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QUC398

CQUC398A12201 / NCT05462990

A randomized, two-arm, placebo-controlled, participant, investigator and sponsor-blinded, proof-of-concept study investigating the efficacy, safety and tolerability of QUC398 in patients with symptomatic knee osteoarthritis

Statistical Analysis Plan (SAP)

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List of abbreviations

AE	Adverse Event
CRF	Case Report Form
CSR	Clinical Study Report
DES	Data Exploration Strategy
DMS	Document Management System
FAS	Full Analysis Set
IA	Interim Analyses
MedDRA	Medical Dictionary for Drug Regulatory Affairs
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
RAP	Reporting & Analysis Process
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial CQUC398A12201.

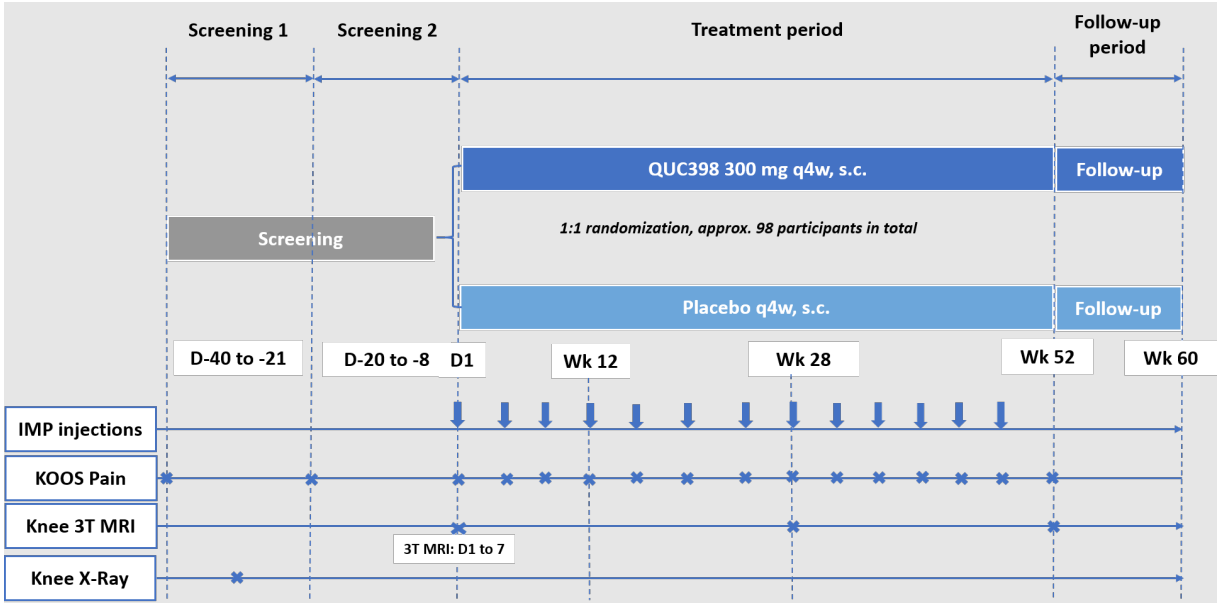
The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

1.1 Study design

This is a non-confirmatory study using a randomized, two-treatment arm, parallel-group, participant, investigator and sponsor-blinded, placebo-controlled design, with the purpose of investigating the efficacy, safety and tolerability of s.c. injections of QUC398 300 mg vs placebo every 4 weeks (q4w), in approximately 98 patients with symptomatic knee OA.

The study consists of a screening period of up to approximately 6 weeks, used to assess eligibility and to taper participants off disallowed medications. At the Day 1 visit, eligible participants will be randomized to one of the treatment arms. Randomized participants will enter the treatment period, during which they will receive q4w s.c. injections of QUC398 300 mg or placebo. The last investigational treatment administration will occur at Week 48 and the end of treatment (EOT) visit will occur 4 weeks later, at Week 52. An end of study (EOS) visit will occur 8 weeks after the EOT visit, at Week 60. The total study duration from screening to EOS is expected to be a maximum of 66 weeks.

