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Novartis Research and Development

Clinical Trial Protocol

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

Clinical Trial Protocol Number: CQUC398A12201 / NCT05462990

Version Number: v03 (Clean)

Compound: QUC398

Brief Title: A proof-of-concept study to examine QUC398 in participants with knee osteoarthritis

Study Phase: IIa

Sponsor Name: Novartis Pharma AG (or its affiliates outside the EEA), Lichtstrasse 35, 4056 Basel, Switzerland

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List of abbreviations

ACLT	Anterior Cruciate Ligament Transection
ACR	American College of Rheumatology
ADA	Anti-Drug Antibodies
ADAMTS-5	A Disintegrin and Metalloproteinase with Thrombospondin Motifs-5
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Events of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AxMP	Auxiliary Medicinal Product
AUC	Area Under the Curve
BMI	Body Mass Index
CCI	[redacted]
BP	Blood Pressure
BUN	Blood Urea Nitrogen
C2M	Matrix Metalloproteinase Cleaved Neoepitope of Type II Collagen
C3M	Matrix Metalloproteinase Cleaved Neoepitope of Type III Collagen
CK	Creatine Kinase
CLr	Renal Clearance
CMO&PS	Chief Medical Office and Patient Safety
COA	Clinical Outcome Assessment
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRPM	matrix metalloproteinase cleaved C-reactive protein from synovia
CSR	Clinical study report
CTC	Common Terminology Criteria
CTIS	Clinical Trials Information System
CTT	Clinical Trial Team
CTX-II	C-terminal Cross-Linked Telopeptide of Type II Collagen
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DDC	Direct Data Capture
DMM	Destabilization of medical meniscus
DMOAD	Disease-Modifying Osteoarthritis Drug
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked Immunosorbent Assay
eGFR	Estimated Glomerular Filtration Rate
EOS	End of Study

EOT	End of Treatment
EOW	Every Other Week
EU-CTR	European Union - Clinical Trials Regulation
eSAE	Electronic Serious Adverse Event
eSource	Electronic Source
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	First-in-Human
FMA	Femoral Medial Anterior Cartilage Subregion of the Knee
FMC	Femoral Medial Central Cartilage Subregion of the Knee
FMP	Femoral Medial Posterior Cartilage Subregion of the Knee
FSH	Follicle Stimulating Hormone
GAG	Glycosaminoglycans
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl Transferase
CCI	[redacted]
GLDH	Glutamate Dehydrogenase
h	Hour
HBsAg	Hepatitis B Virus Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HCVAb	Hepatitis C Virus Antibodies
HIV	Human Immunodeficiency Virus
CCI [redacted]	
HSCT	Hematopoietic Stem Cell Transplant
i.a.	Intra-articular
i.v.	Intravenous
IB	Investigator's Brochure
ICE	Intercurrent Event
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
CCI	[redacted]
IMP	Investigational Medicinal Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISR	Injection Site Reaction
IUD	Intra-Uterine Device

IUS	Intra-Uterine System
KL	Kellgren-Lawrence
KOOS	Knee Injury and Osteoarthritis Outcome Score
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LLOQ	Lower Limit of Quantification
LPLV	Last Patient Last Visit
MAD	Multiple-Ascending Dose
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
mJSN	Medial Joint Space Narrowing
mL	Milliliter(s)
MMP	Matrix metalloproteinase
MMRM	mixed effect model for repeated measures
CCI	[redacted]
MRI	Magnetic Resonance Imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	No Observed Adverse Effect Level
NRS	Numerical Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
OA	Osteoarthritis
OHP	Off-site Healthcare Professional
p.o.	Oral(ly)
PAS	Pharmacokinetic Analysis Set
PC	Personal Computer
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic(s)
PGA	Patient's Global Assessment
PK	Pharmacokinetic(s)
PoC	Proof of Concept
PRO	Patient Reported Outcomes
Pro-C2	Neoepitope generated at synthesis of collagen type II
PT	Prothrombin Time
q4w	Every 4 Weeks
QMS	Quality Management System
QoL	Quality of Life
QTcF	QT Interval Corrected by Fridericia’s Formula
RD	Recommended Dose
RoW	Rest of World
RU	Resource Utilization
s.c.	Subcutaneous

SAD	Single-Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
TLR-2	Toll Like Receptor 2
ULN	Upper Limit of Normal
UTI	Urinary Tract Infection
CCI	[redacted]
WHO	World Health Organization
WoC	Withdrawal of Consent
WOMAC	Western Ontario and McMaster Universities Arthritis Index
WPI	Widespread Pain Index

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g., any background therapy)
Assessment	A procedure used to generate data required by the study
Auxiliary Medicinal Product (AxMP)	Medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product (e.g., rescue medication, challenge agents, background treatment or medicinal products used to assess endpoints in the clinical trial). Concomitant therapy is not considered as AxMP.
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Clinical Outcome Assessment (COA)	A measure that describes or reflects how a participant feels, functions, or survives
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Coded Data	Personal Data which has been de-identified by the investigative center team by replacing personal identifiers with a code.
Cohort	A group of individuals who share a common exposure, experience or characteristic, or a group of individuals followed-up or traced over time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g., 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
Electronic Source Direct Data Capture (eSource DDC)	Any technology that allows the capture of clinical study source data electronically by investigator site staff at the point of care, into an electronic form that has been validated to capture clinical data.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained. The action of enrolling one or more participants

eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Hybrid Trial Design	A trial model incorporating both onsite (traditional site based) and offsite (decentralized) elements within the same study design.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Investigational Product/ Investigational Medicinal Product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference (such as an active comparator) in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.
Investigational Medical Device	Medical Device being assessed for safety or performance in a clinical investigation. This includes devices already on the market and being evaluated for new intended uses, new populations, new materials, or design changes
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study or the participant allocated to an invalid stratification factor
Off-site	Describes trial activities that are performed at remote location by an off-site healthcare professional, such as procedures performed at the participant's home.
Off-site healthcare Professional (OHP)	A qualified healthcare professional, such as include those used in the study e.g., Nurse, Phlebotomist, Physician, who performs certain protocol procedures for the participant in an off-site location such as a participant's home.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e., concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in participants with established disease and in those with newly-diagnosed disease

