NOVARTIS

Clinical Development

RHH646

CRHH646A12201 / NCT05816395

A randomized, placebo controlled, investigator and participant-blinded study investigating safety, tolerability, and efficacy of RHH646 in participants with knee osteoarthritis

Statistical Analysis Plan (SAP)

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Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
07Feb2025	Before DBL	Protocol Amendment and Additional Analyses	Additional analyses are added	2.5.5 Sensitivity Analyses 2.5.7 Subgroup Analyses

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List of abbreviations

AE	Adverse Event
APAP	N-acetyl-para-aminophenol
ATC	Anatomical Therapeutic Chemical
COP	Center Of Pressure
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DAR	Dosage Administration Record
DMS	Document Management System
ECGs	Electrocardiograms
EOS	End of Study
FAS	Full Analysis Set
CCI	[redacted]
IA	Interim Analyses
ICE	Intercurrent Events
JSW	Joint Space Width
CCI	[redacted]
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
CCI	[redacted]
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OA	Osteoarthritis
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Participant-reported Outcomes
PT	Preferred Term
RAP	Reporting & Analysis Process
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SOC	System Organ Class
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

The Reporting & Analysis Process (RAP) documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial ***"CRHH646A12201".***

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

1.1 Study design

This is a non-confirmatory, randomized, investigator and participant blinded, two-arm, placebo controlled, phase 2a study to assess safety, tolerability, and efficacy of orally administered RHH646 in male and female adult participants with symptomatic, mild to moderate radiographic knee osteoarthritis (OA; Kellgren and Lawrence (K&L) grade 2 to 3) in the target knee and with pain requiring analgesic therapy (e.g., n-acetyl-para-aminophenol (APAP) or non-steroidal anti-inflammatory drugs (NSAIDs)).

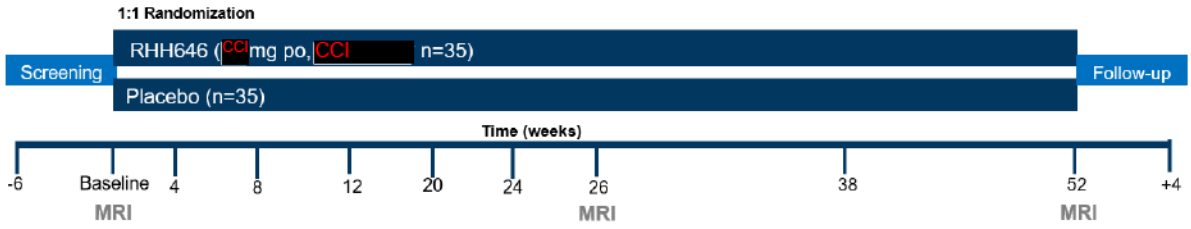
The study comprises a screening period (up to 6 weeks), a treatment period (CCI) and a follow up period (CCI) post last administration of investigational treatment before the End of Study (EOS) visit. The total duration for each participant will be up to 62 weeks (unless follow up of adverse events (AEs) requires the duration to be longer).

Approximately 78 participants will be enrolled and randomized in the trial and treated for 52 weeks. A balanced randomization 1:1 will be used in order to ensure a comparably robust assessment of the primary endpoint in both treatment groups. No stratification is considered.

The primary analysis is intended to evaluate the efficacy of RHH646 after 52 weeks of CCI administration.

An interim analysis (IA) with evaluation of therapeutic effects may be conducted for the primary endpoint. Additional IAs (i.e., of the primary and/or other endpoints) may be conducted to support decision making concerning the current clinical study, Novartis clinical development projects in general, or in case of any safety concerns. IA results will be reviewed by the clinical team.

Figure 1-1 Study design



1.2 Study objectives, endpoints and estimands

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To evaluate the articular cartilage-regenerating capacity of RHH646 in the knee following 1 year of treatment	• Change from baseline in cartilage volume in the index region of the target knee by MRI at Week 52
• To evaluate the safety and tolerability of RHH646 following 1 year of treatment	• AEs Electrocardiograms (ECGs) Vital signs Hematology, blood chemistry, urinalysis
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the pharmacokinetics (PK) of RHH646 in participants with knee OA	• RHH646 plasma concentrations, Cmin, ss at Week 4, and any other PK parameter as appropriate
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
CCI	

Objective(s)	Endpoint(s)
CCI	

1.2.1 Primary estimand(s)

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results.