The primary analysis will be performed when all participants have reached Week 12, or have discontinued prior to Week 12, in order to assess the primary endpoint (KOOS pain at Week 12). Simultaneously, an interim analysis on the structural endpoints will be performed including all available data on cartilage volume and thickness (MRI data at Week 28 and Week 52).



1.2 Study objectives, endpoints and estimands

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the efficacy of q4w s.c. injections of QUC398 300 mg vs placebo in relieving OA pain in the target knee	• 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 q4w s.c. injections of QUC398 300 mg vs placebo in preservation of cartilage in the medial compartment of the target knee	• Change from baseline in cartilage volume of the knee index region at Week 52, as determined from the automated segmentation of 3D-MRI scans
• To assess the efficacy of q4w s.c. injections of QUC398 300 mg vs placebo in relieving OA pain in the target knee over time	• Change from baseline in KOOS Pain subscale at Weeks 1 (Day 5), 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 • Change from baseline in pain assessed by a Pain Numerical Rating Scale (NRS) at Weeks 1 (Day 5), 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52
• To assess the efficacy of q4w s.c. injections of QUC398 300 mg vs placebo in relieving clinical symptoms and improving function in the target knee over time	• Change from baseline in Total KOOS at Weeks 1 (Day 5), 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 • Change from baseline in KOOS subscales: Other symptoms, Function in daily living, Function in sport and recreation, and Knee related quality of life at Weeks 1 (Day 5), 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

Objective(s)	Endpoint(s)
	• Change from baseline in Patient's Global Assessment (PGA) as assessed by NRS at Weeks 1 (Day 5), 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52
• To assess the safety and tolerability of q4w s.c. injections of QUC398 300 mg vs placebo	• Systemic and local Treatment-Emergent Adverse Events (TEAEs) and Serious TEAEs Electrocardiogram parameters (ECGs) Vital signs (Pulse, blood pressure [BP], temperature) • Laboratory tests (Hematology, blood chemistry, coagulation and urinalysis) • Echo-Doppler of thoracic and abdominal aorta

1.2.1 Primary estimand(s)

The primary clinical question of interest is: What is the effect of QUC398 treatment versus placebo on change from baseline at Week 12 in pain intensity in participants with symptomatic knee OA?

The justification for the primary estimand is that it will capture the effect of the study drug, the effect of additional basic pain medication, and the use of rescue medications as per protocol.

The primary estimand is described by the following attributes:

1. Population: participants suffering from symptomatic knee OA. Further details about the population are provided in Section 5 - Protocol.
2. Endpoint: efficacy is to be measured using the change from baseline to Week 12 of the double-blind study period in the KOOS pain subscale score.
3. Treatment of interest: the randomized treatments (the investigational treatment QUC398 or the control treatment) plus, if needed, intake of the allowed basic pain medication and the use of rescue medication outside of the 48 hours window prior to a visit. Further details about the investigational treatment and control treatment are provided in Section 6 - Protocol.
4. Identification of possible Intercurrent Events (ICEs):
   - At least one dose administration missed before Week 12
   - Use of rescue medication within the 48 hours prior to an assessment, or for more than three days in the seven days leading up to an assessment (assessment day not included),
   - Unforeseen use of prohibited medication
5. Summary measure: the difference between treatments in the mean changes from baseline to Week 12 of the double-blind study period in KOOS pain subscale score.

1.2.2 Secondary estimand(s)

There are three secondary objectives in relation to efficacy. Based on the type of endpoint and time of evaluation they can be split into two overall clinical questions of interest:

- the effect of QUC398 versus placebo in preserving of cartilage in the medial compartment of the target knee, measured by the change in volume of the knee index region at week 52 (MRI)
- the effect of QUC398 vs placebo over time (Weeks 1 (Day 5), 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52) in relieving OA pain, clinical symptoms and function in the target knee (PRO).

Given the difference in impact of rescue medication on the PRO endpoints and the structure endpoints, two secondary estimands are considered.

1.2.2.1 First secondary estimand

The justification for the first of the secondary estimands of cartilage preservation is that it will capture the effect of the study drug, as it applies to the objective related with difference between QUC398 and placebo in change in volume of the knee index region at week 52.