Participant	A trial participant (can be a healthy volunteer or a patient). "Participant" terminology is used in the protocol whereas term "Subject" is used in data collection
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient about the status of a participant's health condition without amendment or interpretation of the patient's report by a clinician or anyone else
Period	The subdivisions of the trial design (e.g., Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias.
Randomization number	A unique identifier assigned to each randomized participant
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Run-in Failure	A participant who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to participant's intervention or other treatment)
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Telemedicine	Electronic information and telecommunications technologies (both video-based and audio-only) to facilitate the delivery of health care and health related education where participant and Investigator and site personnel are not in the same location.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.

Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g., as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and biological samples (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not agree to further protocol required assessments. This request should be in writing (depending on local regulations) and recorded in the source documentation. Opposition to use data/biological samples occurs in the countries where collection and processing of personal data is justified by a different legal reason than consent.

Amendment 03 (November 2023)

Amendment rationale

This amendment is generated to implement learnings from ongoing and previous trials in osteoarthritis (OA), which are expected to facilitate the trial processes and reduce the burden to patients and sites.

Additional changes were implemented CCI (i.e., clarification of exclusion criterion 12 for estimated glomerular filtration rate, clarification for rescue medication use taking packaging insert and investigator instructions into account).

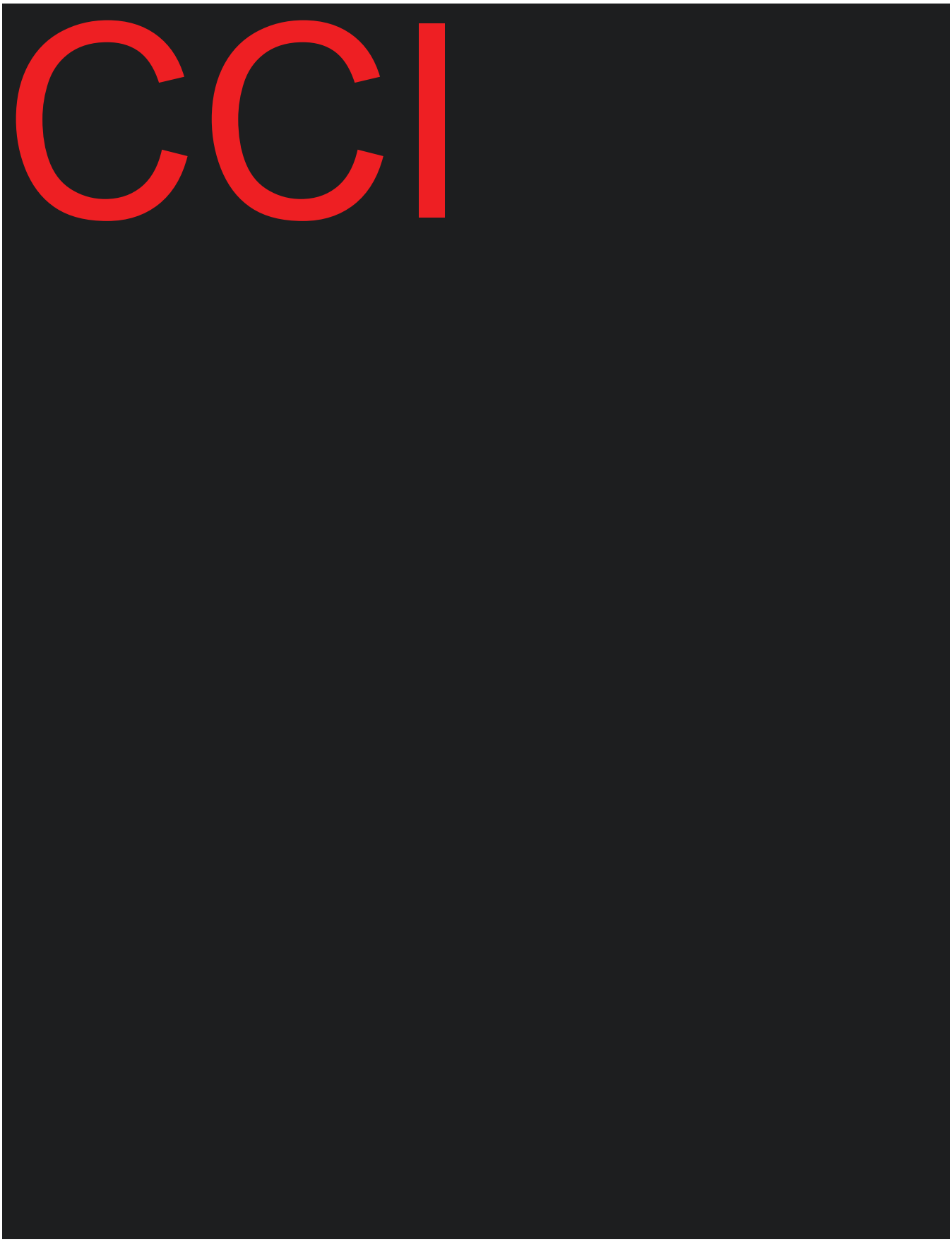
The sponsor is making necessary changes to be prepared for the upcoming and required transition of this study to the EU Clinical Trials Regulation (CTR) 536/2014. Mandatory elements to become compliant with the EU CTR are added, including sponsor information on the cover page, and definition and safety reporting of auxiliary medicinal products (AxMPs). The specific EU CTR requirements (e.g., safety reporting requirements for AxMPs) will apply once this trial has been transitioned to the EU CTR.