The primary clinical question of interest is:

What is the effect of CCI, orally administered RHH646, with acceptable compliance, on knee cartilage volume after 52 weeks of treatment in participants with symptomatic, mild to moderate knee OA?

The primary estimand is described by the following attributes:

1. **Population:** Participants with symptomatic, mild to moderate radiographic knee OA (K&L grade 2 to 3) in the target knee and with pain requiring analgesic therapy. Further details about the population are provided in the protocol.
2. **Primary variable:** Change from baseline to Week 52 in cartilage volume in the index region of the target knee.
3. **Treatment of interest:** Randomized treatment (CCI mg CCI RHH646 or placebo) with dose adjustments and interruptions as allowed per protocol.

Handling of intercurrent events (ICEs)

Unacceptable non-compliance to treatment: Hypothetical strategy – to estimate what the treatment effect would have been at Week 52 if all participants adhered to the initially randomized treatment through that time point, under the hypothesis that participants with assessments impacted by ICEs would have efficacy outcomes like those of similar participants in their treatment group who continue their randomized treatment.

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

Intercurrent event		Handling of event
Missed treatment doses	More than 66% of scheduled doses missed during the 52 week treatment period.	Data collected after this ICE will not be evaluated for the purposes of this estimand

The summary measure

The difference between treatments in the mean changes from baseline to Week 52 in cartilage volume in the index region of the target knee.

2 Statistical methods

2.1 Data analysis general information

The analyses will be performed by Novartis using SAS software (version 9.4 or higher) or R software (latest available version).

The analyses will be conducted on all participant data at the time of IA and when the trial ends (EOS).

2.1.1 General definitions

The term study drug or investigational treatment refers to RHH646 or Placebo, while the term investigational drug refers exclusively to RHH646.

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 evaluations, the last available assessment on or before the date of start of investigational treatment is taken as '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 safety parameters, 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 Day 1 scheduled 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 between Day -14 and Day 1.

On-treatment assessment/event

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

1. ***pre-treatment period***: from day of participant's informed consent to before the first administration of investigational treatment
2. ***on-treatment period***: from date of first administration of investigational treatment to *33* days after date of last administration of investigational treatment (including start and stop date)

Note: If dates are incomplete in a way that clear assignment to pre-, on-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 AEs will summarize on-treatment events, with a start date during the on-treatment period (***treatment-emergent*** AEs).

2.2 Analysis sets

Participants will be analyzed according to the treatment assigned .

The **Full Analysis Set (FAS)** will include all participants who received any investigational treatment.

The **Safety Analysis Set** will include all participants who received any investigational treatment. For this study, the FAS and the Safety Analysis set are identical.

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 investigational treatment and with no protocol deviations that impact PK data.

2.3 Participant disposition, demographics and other baseline characteristics

2.3.1 Participant disposition

A summary disposition for all screened participants will be presented. 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 will be listed.

2.3.2 Demographics and other baseline characteristics

All data for background and demographic variables, including baseline hsCRP categories (<2 or >=2) and baseline KL score, will be listed by treatment group and participant. Summary statistics will be provided 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 history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and participant.

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

2.4.1 Investigational treatment / compliance

The Safety Analysis 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 RHH646 will be summarized by means of descriptive statistics.

2.4.2 Prior, concomitant and post therapies

Concomitant medications, and prohibited medications, as well and significant non-drug therapies prior to and after the start of the investigational treatment will be summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by preferred term, and treatment group.

2.5 Analysis supporting primary objective(s)

The primary aim of the study is to evaluate the effect of CCI , orally administered RHH646, with acceptable compliance, on knee cartilage volume after 52 weeks of treatment, and evaluation of safety and tolerability of RHH646 in participants with symptomatic, mild to moderate knee OA.