The first of the secondary estimands is described by the following attributes:

1. Population: participants suffering from symptomatic knee OA.
2. Endpoint: efficacy is to be measured using the change from baseline to week 52 in cartilage volume of the knee index region.
3. Treatment of interest: the randomized treatment (the investigational treatment QUC398 or the control treatment)
4. Identification of possible ICEs:
    - At least two missed dose administrations
    - Unforeseen use of prohibited medication that would require permanent treatment discontinuation (i.e. corticosteroids, biologics)
5. Summary measure: the difference between treatments in the mean changes from baseline to week 52 in cartilage volume.

1.2.2.2 Second secondary estimand

The justification for the second of the secondary estimands of relieving OA pain, clinical symptoms and function in the target knee is that it will capture the effect of the study drug, and the effect of additional basic pain medication, and the use of rescue medications as per protocol.

The second of the secondary estimand is described by the following attributes:

1. Population: participants suffering from symptomatic knee OA.
2. Endpoint: efficacy is to be measured using the change from baseline to Weeks 1 (Day 5) 4, 8, 12, 20, 24, 28, 32, 36, 40, 44, 48, and 52 for the corresponding assessment tool (e,g. KOOS and the subscales, pain NRS and PGA (NRS)) and method.

3. Treatment of interest: the randomized treatment (the investigational treatment QUC398 or the control treatment) plus, if needed, intake of the allowed basic pain medication and the use of rescue medication outside of the 48 hours window prior to a visit.
4. Identification of possible ICEs:
   - First time a dose administration is missed
   - At least two missed dose administrations
   - Use of rescue medication within 48 hours of a visit or for more than three days in the seven days prior to the visit/assessment
   - Use of prohibited medication (for which rescheduling is not allowed) (except live or live-attenuated vaccines)
   - Prohibited pain medication i.e. diacetylrhein, centrally acting analgesics, acetylsalicylic acid >325 mg/day, paracetamol/acetaminophen >3000mg/day, opioids, or systemic NSAIDs that would have required visit rescheduling, if used within 48 hours prior to a visit/assessment
5. Summary measure: the difference between treatments in the mean changes from baseline to Weeks 1 (Day 5) 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 in the scores collected according to the corresponding tool and method.

2 Statistical methods

2.1 Data analysis general information

The primary analysis was conducted after all participants have completed Week 12 or discontinued treatment prior to Week 12. Simultaneously, an interim analysis on the structural endpoints was performed including all available data on cartilage volume and thickness (MRI data at Week 28 and Week 52). The final analysis will be conducted on all participants' data at the time the trial ends. Additional 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.

The analysis will be performed in-house by Novartis, and will be carried out using SAS software, version 9.4 or higher.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

2.1.1 General definitions

The term study drug or investigational treatment refers to QUC398 or Placebo, while the term investigational drug refers exclusively to QUC398.
Following ITT principle, all assessments from randomization to each dosing timepoint will be included in the analyses, indendent if patients received wrong treatment or had a treatment switch.

Date of first administration of investigational drug

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

Date of last administration of investigational drug

The date of last administration of investigational drug is defined as the last date when a nonzero dose of investigational drug 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 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 (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 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 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 1 and Day 10. For KOOS pain assessments, baseline is defined as day 1, but if treatment is administered prior to the assessment on day 1 or day 1 is missing, the screening visit 3 will be used as the baseline value.

For category CCI chart and PGA, the assessment collected on Day 1 is taken as baseline.

For cartilage volume and thickness, the assessment collected in the period of +/- 40 days from Day 1 is taken as baseline. On-treatment assessment/event

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

1. ***pre-treatment period***: from day of participant's informed consent to before date of first administration of investigational treatment
2. ***on-treatment period***: from date of first administration of investigational treatment to end of study (EOS) assessments at week 60.
3. ***post-treatment period***: 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.