CCI Therefore, joint space width measurement for assessing eligibility is changed to semiquantitative joint space narrowing (JSN). The target JSN 1-2 covers the previous joint space width range, is accepted in the field as a marker for moderate OA and ensures the presence of cartilage despite detectable degeneration. The change is also relevant for alignment with other Novartis OA programs.

Additional changes are included to remove inconsistencies, provide clarifications, and improve wording.

These modifications are considered substantial.

Changes to the protocol


CCI


CCI

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

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

Amendment 02 (September 2022)

Amendment rationale

The main purpose of this global protocol amendment is to add additional safety monitoring measures (i.e., transthoracic ultrasonographic evaluations of the aorta and a corresponding exclusion criterion). This is in relation to the CCI [redacted]. Additional changes are included to remove inconsistencies, provide clarifications, and improve wording.

These modifications are considered substantial. This amendment is issued before the study start.

Changes to the protocol

CCI [redacted]

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

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

Amendment 01 (June 2022)

Amendment rationale

The main purpose of this global protocol amendment is to address feedback from Health Authorities (HA) and Ethics Committees (EC) received during the review of the protocol including the clarification of the eligibility criteria for patients with an increased cardiovascular risk as well as those with renal impairment and/or liver disease, and the addition of safety assessments (e.g., injection site exam, patient monitoring post-injection). Additional changes are included to remove inconsistencies, provide clarifications, and improve wording.

These modifications are considered substantial. This amendment is issued before the study start.

Changes to the protocol


CCI

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

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

Protocol summary

Protocol number	CQUC398A12201
Full Title	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.
Brief title	A proof-of-concept study to examine QUC398 in participants with knee OA.
Sponsor and Clinical Phase	Novartis. Phase IIa.
Investigation type	Drug.
Study type	Interventional.
Purpose	This is a phase IIa study to establish the effect of QUC398 on pain and cartilage preservation in participants with symptomatic knee OA.
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 at week 12.
Secondary Objectives	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 at Week 52. 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. To assess the efficacy of q4w s.c. injections of QUC398 300 mg vs placebo in relieving additional clinical symptoms and improving function in the target knee over time. To assess the safety and tolerability of q4w s.c. injections of QUC398 300 mg vs placebo.
Study design	This is a non-confirmatory study using a randomized, placebo-controlled, parallel-group, participant, investigator and sponsor-blinded design.
Rationale	There is a strong unmet need for a disease-modifying osteoarthritis drug (DMOAD) that can slow or halt OA disease progression. ADAMTS-5 is the main enzyme responsible for the degradation of aggrecan in the cartilage. Inhibition of ADAMTS-5 has the potential to reduce cartilage degradation in OA and to induce symptomatic relief by preventing the generation of aggrecan fragments which act as pain signal triggers. CCI [redacted] The benefits on pain and structure of the inhibition of ADAMTS-5 have been assessed in pre-clinical studies, and safety has been demonstrated in phase 1 clinical trials, but its role as a therapeutic target for patients with OA is still to be defined.

Study population	The study population consists of male and female adult patients between 40 and 80 years of age with symptomatic, mild to severe radiographic knee OA (Kellgren-Lawrence [KL] grade 2-4). Approximately 98 participants are planned to be randomized in the study.

Key Inclusion criteria	• Weight ≥ 50 kg and a body mass index (BMI) between 18 -35 kg/m^2, at Screening 1
	• Kellgren-Lawrence grade 2 to 4 in the tibio-femoral compartment in the target knee confirmed by radiography in standing weight-bearing fixed flexion position and posterior-anterior view, at Screening 1
	• Radiographic medial joint space narrowing (mJSN) 1-2 within the medial tibio-femoral compartment of the target knee, confirmed by Xray at Screening 1
	• Symptomatic OA with moderate to severe pain (corresponding to Pain NRS ≥ 5 to ≤ 9) in the target knee for the majority of days in the last 3 months prior to Screening 1, as per participant's judgement
	• Symptomatic OA with moderate to severe pain (corresponding to Pain NRS ≥ 5 to ≤ 9) in the target knee at Screening 1 and 2.
	• Moderate to severe OA pain (corresponding to Pain NRS ≥5 to ≤9) in the target knee during the last 7 days prior to Screening 3, confirmed by:
	  • Completed pain diary for at least 6 of the last 7 days prior to Screening 3, AND
	  • Diary reported Pain NRS ≥5 to ≤9 for at least 6 of the last 7 days prior to Screening 3
	• KOOS pain subscale ≤ 60 in the target knee at Screening 1, Screening 2, and Screening 3

Key Exclusion criteria	• Painful ipsilateral hip OA defined as a Pain NRS ≥3 on the majority of days in the last 3 months prior to Screening 1, as reported by the patient. • Symptomatic, patello-femoral pain in the target knee as per investigator's examination at Screening 1. • Severe malalignment > 7.5º in the target knee (either varus or valgus), measured using standardized knee X-ray at Screening 1. • Patient unable or unwilling to undergo MRI or presenting absolute contraindications to MRI. • Previous exposure to any ADAMTS-5 drug, including QUC398. • History or current diagnosis of relevant cardiovascular diseases and ECG abnormalities.
Study treatment	QUC398 150 mg/mL, solution for s.c. injection (1 mL). 2 injections will be applied per dose to complete the 300mg. Placebo 0 mg/mL, solution for s.c. injection (1 mL). 2 injections will be applied per dose to ensure blinding.