2.5.1 Primary endpoint(s)

The primary efficacy endpoint is the change from baseline in cartilage volume in the index region of the target knee by MRI at Week 52.

The primary safety endpoints of the study are of AEs, ECGs, vital signs, and clinical laboratory assessments. For the analyses of these endpoints see Section 2.7

2.5.2 Statistical hypothesis, model, and method of analysis

The primary efficacy endpoint will be analyzed using a mixed effect model for repeated measures (MMRM). The model will include baseline, treatment, time-point, and treatment by time-points as fixed effects. An unstructured covariance will be assumed; if not possible, other appropriate covariance structures may be explored. A two-sided 90% confidence interval for the treatment effect (i.e., RHH646 minus placebo) at Week 26 and Week 52 will be reported.

2.5.3 Handling of intercurrent events

Handling of the ICE will follow a hypothetical strategy. Assessments impacted by an ICE will 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).

A summary table will describe the number of ICEs by treatment. A listing will be created for all participants with ICEs, including type and time point, if applicable.

2.5.4 Handling of missing values not related to intercurrent event

Some missing data may be expected due to participants occasionally missing a study visit while continuing with the randomized treatment. Such data will be implicitly imputed by the MMRM under the MAR assumption.

2.5.5 Sensitivity analyses

Three sensitivity analyses will be performed to take into account of the quality of MRI.

1) In the MMRM model, the grade of image quality will be added as an additional factor.
2) The same as the main analysis in section 2.5.2 except that only the data with good image quality will be included in the analyses.

3) The same as the main analysis described in section 2.5.2 with an added interaction term of baseline by visit.

Upon the review of the ICEs, additional sensitivity analysis may be specified in an amendment to this SAP, to test sensitivity to the assumption that the ICEs render impacted assessments following a MAR mechanism.

2.5.6 Supplementary analyses

To estimate the treatment effect under real-world conditions, the data might be analyzed according to treatment policy instead of hypothetical strategy.

2.5.7 Subgroup analyses

A subgroup analysis will be performed on the primary endpoint for the subgroups CCI [redacted] The primary efficacy endpoint will be analyzed using a mixed effect model for repeated measures (MMRM). The model will include baseline, treatment, time-point, subgroup, treatment by time-points, subgroup by treatment, subgroup by time-points and subgroup by treatment by time-points as fixed effects.

2.6 Analysis supporting secondary objectives

2.6.1 Secondary endpoint(s)

The secondary objective is to evaluate the pharmacokinetics of RHH646 in participants with knee OA, by the means of RHH646 plasma concentrations, Cmin, ss at Week 4, and other PK parameters as appropriate.

2.6.2 Statistical hypothesis, model, and method of analysis

Descriptive summary statistics of RHH646 Cmin, ss at Week 4 will be provided by treatment and visit/sampling time point, including the frequency of concentrations below the lower limit of quantification (LLOQ), which will be reported as zero.

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

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

For time points later than Week 4, individual participant concentrations will be listed.

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.

Safety summaries (tables, figures) include only data from the on-treatment period except baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post

treatment deaths will be provided. In particular, summary tables for AEs will summarize on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

2.7.1 Adverse events (AEs)

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

The number (and percentage) of participants with treatment-emergent AEs (events started after the first dose of the study medication or events prior to start of the treatment but increased in severity based on the preferred term) will be summarized by treatment, primary system organ class (SOC) and preferred term (PT), and maximum severity.

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

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

If, for the same participant, several consecutive AEs (irrespective of start treatment causality, seriousness, and severity) occurred with the same SOC and PT:

- A single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.
- More than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.

For occurrence, the presence of at least one SAE has to be checked in a block e.g. among AEs in a ≤ day gap block. If at least one SAE is occurring, then one occurrence is calculated for that SAE.

2.7.2 Deaths

All deaths will be listed using Safety set and post treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened subjects.

2.7.3 Laboratory data

All laboratory data (hematology, blood chemistry, urinalysis), including IL-6 cortisol, and testosterone, 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. Change from baseline of lab parameters will be plotted over time by treatment group.

