days (+3 days window period) after the last investigational treatment. The average amount of concomitant, rescue and prohibited medications will be presented by treatment group.

2.5 Analysis supporting primary objectives

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.

2.5.1 Primary endpoint

The primary efficacy endpoint of the study is the change from baseline to week 12 in the KOOS pain sub-scale. The KOOS pain sub-scale score will be analyzed on a 100 points scale, lower scores indicating more pain.

The full analysis set will be used for efficacy analyses.

2.5.2 Statistical hypothesis, model, 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.

2.5.3 Handling of intercurrent events of primary estimand

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 1-2. Data affected by the ICE will instead be considered missing and implicitly imputed by the MMRM under the 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). Handling of missing values not related to intercurrent events

The MMRM model used for the analysis of the primary endpoints implicitly imputes missing data under a missing at random (MAR) assumption. Following the KOOS Scoring 2012 guidance, the KOOS pain sub-scale will be considered as missing if responses are provided for less than 50% of items. Analysis of total KOOS score and other KOOS sub-scales including daily function, quality of life, sports and recreation, and symptoms will follow the same primary estimand strategy as pain assessment as well as NRS pain outcomes.

2.5.4 Sensitivity analyses

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

In addition to the primary model for the change from baseline in KOOS pain score, the model will also be adjusted for age and sex to account for any imbalances and observe any differences in the estimate.

KOOS pain, KOOS-subscales, total KOOS and NRS pain outcomes will also be analyzed based on PD analysis set to show the estimates from the primary analysis did or did not affect the outcome of the primary analysis. Additional analysis may also be carried out to assess the results for participants who experienced an AE and/or protocol deviation determined to potentially impact pain perception for each pain outcome. For this additional analysis, these

events will be considered as an additional ICE in the estimand. The decision to include these events as an ICE will be assessed and will be made only considering blinded data.

2.5.5 Supplementary analyses

Rescue medications/prohibited medications/basic pain medication from the pain diary summaries will be included by treatment and overall. Derived variables of interest will includes number of pills and number of days taken during the treatment period. In case of any imbalances between treatment groups observed in the use of concomitant and/or rescue medications, the inclusion of pain medication use as a covariate will be adjusted in the MMRM model.

Additional analysis 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 collected). MMRM model will be applied similar to the primary analyses to obtain the estimates under treatment policy

2.6 Analysis supporting secondary objectives

2.6.1 Secondary endpoints

For comparability with the primary analysis, the analysis of these key secondary endpoints will be performed following the same estimand strategy as the primary analysis described in Section 2.5.

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 change from baseline in synovitis measured from K-trans. based on active appearance models for the segmentation of synovial tissue thereby creating a 3-dimensional region of interest mask around by DCE-MRI at baseline and Week 12 K-trans of synovial tissue will be measured and data will be analyzed using ANCOVA adjusting for baseline. Similar analyses as described above will be made using the PD analysis set for structural features.To assess the efficacy of DFV890 vs. placebo in improving participants' report of knee symptoms and associated problems over time. The variables associated with this objective is the change in KOOS sub-scales (other symptoms, function in daily living, function in sport and recreation, knee-related quality of life) and total KOOS from baseline to weeks 2, 4, 8, and 12.
- To assess the efficacy of DFV890 vs. placebo in relieving OA pain over time. The variables associated with this objective are: 1. change in KOOS pain sub-scale, from baseline to weeks 2, 4, 8, and 12; 2. change in numeric rating scale (NRS) for pain from baseline to weeks 2, 4, 8 and 12. 3. change in numeric rating scale (NRS) from the pain diary using the 7 days prior to the KOOS assessment plus the day of the KOOS assessment. For the pain diary assessment baseline will be analyzed in two ways 1. using a baseline at the time of the KOOS pain score baseline visit and 2. using the average

score for all values collected in the last 7 days prior to the baseline assessment and the baseline assessment (before the start of treatment). Post-baseline timepoints will correspond to the time of KOOS evaluation of the closest assessment prior to weeks 2, 4, 8 and 12. Pain measurements and sub-scales of KOOS will follow the same analysis as the primary estimand for KOOS pain (considering ICEs).

2.6.2 Statistical hypothesis, model, and method of analysis

The variables described in Section 2.6.1 (except for Ktrans and synovitis score) will also be analyzed using an MMRM model and the covariance structure will be explored similar to the analyses described for the primary endpoint.

2.6.3 Handling of missing values/censoring/discontinuations

The MMRM model used for the analysis of the secondary endpoints implicitly imputes missing data under a missing at random assumption. Following KOOS Scoring 2012 guidance, a KOOS sub-scale will be considered as missing if responses to fewer than 50% of items are provided.