Efficacy assessments	Change from baseline in Knee Injury and Osteoarthritis Outcome Score (KOOS) Pain sub-scale at Week 12. Change from baseline in cartilage volume of the knee index region at Week 52, as determined from the automated segmentation of 3D-MRI scans. 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. 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. 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.
CCI	
Key safety assessment	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, CCI and urinalysis).
Other selected assessments	CCI

	CCI [redacted]
Data 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 and participant as random effect. An unstructured covariance will be assumed:CCI [redacted] A two-sided 90% confidence interval for the treatment effect (i.e., QUC398 minus placebo) at Week 12 will be reported.
Key words	Knee osteoarthritis, articular cartilage, ADAMTS-5, pain, magnetic resonance imaging, ARGS, PRO, biosensors.

1 Introduction

1.1 Background

Osteoarthritis (OA), the most common joint disorder in adults, is a serious, chronic, progressive joint disease with no known cure, and has been associated with an increased risk of premature mortality (Hunter, Bierma-Zeinstra 2019; OARSI 2016; Kluzek et al 2016). OA manifests clinically with joint pain, swelling and stiffness in the affected joint that can lead to activity limitations, and it is also associated with sleep interruption, fatigue, depression, anxiety, loss of independence and reduced quality of life (OARSI 2016). The lifetime risk of developing symptomatic knee and hip OA is 45% and 25%, respectively. OA accounts for over 90% of knee and hip arthroplasties (Culliford et al 2012).

All presently available pharmacologic therapies for OA provide symptomatic relief by transiently reducing pain, but do not delay structural progression of OA (Bannuru et al 2019; Kolasinski et al 2020). In addition, long-term use of these therapies is associated with serious adverse effects, including fall-related bone fractures and substance dependence and / or abuse in patients receiving opioids, and cardiovascular risk and upper gastrointestinal bleeding in patients receiving nonsteroidal anti-inflammatory drugs (NSAIDs) (Fernandes et al 2013; McAlindon et al 2014; Nissen et al 2016; Chan et al 2017; Solomon et al 2017; Kolasinski et al 2020).

Total joint replacement surgery is considered when adequate attempts of symptomatic pharmacologic therapies fail (Bannuru et al 2019; Kolasinski et al 2020). However, not all patients are satisfied with the result or benefit from joint replacement surgery (Hawker et al 2013), and in younger patients especially, limitations of physical activity imposed by artificial joints are undesirable.

Therefore, there is a strong unmet need for a disease-modifying osteoarthritis drug (DMOAD) that can slow or halt OA disease progression by inhibiting structural deterioration, and improve symptoms. Although many putative agents have been investigated, no pharmaceutical agent has been approved for clinical use as a DMOAD (Tonge et al 2014; Karsdal et al 2016; Oo et al 2018; Alcaraz et al 2019).

A disintegrin and metalloproteinase with thrombospondin motifs-5 (ADAMTS-5) is the main enzyme responsible for aggrecan degradation in cartilage (Stanton et al 2005), which is a hallmark of OA. Further cleavage of fragmented aggrecan by matrix metalloproteinases (MMPs) releases a 32-amino acid fragment which is a Toll-Like Receptor 2 (TLR-2) ligand. This fragment of aggrecan activates TLR-2 receptors, exacerbating pain in the OA joint (Lees et al 2015). Therefore, inhibition of aggrecan fragment generation by ADAMTS-5 has the potential to reduce cartilage degeneration and pain (Miller et al 2016).

CCI [redacted]

QUC398 has been extensively evaluated in *in vitro* and *in vivo* studies. The pharmacological activity of QUC398 has been evaluated in *in vivo* studies with the cynomolgus monkey, mouse, and rat species. Results from these studies have shown that QUC398 is a potent inhibitor of ADAMTS-5 and is effective at preventing the generation of aggrecan fragments (glycosaminoglycans [GAG], ARGS, an amino-terminal neoepitope of aggrecan) in bovine and human explants.

1.2 Purpose

This is a phase IIa proof-of-concept (POC) study to establish the effect of QUC398 on pain and cartilage preservation, in patients with symptomatic knee OA. While the benefits on pain and structure of the inhibition of ADAMTS-5 have been demonstrated in pre-clinical studies (Glasson et al 2005; Miller et al 2016), its role as a therapeutic target for patients with OA is still to be defined.

The effect of QUC398 on pain in the target knee of patients with symptomatic knee OA will be evaluated after 12 weeks of treatment, and the effect on preservation of cartilage volume in the target knee after 52 weeks of treatment.

2 Objectives, endpoints and estimands

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the efficacy of 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 • 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

Objective(s)	Endpoint(s)
• 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
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
CCI	

Objective(s)	Endpoint(s)
CCI	

Objective(s)	Endpoint(s)
CCI	

2.1 Primary estimands

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 (e.g., premature discontinuation of treatment).