2.7.4 Other safety data

2.7.4.1 ECG

ECG data are summarized by treatment. The corresponding treatment for each ECG will be assigned as follows:

If ECG collection date/time is before dosing date/time on Day 1, no treatment will be assigned. While baseline does not have an assigned treatment, for the change from baseline

summary tables, baseline will be summarized under each treatment to aid in the interpretation of the change from baseline summaries.

If ECG collection date/time is on or after dosing date/time on Day x but before the next dosing date/time (or before end of study if the next dosing date/time is not available) then treatment is the actual treatment received on Day x.

If ECG collection date/time is after the last dosing date/time + *60* days, no treatment will be assigned. If dosing time and/or ECG collection time is missing but the dates are the same, the ECG will be assigned to the actual treatment received on that day.

Data analysis

12-lead ECGs including PR, RR, QRS, QT, QTcF intervals and HR will be obtained for each participant during the study. ECG data will be read and interpreted.

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

- QT, QTcFNew 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

A listing of all ECG assessments will be produced and notable values will be flagged.

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, participant, and visit, and if ranges available, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

2.8 Pharmacokinetic endpoints

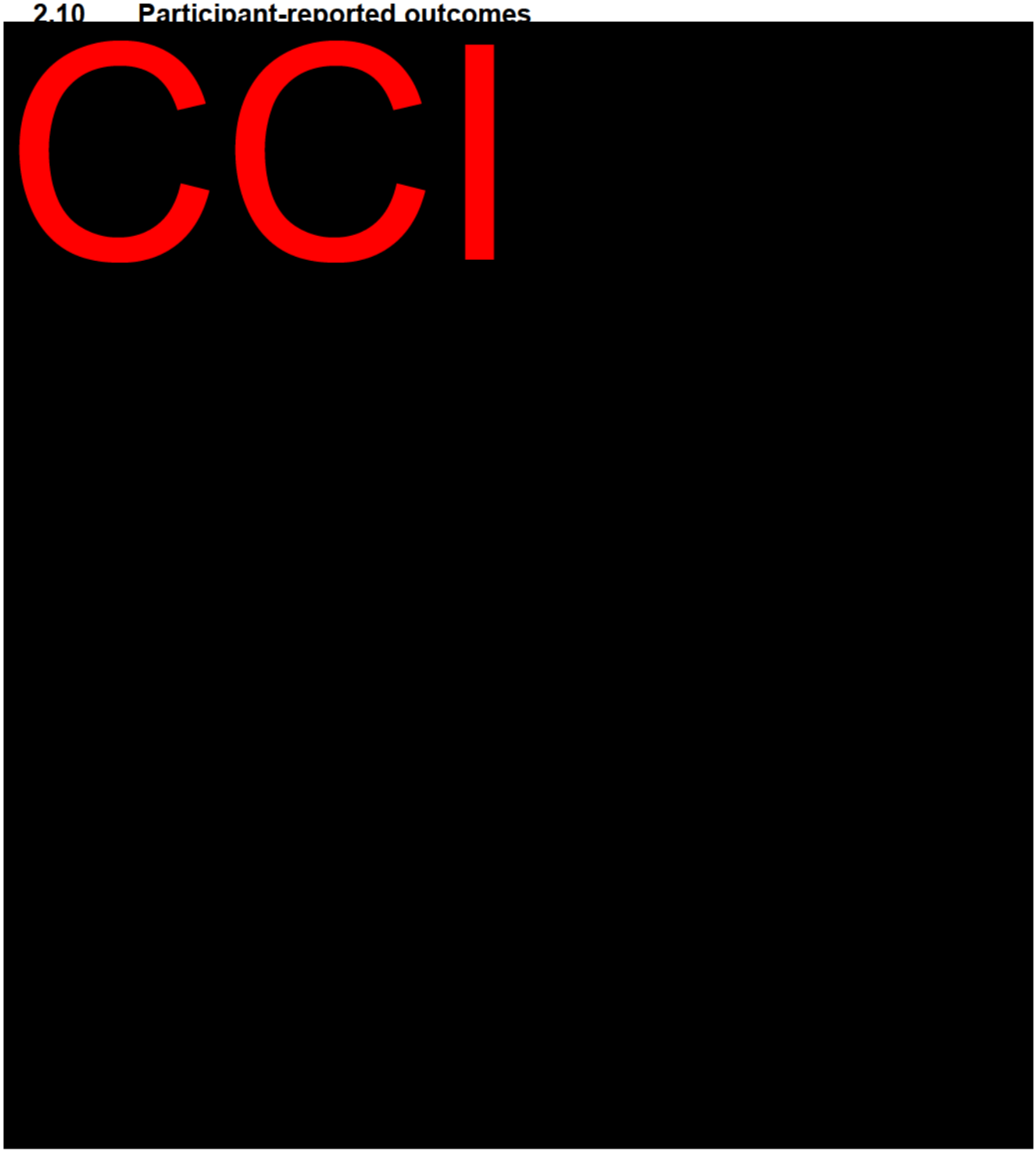
See Section 2.6

2.9 PD and PK/PD analyses

Exploratory analysis to investigate the relationship between the PK data and efficacy measures may be performed.

Results will be reported separately.

2.10 Participant-reported outcomes



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2.11 Biomarkers

2.11.1 CCI

CCI

2.11.2 CCI

CCI

2.12 Other Exploratory analyses

CCI

CCI

2.13 Interim analysis

An interim analysis is planned to be carried out after either a minimum of 46 participants have completed Week 52, or a minimum of 66% (2/3) of the total number of assessments (Week 26 and/or Week 52) for the cartilage volume are collected. The data will be examined as a preliminary evaluation of therapeutic effect.

IA results will be reviewed by the clinical team.

The clinical team may communicate interim results (e.g., information needed for planning/modifying another study) to relevant Novartis teams for information, consulting and/or decision purposes.

Interim results may be used to prepare abstracts to scientific meetings.

3 Sample size calculation