2.7 Safety analyses

For all safety analyses, the safety analysis set will be used. All listings and tables will be presented by treatment group and by treatment period. Safety summaries include only on-treatment assessments (refer to Section 2.1.1); AE listings will include all assessments collected in the CRF pages with a flag to differentiate the adverse events that occurred during the treatment period and after the end of treatment.

Safety assessments include AEs, laboratory data, vital signs, deaths and ECGs. All Section 16 safety listings and Section 14 will be reported using Safety set. The Safety set will be used for all safety summaries. Safety summaries include only on-treatment assessments (refer to Section 2.1.1), with a start date during the on-treatment period (treatment-emergent AEs).

For selected items, change from baseline summaries generated for laboratory values, ECG, vital signs may use data before start of investigational treatment for baseline calculations.

2.7.1 Adverse events (AEs)

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 (events started after the first dose of study medication or events present prior to start of treatment but increased in severity) will be summarized by treatment and maximum severity. Adverse events will be recorderd under the signs, symptoms, or diagnosis associated with them. The severity grade is defined as follows:

- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation.

The number (and proportion) of participants with skin rash will be summarized by treatment. Skin rash is indicated as adverse event of special interest (AESI) in the SSP (safety surveillance plan). In addition, reduction in neutrophil count will be treated as AESI. A summary table of neutrophil counts will be provided by treatment group and visit/time and will be categorized as follows: <0.5 x10^9/l, 0.5 x10^9/l to < 1.0 x10^9/l, 1.0 x10^9/l to < 1.5 x10^9/l, 1.5 x10^9/l to < 2.03 x10^9/l.

2.7.2 Deaths

The deaths (if any) resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided as listings.

2.7.3 Laboratory data

All laboratory data will be listed by treatment group, treatment period, participant, and visit/time, and if normal ranges are available, abnormalities will be flagged. A separate listing is provided presenting all parameters in a participant with any abnormal values.

Summary statistics will be provided 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.

2.7.4 Other safety data

2.7.4.1 ECG and cardiac imaging data

All single 12-lead ECG data (included but not limited to PR, QRS, QT, QTcF and RR intervals) will be listed by treatment group, participant and visit/time, and abnormalities will be flagged. Summary statistics will be provided by treatment group and visit/time.

Data analysis

The number and percentage of participants with notable ECG values will be presented.

- QT, QTcF
  - New value of > 450 and ≤ 480 ms
  - New value of > 480 and ≤ 500 ms
  - New value of > 500 ms
  - Increase from baseline of > 30 ms to ≤ 60 ms
  - Increase from baseline of > 60 ms
- HR
  - Increase from baseline >25% and to a value > 100 bpm
  - Decrease from baseline >25% and to a value < 50 bpm
- PR
  - Increase from baseline >25% and to a value > 200 ms
  - New value of > 200 ms