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.
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.
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 treatment groups in the mean changes from baseline to Week 12 of the double-blind study period in KOOS pain subscale score.

Handling of possible ICEs:

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 or use of prohibited medication that would require permanent discontinuation, the assessments collected post-ICE occurrence will not be evaluated for the purposes of this estimand (see Section 12.4.3 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 study treatment discontinuation, only the assessment following immediately this ICE will not be evaluated for the purposes of this estimand (see Section 12.4.3 for the imputation method). Although data post-ICEs are not required for the primary estimand, these assessments will be collected for estimation of secondary and/or supportive estimands.

2.2 Secondary estimands

There are three secondary objectives in relation to efficacy (Table 2-1). 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.

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 treatment groups in the mean changes from baseline to Week 52 in cartilage volume.

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, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 for the corresponding assessment tool 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 usage 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 as per Table 6-3) (except live or live-attenuated vaccines)
   - Prohibited pain medication as per Table 6-3 (i.e., diacetylrhein, centrally acting analgesics, acetylsalicylic acid >325 mg/day, paracetamol/acetomionophen >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 treatment groups 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.

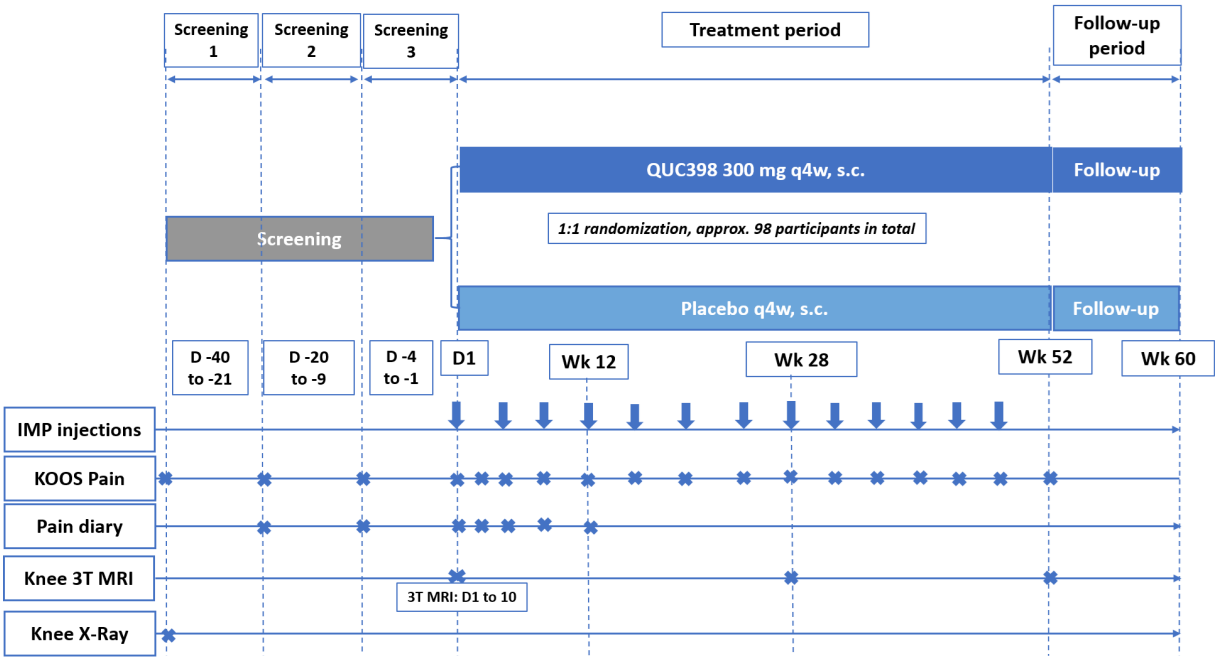
All ICEs for both secondary estimands will be handled by a hypothetical strategy to estimate what the treatment effect would have been at time point considered if all patients adhered to the initially randomized treatment through that time point.

The data necessary for this estimand 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 study treatment will not be evaluated for the purposes of this 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 this estimand.

3 Study design

Figure 3-1 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-prohibited medications. Between Day -4 to -1 visit, eligible participants will be randomized to one of the treatment arms. On Day 1 randomized participants will enter the treatment period, during which they will receive q4w s.c. injections of QUC398 300 mg or placebo. The last study 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, in order to assess the primary endpoint (KOOS pain at Week 12).

Baseline: In this study, baseline is defined for all the variables except for MRI as the values obtained at Day 1 before the first dose of the study drug. Regarding MRI, baseline is defined as the scan performed between Day 1 and Day 10.

Screening period

The screening period consists of 3 visits as listed in the assessment schedule (Table 8-1).

Screening 1: Following the signing of the informed consent, participants will undergo assessments to confirm their eligibility. The required assessments may be conducted over several days if it is in the best interest of the participants, or for logistical reasons. X-ray will be performed in the target knee and sent for central assessment by an independent reviewer, to assess participant's eligibility. The order of assessments that should be followed to minimize participant burden is described in Section 8.1. Participants treated with prohibited concomitant medications will initiate a washout period at Screening 1 (see Table 6-3). Screening 1 may be scheduled up to 40 calendar days prior to Day 1 but should ideally occur as close as possible prior to Day 1.