In efficacy analyses, the data on EOT/EOS visits for patients who discontinued early will be handled as follows:

- For early terminators, the data on EOT/EOS visits will be mapped to nearest visit based on the study assessment day and protocol study visit.
- In efficacy outputs without ICE considered (e.g., summaries, box plot, mean SE, model based), the data on EOT/EOS visits will be excluded from analyses.

For cartilage volume and thickness, the assessments collected +/- 60 days from planned protocol day for Week 28 (197 day from protocol planned assessment day) and +/- 90 days for Week 52 (365 day from protocol planned assessment day) will be included in the analyses.

The joint with score of "Not applicable" or "No pain" will not be considered as a painful joint.

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
2. SYMPTOMS
3. ADL
4. SPORT/REC
5. 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

2.2 Analysis sets

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

The safety analysis set will include all participants that received any study drug. The FAS and Safety set are identical in this study.

The PK analysis set (PAS) will include all participants with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received QUC398 and with no protocol deviations that impact PK data.

Participants will be analyzed according to the initial treatment received.

2.3 Participant disposition, demographics and other baseline characteristics

2.3.1 Participant 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 will be listed.

Screened participants not randomized will be listed.

2.3.2 Demographics and other baseline characteristics

All data for background and demographic variables will be listed 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, 25^{th} and 75^{th} percentile may be also presented.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment and participant. Relevant medical histories and current medical conditions at baseline will be summarized. A listing by SOC/PT for each participant by treatment will be reported.

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

2.4.1 Investigational treatment / compliance

The Safety set will be used for the analyses below.

Dose administration will be listed by treatment, date, and time. The duration from first to last dose (in days) of the exposure to QUC398 will be summarized by means of descriptive statistics. The average amount of concomitant, rescue and prohibited medication will be presented by treatment group.

2.4.2 Prior, concomitant and post therapies

Concomitant, rescue, and prohibited medications, as well as significant non-drug therapies prior to and after the start of the investigational treatment will be listed and summarized using the WHO Anatomical Therapeutic Chemical (ATC) dictionary using the latest version available prior to clinical database lock, by preferred term, and treatment with a flag to differentiate those which started more than 28 days after the last investigational treatment.

2.5 Analysis supporting primary objective(s)

The primary aim of this study is to evaluate the efficacy with q4w s.c. injections of QUC398 300 mg. To this end, a statistical analysis will be done to compare change from baseline in KOOS pain subscale at Week 12 for participants receiving QUC398 vs those receiving placebo.

2.5.1 Primary endpoint(s)

The primary endpoint of the study is the change from baseline in KOOS pain subscale at Week 12 assessed on the full analysis set (FAS). KOOS pain subscale score will be analyzed on 100 points scale, low scores meaning high pain.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary efficacy variable, change from baseline in KOOS pain subscale, will be analyzed using a mixed effect model for repeated measures (MMRM). The model will be fit to all evaluable data collected from the randomized participants through the Week 12. The model will include baseline, treatment, time point, treatment by time points as fixed effects. . An unstructured covariance will be assumed; CCI [redacted] etc. A two-sided 90% confidence interval for the treatment effect (i.e., QUC398 minus placebo) at Week 12 will be reported.

2.5.3 Handling of intercurrent events

All ICEs will be handled by a hypothetical strategy to estimate what the treatment effect would have been at Week 12 if all participants adhered to the initially randomized treatment through that time point.

In the case of ICEs such as missing at least one dose administration before week 12 or use of prohibited medication that would require permanent discontinuation, the assessments collected post-ICE occurrence will not be evaluated for the purposes of the primary estimand (see Section 12.4.3 – Protocol for the imputation method). For ICEs such as use of rescue medication within the 48 hours prior to an assessment, or for more than three days in the seven days leading to an assessment, or use of prohibited medication not leading to investigational treatment discontinuation, only the assessment following immediately this ICE

will not be evaluated for the purposes of the primary estimand (see Section 12.4.3 - Protocol for the imputation method).
Assessments collected post-ICE (all or just immediately) will 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 who continue their randomized treatment). In case of an unexpectedly high number of discontinuations (in particular due to a similar reason) from the investigational treatment are observed, the assumptions underlying the strategy considered might be revised and modified as appropriate.