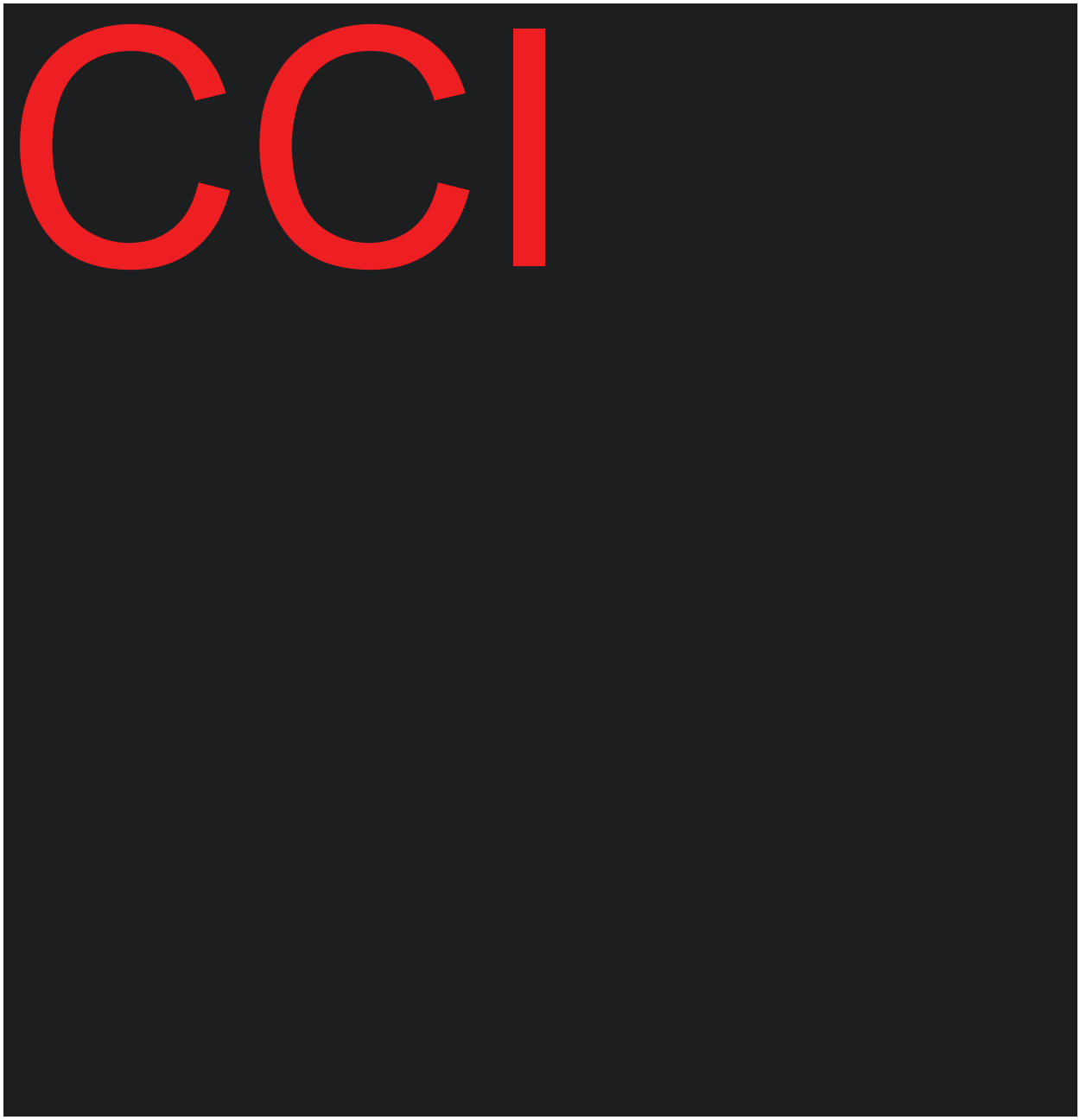
- QRS
  - Increase from baseline >25% and to a value > 110 ms
  - New values of QRS > 110 ms

ECG data will be summarized by presenting summary statistics of observed data and change from baseline by time point. The definition of baseline is provided in Section 2.1.1.

2.7.4.2 Vital signs

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


CCI



2.12 Interim analysis

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. There is no formally planned interim analysis IA.

3 Sample size calculation

3.1 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 rash or other reasons.

3.2 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.

4 Change to protocol specified analyses

No changes from protocol specified analysis were made.

5 Consideration due to COVID-19

Due to the COVID-19 pandemic, it may not be possible to perform some procedures as per protocol. All deviations due to COVID-19 will be listed separately to other deviations and may also be tabulated.

Observations that were impacted due to COVID-19, may be excluded from the primary analyses, for example including (but not limited to) observations taken at participant's house instead of site, and separately explored to identify if there is an impact of them on the analyses.

6 Appendix

6.1 Imputation rules

6.1.1 Study drug

Not applicable

6.1.2 AE, ConMeds and safety assessment date imputation

All imputations for any missing date information will follow the Tables 6-1 and 6-2 att'd below.

Table 6-1 Imputation of start dates (AE, CM) and assessments (LB, EG, VS)

Missing Element	Rule
day, month, and year	• No imputation will be done for completely missing dates
day, month	• If available year = year of investigational treatment start date then • If stop date contains a full date and stop date is earlier than investigational treatment start date then set start date = 01JanYYYY • Else set start date = investigational treatment start date. • If available year > year of investigational treatment start date then 01JanYYYY • If available year < year of investigational treatment start date then 01JulYYYY
Day	• If available month and year = month and year of investigational treatment start date then • If stop date contains a full date and stop date is earlier than investigational treatment start date then set start date= 01MONYYYY. • Else set start date = investigational treatment start date. • If available month and year > month and year of investigational treatment start date then 01MONYYYY • If available month and year < month year of investigational treatment start date then 15MONYYYY

Table 6-2 Imputation of end dates (AE, CM)

Missing Element	Rule (*=last treatment date plus <*30*> days not > (death date, cut-off date, withdrawal of consent date))
day, month, and year	Completely missing end dates (incl. ongoing events) will be imputed by the end date of the on-treatment period*
day, month	If partial end date contains year only, set end date = earliest of 31DecYYYY or end date of the on-treatment period *
day	If partial end date contains month and year, set end date = earliest of last day of the month or end date of the on-treatment period*

Any AEs and ConMeds with partial/missing dates will be displayed as such in the data listings.