Screening 2: It should be scheduled between 20 and 9 calendar days prior to Day 1. Participants will go to the clinical site for pain assessment and review of the results of the Screening 1 assessments. If the participants are still eligible, they will be instructed to complete a pain diary every day from this visit until the Week 12 visit, and to wear the CCI sensor during daytime from this visit until the Week 4 visit. Participants will be requested to undergo Echo-Doppler of thoracic and abdominal aorta at Screening 2 or between Screening 2 and Screening 3.

Screening 3 (phone call): Eligibility will be re-assessed based on the results of the pain diary and KOOS pain of 7 days prior to the phone call, and on the results of the Echo-Doppler of thoracic and abdominal aorta. The investigator may schedule the call between Day -4 and Day -1, allowing the participant to complete at least 7 days of the pain diary and the KOOS pain questionnaire. If eligibility is confirmed, the participant will be randomized to one of the treatment arms.

Treatment period

The treatment period will consist of 15 visits:

- Treatment initiation visit on Day 1: first study treatment administration.
- Participants will have on-site assessments on Day 1, Day 5, Week 4, Week 8, and Week 12, as outlined in the assessment schedule.
- After Week 12, participants may have the possibility to perform some visits in an off-site setting if allowed by local legislation and if feasible based on local capabilities:
  - On-site visits: Week 28 (including a knee MRI) and Week 40;
  - On-site or off-site visits (as applicable): Weeks 16, 20, 24, 32, 36, 44, 48. Off-site visits will include s.c. administration of QUC398 300 mg or placebo, as well as pain assessment with PROs and blood / urine sampling according to the Assessment Schedule.
- An on-site EOT visit will occur at Week 52, i.e., 4 weeks after the last study treatment administration, and will include a knee MRI.

During the treatment period, participants will undergo efficacy, safety, PK and PD assessments as outlined in the assessment schedule (Table 8-1).

Follow-up period

Participants will be followed up for 8 weeks after the EOT visit:

- An optional visit will occur at Week 56, during which blood samples will be taken for PK and PD assessment. Participants may have the possibility to perform this visit in a remote setting, if allowed by local legislation and feasible based on local capabilities.
- An on-site EOS visit will then occur at Week 60, i.e., 8 weeks after the EOT visit.

Assessments will be performed as listed in the assessment schedule (Table 8-1)

SARS-CoV-2

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

If a COVID-19 vaccine is available, vaccination of trial participants with non-live vaccines will be permitted during the study duration, as described in Section 6.2.1.

3.1 Off-site procedures

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

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

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

Procedures for off-site visits utilizing the above listed elements are further detailed in the Operational Manual for study CQUC398A12201.

3.1.1 Responsibility of Investigators

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

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

3.1.2 Responsibility of off-site healthcare professionals (OHPs)

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

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

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

3.1.3 Telemedicine

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

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

3.1.4 Data flow

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

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

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

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

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

The platform maintains a secure, GCP-compliant audit trail and uses measures such as encryption and access controls to ensure that data privacy and security is maintained. Additional details will be provided in the Operational Manual for study CQUC398A12201.

4 Rationale

4.1 Rationale for study design

The design of this study addresses the primary objective of assessing the ability of QUC398 to alleviate pain in patients with symptomatic knee OA, and the secondary objective of evaluating the capability of QUC398 to preserve cartilage.

This study takes into account (i) the clinical need; (ii) clinical and preclinical data on QUC398; (iii) current practice with s.c. injectable drugs; and (iv) the burden on patients with symptomatic knee OA.

The combination of well-established Patient Reported Outcomes (PROs) such as KOOS (Roos et al 2003) and of MRI measuring the cartilage volume in the index region will ensure appropriate evaluation of the QUC398 effect from a symptomatic, functional and morphological (cartilage structure) standpoint.

For the investigation of the QUC398 treatment effect on OA pain, the study has been designed as participant, investigator and sponsor-blinded in order to ensure that mentioned parties remain in a state of equipoise, so that a putative difference between the treated and control groups can be interpreted as an effect of study treatment.

Based on preclinical data with QUC398 and literature on pain and structural progression of OA in patients with symptomatic knee OA, a 12-week treatment period with QUC398 is considered adequate to evaluate a change in pain in the target knee, and a 52-week treatment period to evaluate the preservation of the cartilage.

Inclusion criteria (e.g., radiographic knee OA Kellgren-Lawrence [KL] grade 2-4, medial joint space narrowing (mJSN) 1-2 (Altman, Gold 2007), age 40-80 years, baseline KOOS level ≤60, baseline pain level (NRS ≥ 5 to ≤ 9) have been selected to enrich for patients with symptomatic and progressive knee OA in order to (i) focus on pain improvement in a high risk population; (ii) evaluate the halt in cartilage breakdown.

In order to maximize the chances of selecting patients with primary OA, patients aged < 40 years are excluded, as their knee OA is often caused by trauma, and patients are expected to have OA in another large joint. Patients should have had pain on the majority of days of the last 3 months to ensure that the pain is chronic and not due to a flare. The inclusion of patients with Widespread Pain Index (WPI) ≤ 4 is to minimize bias potentially affecting the reporting of pain and function by the presence of generalized pain (Yazici et al 2020).

4.1.1 Rationale for choice of background therapy

It is necessary to standardize and document participants' pain medication as it can potentially confound study results; this is particularly important since the primary endpoint of the study is based on a pain assessment. Therefore, only the use of paracetamol/acetaminophen, up to 3000 mg/day, alone or in combination with low-dose codeine (e.g., co-codamol) is allowed as basic (non-rescue) medication for pain control until the EOT visit (Week 52).