2.5.4 Handling of missing values not related to intercurrent event

Some intermittently 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. Following KOOS Scoring 2012 guidance, the KOOS pain subscale will be considered as missing if responses are provided for less than 50% of the items. For overall visit, KOOS score will be derived as per protocol planned day if KOOS assessment is missing for any visit.

2.5.5 Sensitivity analyses

The robustness of conclusions from the primary analysis to the assumptions that missing data arise from an MAR mechanism may be stress-tested via a delta adjustment tipping-point sensitivity analysis. Additionally, analyses may be conducted for primary estimand models which will include baseline, treatment, time point, treatment by time points, and baseline by time points as fixed effects.

2.5.6 Supplementary analyses

The average amount including dose and number of tablets of concomitant and rescue medications will be presented by treatment.

Also, additional analyses may be carried out when the assessments for participants who use rescue medication within 48 hours prior to the visit and/or for at least three days are included, and/or when the estimands strategy would be a treatment policy strategy (i.e. participants who interrupt treatment and/or have unforeseen changes in the dose of allowed concomitant/rescue medications will be treated in the same manner as those that continue the treatment as planned and do not have a unforeseen dose changes. The same MMRM model as for the primary estimation will be adopted.

Additional analysis may also be carried out to assess the results for participants who experienced an AE or protocol deviation determined to potentially impact pain perception. 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 study data.

2.6 Analysis supporting secondary objectives

2.6.1 Secondary endpoint(s)

The secondary efficacy objective are as follows:

- To assess the efficacy of q4w s.c. injections of QUC398 300 mg vs placebo in preservation of cartilage in the medial compartment of the target knee. The variable associated with this objective is change from baseline in cartilage volume of the knee index region at Week 52, as determined from the automated segmentation of 3D-MRI scans.
- To assess the efficacy of q4w s.c. injections of QUC398 300 mg vs placebo in relieving OA pain in the target knee over time. The variables associated with this objective are the change from baseline in KOOS Pain subscale, and in Pain NRS at Weeks 1 (Day 5), 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52.
- To assess the efficacy of q4w s.c. injections of QUC398 300 mg vs placebo in relieving clinical symptoms and improving function in the target knee over time. The variables associated with this objective are the change from baseline in Total KOOS, KOOS subscales (Other symptoms, Function in daily living, Function in sport and recreation, Knee related quality of life), and in Patient's Global Assessment (PGA) as assessed by NRS at Weeks 1 (Day 5), 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52.

2.6.2 Statistical hypothesis, model, and method of analysis

The secondary efficacy variable, change from baseline over time in KOOS pain subscale, KOOS total score, KOOS subscale for other symptoms, function in daily living, function in sport and recreation, knee and related quality of life score, and pain NRS will be analyzed using a mixed effect model for repeated measures (MMRM). The model will include baseline as a covariate, treatment, time point, treatment by time points as fixed effects. A two-sided 90% confidence interval for the treatment effect (i.e., QUC398 minus placebo) will be reported.

For the secondary efficacy variable, change from baseline in cartilage volume of the knee index will be analyzed using a MMRM. The model will be fit to all available data collected from the randomized participants at scheduled assessments during the adherence to randomized treatment, that is, through week 52 or the latest time point prior to an ICE. If deemed appropriate, the endpoint measure data will be transformed to reduce skewness of the distribution and facilitate analysis. The model will include baseline as a covariate, treatment, time point, treatment by time points as fixed effects. A two-sided 90% confidence interval for the treatment effect (i.e., QUC398 minus placebo) will be reported.

2.6.3 Handling of intercurrent events

All ICEs for both secondary estimands will be handled by a hypothetical strategy to estimate what the treatment effect would have been at time point considered if all patients adhered to the initially randomized treatment through that time point.

The data necessary for these estimands is the observed data while adhering to the initial randomized treatment. Therefore, the data collected after an ICEs such as the second missed dose administration or use of prohibited medication that would have required permanent discontinuation from investigational treatment will not be evaluated for the purposes of the corresponding estimand. For ICEs such as the first missed dose administration and the use of rescue medication within 48 hours prior to an assessment, or for more than three days within seven days prior to an assessment, or prohibited medication not leading to discontinuation , only the data associated with the assessment immediately following that ICE will not be evaluated for the purposes of the corresponding estimand.