Any AEs and ConMeds which are continuing as per data cut-off will be shown as 'ongoing' rather than the end date provided.

6.1.3 Other derivations and imputations

Category	Number of pills	Number of days	Average dose	Dataset to used
Rescue medication	CMCAT="Other pain medication" and CMROUTE="Oral" and then with the help of CMDOSFRQ and CMDUR (CMSTDTC-	CMCAT="Other pain medication" and CMROUTE="Oral" and then with the help of CMDUR (CMSTDTC-	Average dose will be calculated if a link is provided before DBL to combine the variables from	CM

	CMENDTC) we will calculate number of pills No screening records will be included. From Day 1 till post treatment follow up summaries will be considered with respect to treatments (10 and 25mg and post treatment followup of 25mg and placebo). The header of the summary table will divided as 10mg,25mg,post treatment followup and Placebo (rescue medication are mentioned by Franziska in excel sheet)	CMENDTC) we will calculate number of days No screening records will be included. From Day 1 till post treatment follow up summaries will be considered with respect to treatments (10 and 25mg and post treatment followup of 25mg and placebo). The header of the summary table will divided as 10mg,25mg,post treatment followup and Placebo (rescue medication are mentioned by Franziska in excel sheet)	FACM and CM datasets.	
Concomitant pain medication	FATEST=”Number of basic pain medication” and sum of (FASTRESN) No screening/baseline records will be included. From Day 1 till Day 84 summaries with respect to treatments (10 and 25mg). The header of the summary table will divided as 10mg,25mg and Placebo	FATEST=”Number of basic pain medication” and count of non missing/non-zero (FASTRESN) No screening/baseline records will be included. From Day 1 till Day 84 summaries with respect to treatments (10 and 25mg). The header of the summary table will divided as 10mg,25mg and Placebo	Average dose will be calculated if a link is provided before DBL to combine the variables from FACM and CM datasets.	FACM
The number of pills taken during the treatment period for each participant is derived with CMDOSFRQ, and CMDUR under variables, CMCAT=”Other pain medication” and CMROUTE=”Oral”.				

6.1.4 Other derivations and imputations

Not applicable

6.2 Statistical models

6.2.1 Analysis supporting primary objective(s)

The KOOS subscales will be derived based on the 2012 User's Guide to: Knee injury and Osteoarthritis Outcome Score KOOS (2012) shown below. The number of items needed for each calculation for each subscale is also shown. Additionally, the total KOOS score will be calculated by summing the 5 subscales for each particpiant and dividing by 5.

1. PAIN $100 - \frac{Mean\ Score(P1 - P9) \times 100}{4} = KOOS\ PAIN$
2. SYMPTOMS $100 - \frac{Mean\ Score(S1 - S7) \times 100}{4} = KOOS\ Symptoms$
3. ADL $100 - \frac{Mean\ Score(A1 - A17) \times 100}{4} = KOOS\ ADL$
4. SPORT/REC $100 - \frac{Mean\ Score(SP1 - SP5) \times 100}{4} = KOOS\ Sport - Rec$
5. QOL $100 - \frac{Mean\ Score(Q1 - Q4) \times 100}{4} = KOOS\ QOL$

	Number of items needed for calculation of subscale score (2012 rule for missing items)
Pain	5
Symptoms	4
ADL	9
Sport/Rec	3
QOL	2

For the KOOS pain subscale the questions are as follows where questions P5-P9 are included for WOMAC:

P1: How often do you experience pain?
P2: Twisting/Pivoting on your knee
P3: Straightening knee fully
P4: Bending nkee fully
P5: Walking on flat surface (pain)
P6: Going up and down stairs
P7: At night while in bed
P8: Sitting or lying
P9: Standing upright

7 References

Beals C, Baumgartner R, Peterfy C, et al (2017) Magnetic resonance imaging of the hand and wrist in a randomized, double-blind, multicenter, placebo-controlled trial of infliximab for rheumatoid arthritis: Comparison of dynamic contrast enhanced assessments with semi-quantitative scoring. PLoS ONE p. e0187397.

Hodgson RJ, Barnes T, Connolly S, et al (2008) Changes underlying the dynamic contrast-enhanced MRI response to treatment in rheumatoid arthritis. Skeletal Radiology; 37:201-7.

The 2012 User's Guide to: Knee injury and Osteoarthritis Outcome Score KOOS (2012). Website: .KOOS.nu.