4.2 Rationale for dose/regimen and duration of treatment

The s.c. dose of QUC398 300 mg, injected every 4 weeks (q4w), in the present study represents the maximum dose level tested in the SAD/MAD studies in healthy subjects and knee OA patients and aims at achieving maximum inhibition of cartilage breakdown, represented by ARGS levels, and to increase the likelihood to achieve a meaningful pain reduction at Week 12. This dose was safe and well-tolerated in the preceding studies. For detailed information on the safety outcomes of the SAD/MAD studies, please refer to Section 4.5.2.

In the phase 1a SAD study (CCI [redacted]) a single s.c. dose of QUC398 at 300 mg resulted in a continued downregulation of serum ARGS levels around or below the LLOQ of the analytical assay for approximately 49 days, which is considered a relevant biomarker for clinical efficacy. A monthly dose of QUC398 at 300 mg is therefore expected to achieve a continuous and significant reduction of ARGS.

The dosing frequency in the MAD study was weekly and EOW, while the proposed regimen in the present study is q4w. The exposure after weekly s.c. administrations of QUC398 300 mg is about [redacted]-fold higher compared to a single dose administration, i.e., the exposures expected with this q4w dosing regimen are covered by the exposures produced in the MAD study in knee OA patients.

The safety margins at the no observed adverse effect level (NOAEL) in mice and monkeys versus the serum exposure of QUC398 following weekly s.c. injections of 300 mg (MAD study) were at least [redacted]-fold (AUC based) and [redacted]-fold (Cmax based). This representation under predicts the safety margins and should be updated once the predicted exposure following q4w administrations of 300 mg QUC398 are available. The NOAEL doses were set to the highest technical feasible doses in the preclinical safety studies and might provide the most conservative estimation of the safety margins.

Table 4-1 Safety margins for human exposure after multiple dose administration on Day 29 (Day 36 for 300 mg weekly) in study MS200572-0003 vs NOAEL in preclinical species

	Based on Mouse 200 mg/kg AUClast 68840 µg/mL*h [a] Cmax 1310 µg/mL		**Based on Cynomolgus Monkey 150 mg/kg** AUClast 510162 µg/mL*h [b] Cmax 4038 µg/mL	
QUC398 Dose (Human)	**AUC based safety margin [c]**	**Cmax based safety margin**	**AUC based safety margin [c]**	**Cmax based safety margin**
75 mg q2W	[redacted]	[redacted]	[redacted]	[redacted]
150 mg q2W				
300 mg q2W				
300 mg q1W				

AUC = area under the curve; AUClast = area under the serum concentration versus time curve from time zero until tlast (after first or last dose); Cmax = maximum observed concentration.

[a] AUClast as area under the curve corresponding to time=0h to 672h after a single dose. Animals in the repeated dose group will have been exposed to higher values but no extrapolation of the AUC after the last dose was performed.

[b] AUClast as the area under the curve from the last dosing event (504h) to the last sampling point (672h). AUCs over this dosing interval were not extrapolated to the 4-week study duration as steady state was possibly not yet reached after the 4th dose.

[c] AUCtau at last dosing interval in study MS200572-0003 was used for the human as most conservative assessment.

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

No structure modifying (anti-catabolic or anabolic) compound has been approved to date to treat OA. Placebo will be used as the comparator to provide objective control for the evaluation of treatment effects on efficacy (i.e., pain, function and structure), safety, tolerability and PD, with a background of mandated pain medication to meet standard of care for OA pain.

4.4 Purpose and timing of interim analyses/design adaptations

The analysis of the primary endpoint will be performed after all participants have completed Week 12 or discontinued prior to 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).

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.

Additional information is presented in the interim analysis section.

4.5 Risks and benefits

The risk to patients in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, and stopping rules.

Risks associated with QUC398, imaging procedures and blood draws are described in separate sections below. For risks associated with paracetamol/acetaminophen, with or without low dose opioids, the investigator should refer to the product's insert for further information.

4.5.1 Benefits

It is not known whether there will be a benefit for the patients with symptomatic knee OA participating in this study. Preclinical data indicate a possible chondroprotective and symptom-alleviating effect, while clinical data show a good safety profile.

So far, no approved therapy exists addressing the unmet medical need of cartilage protection in patients with degenerative cartilage disorders. Therefore, no such therapies will be withheld by joining this study.

4.5.2 Risks associated with QUC398

QUC398 is a not fully human nanobody and may induce immunogenicity in humans. In the non-clinical and clinical studies thus far, ADAs have been detected, but were not associated with any impact on safety, PK or PD of QUC398.

QUC398 showed a favorable safety profile with no systemic hypersensitivity reactions to the highest tested doses in repeated dose preclinical toxicity studies for up to 39 weeks, and in the two phase 1 studies in humans, in the SAD study using doses up to 300 mg and in the MAD study, up to and including the dose of 300 mg s.c. weekly for 6 weeks.

Potential adverse events may include local injection site reactions (ISR), such as local pain, swelling or inflammation, and will be monitored clinically. In the FIH, SAD study CCI [redacted], ISRs were experienced by 11.1% of the healthy participants and there were no severe ISRs. In the MAD study (MS200572-0003), ISRs were experienced by a mean of 33.3% of all patients treated with QUC398, including 33.3% and 50.0% of participants in the QUC398 300 mg every other week and 300 mg weekly cohorts, respectively. There were no severe ISRs.