2.6.4 Handling of missing values not related to intercurrent event

Some intermittently missing data may be expected due to participants occasionally missing a study visit while continuing with the randomized treatment. For these cases, the analysis model assumes that participants with missing data (included data not evaluable due to ICEs) would have efficacy outcomes like those of similar participants in their treatment group who continue their randomized treatment through the time point at which data are missing. This type of assumption is referred to as missing at random (MAR).

2.7 Safety analyses

All safety analyses will be based on the Safety set unless otherwise specified. Safety summaries include only on-treatment assessments (refer to Section 2.1.1); safety listings include all assessments with those more than 28 days after last investigational treatment flagged.

Safety assessments include AEs, laboratory data, vital signs, deaths and ECGs. All Section 16 safety listings are presented using FAS, and Section 14 using Safety set unless otherwise specified. 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.

EOT/EOS data for patients who discontinued early will not be pooled with EOT/W52 data of patients which completed the treatment/study. Those data will be pooled to the actual discontinued visit based on the discontuation date using the protocol planned day visit with +/- 60 days window.

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 adverse events (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 and preferred term, and maximum severity.

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

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.

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 the Safety set and post treatment deaths will be flagged. A separate listing of deaths prior to starting treatment will be provided for all screened participants.

2.7.3 Laboratory data

All laboratory data will be listed by treatment, participant, and visit/time and if normal ranges are available abnormalities will be flagged. All laboratory data will be summarized by treatment, 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

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 + *30* 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 handling

When ECG triplicates are collected at any assessment, the average of the ECG parameters at that assessment will be used in the analyses. If triplicates are not collected, the average will still be calculated with the available assessments.

Data analysis

12-lead ECGs including PR, 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 using the Safety set by treatment as follows:

- 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 > 120 ms
  - New values of QRS > 120 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 (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

2.7.4.3 Echo-Doppler data

Echo-Doppler data will be listed by treatment and participant for the EOT visit.

2.8 Interim analysis

Refer to Section 2.1.

3 Sample size calculation

A positive treatment effect is indicated by an increase in the KOOS pain subscale score at Week 12. Assuming a true treatment difference in KOOS pain score of 10 points and a standard deviation of 19, a sample size of 90 evaluable participants provides approximately 80% power that the primary analysis will be statistically significant at one-sided 5% significance level. In order to account for possible early discontinuations an approximate 10% dropout rate is considered, thus the number of participants enrolled will be approximately 98.

CCI [redacted]

4 Change to protocol specified analyses

No changes from protocol specified analysis were made.

5 Considerations due to the COVID-19

Due to the COVID-19 pandemic, it might 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

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 <*60*> 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 imputations

Not applicable.

6.2 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).

6.3 Laboratory parameters derivations

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (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.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. 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.

6.4 Statistical models

6.4.1 Analysis supporting primary objective(s)

Refer to Section 2.5.1. 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 participant and dividing by 5.

1. PAIN $100 - \frac{\text{Mean Score (P1–P9)}\times 100}{4} = KOOS\ Pain$

2. SYMPTOMS $100 - \frac{\text{Mean Score (S1–S7)}\times 100}{4} = KOOS\ Symptoms$

3. ADL $100 - \frac{\text{Mean Score (A1–A17)}\times 100}{4} = KOOS\ ADL$

4. SPORT/REC $100 - \frac{\text{Mean Score (SP1–SP5)}\times 100}{4} = KOOS\ Sport/Rec$

5. QOL $100 - \frac{\text{Mean Score (Q1–Q4)}\times 100}{4} = KOOS\ QOL$

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	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

6.4.2 Analysis supporting secondary objective(s)

Refer to Section 2.6.1. The NRS score will be transformed from its original 0-10 scale to a 0-100 scale by taking the raw score, dividing by the maximum score, and multiplying by 100. We show the corresponding formula below:

NRS = (Total raw score/maximum score) x 100

7 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.

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