A positive treatment effect is indicated by an increase in cartilage volume at Week 52. A standard deviation of approximately CCI of change from baseline to Week 52 was observed on the preliminary data from OA patients CCI Under this assumption, a sample size of 35 evaluable participants per arm, i.e., 70 participants in total (randomization ratio 1:1), will provide at least 80% power that the primary analysis will be statistically significant at one-sided 5% significance level for a true effect size of CCI and at least 90% power for a true effect size greater than CCI

In absence of prior evidence of clinical benefit gained from structural improvements, this range of true effect sizes is considered reasonable in the context of this Proof-of-Concept study, with the goal to not miss out on relevant anabolic effects beyond the prevention of further cartilage degradation. In order to account for potential early discontinuations an approximate 10% dropout rate is assumed, thus the number of participants enrolled will be approximately 78.

4 Change to protocol specified analyses

No changes from protocol specified analysis were made.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Not applicable.

5.1.2 AE date imputation

Table 5-1 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 5-2 Imputation of end dates (AE, CM)

Missing Element	Rule (*=last treatment date plus 33 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.

5.1.3 Concomitant medication date imputation

See Section 5.1.2

5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1).

5.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI CTCAE version *5.0.* The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in the Novartis internal criteria for CTCAE grading of laboratory parameters. The latest available version of the document based on the underlying CTCAE version *5.0* at the time of analysis will be used.

For laboratory tests where grades are not defined by CTCAE version *5.0,* results will be graded by the low/normal/high classifications based on laboratory normal ranges.

Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

Imputation Rules

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as ‘<X’ (i.e. below limit of detection) or ‘>X’, prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading.

6 Reference

ICH E9(R1) Harmonized Guideline: addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials. Final version on 20 November 2019.

CCI [redacted]

CCI [redacted]

Roos EM, Engelhart L, Ranstam J, et al (2011) ICRS Recommendation Document: Patient-Reported Outcome Instruments for Use in Patients with Articular Cartilage Defects. Cartilage; 2(2):122-36.