In the SAD study, there were no deaths, SAEs, or TEAEs leading to discontinuation during the study. Overall, 40 (74.1%) participants reported at least 1 TEAE; 12 (66.7%) participants on placebo and 28 (77.8%) participants on QUC398. The most prevalent TEAEs were nasopharyngitis, headache, contact dermatitis, ISR and myalgia. The majority of TEAEs were mild in severity. One participant, receiving 150 mg QUC398, reported a severe TEAE of back pain (worsening of existing back pain), which was assessed as unrelated to QUC398.

In the MAD study, there were no deaths and 31 (96.9%) participants reported at least 1 TEAE; 8 (100%) participants on placebo and 23 (95.8%) participants on QUC398. The most common TEAEs reported for all treatments were headache, arthralgia, ISR and muscle tightness. Two participants presented with a serious TEAE (grade 3): (i) an asthmatic crisis (grade 3) considered to be provoked by a flu and not considered to be related to QUC398 by the investigator, and (ii) a participant with increase in knee OA pain (grade 3) who was receiving placebo. Two participants were discontinued from study treatment due to musculoskeletal TEAEs. The events were not considered treatment-related. Ten participants reported TEAEs that were assessed as related to the study treatment; (i) 8 participants treated with QUC398 presented with ISRs; (ii) 1 participant, receiving 300 mg QUC398 every other week, had injection pain; (iii) 1 participant, receiving 300 mg QUC398 weekly, reported musculoskeletal stiffness.

In the SAD and the MAD studies, there were no relevant effects on ECG variables and waveforms or on blood pressure variables.

Detailed information can be found in the Investigator's Brochure.

To mitigate the possible risk of severe hypersensitivity reactions in humans, participants with a history of hypersensitivity reactions to the study treatment or any of the excipients, or to drugs of similar classes, will be excluded from participation in this study.

Participants should be observed for a minimum of 15 minutes after every study treatment administration for any potential hypersensitivity reaction. During the observation period it is recommended that an investigator/medical doctor is on site. Participants who experience any grade of systemic hypersensitivity (e.g., rash, not related to the injection site, wheezing, anaphylactic reaction) will not be re-dosed. Study stopping rules for hypersensitivity are found in Section 9.3.

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

4.5.3 Hypothetical risks for QUC398

Hypothetical risk and recommended treatment of infection

In non-clinical studies, there was no evidence of infections following treatment with QUC398. Based on the current available data from previous single-ascending dose and multiple ascending dose studies there has been no evidence of increased risk of infections related to QUC398 administration.

As with any immune-modulating compound, there is a theoretical risk of immune system impairment, which might increase risk of infection in treated participants. However, QUC398 is not expected to elicit broad immune suppression. Moreover, the target ADAMTS-5 is not essential for health. To mitigate potential risks of immune suppression and infection in this study, exclusion criteria include other immune suppressive treatments administered 28 days or 5 half-lives, whichever is longer, prior to screening. Participants will also be excluded with known or suspected immunodeficiency state or evidence of active or latent, serious bacterial, fungal or viral infections. See Section 5.2.

CCI

Some publications based on animal models of CCI or analyzing tissues from patients that required surgery for complications CCI, suggested that the CCI CCI in the blood vessels' wall, induced by inflammation and ageing, is associated with an increased risk of CCI. CCI This risk is categorized as theoretical for QUC398 because of the lack of causal evidence connecting CCI

No CCI or any other cardiovascular events have been observed neither in pre-clinical studies nor in clinical trials for QUC398.

To investigate this hypothetical risk, the level of CCI, will be monitored during the study as a potential CCI. Additionally, participants with a history of heart failure Class III and IV, unstable angina, myocardial infarction, coronary artery bypass graft surgery, recent percutaneous coronary intervention, valvular and/or aortic defects, aortic or brain aneurysms, or uncontrolled hypertension will be excluded from participation in this study.

4.5.4 Risks associated with basic pain medication

Even though paracetamol/acetaminophen most likely does not cause serious liver damage in recommended doses, it can cause elevation in the liver enzymes. In case of elevation of liver function test, please refer to Section 16.2.

4.5.5 SARS-CoV-2 risks

In response to the COVID-19 pandemic site-specific procedures should be implemented to minimize COVID-19 infection risks for participants and site staff as per local guidance. These documents may cover, but are not limited to, local COVID-19 testing, infection prevention/control, hygiene and social distancing measures. Investigator must instruct participants to contact the investigator immediately if the participants develop any symptoms and/or signs of infection (e.g., fever, loss of smell, loss of taste, muscle aches, persistent or productive cough, abdominal pain, vomiting, nausea, shortness of breath, dysuria and/or diarrhea).

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

No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving QUC398, therefore only vaccination with non-live vaccines is allowed during the study. Live or live-attenuated vaccines are not allowed from 12 weeks prior to planned Day 1 and until 60 days after the last treatment.

4.5.6 Risks associated with imaging procedures

For screening purposes, a fixed flexion knee Xray view is required. The total amount of radiation exposure per participant from this X-ray view will be about 5 µSv. This amount of radiation is equivalent to approximately 17 hours of background exposure (approx. 0.3 µSv per hour at sea level). For effective radiation doses under 3 mSv (300 mrem), the risk is considered to be "minimal". Therefore, the radiation exposure in this study involves minimal risk and is necessary to ensure eligibility of patients.

Magnetic resonance imaging (MRI) will be used in this study to monitor the effects of QUC398 on cartilage structure and composition. MRI is a non-invasive radiology technique that has no radiation exposure. Thus, in principle, MRI scans can be repeated in the same patient as often as necessary. The MRI scanning equipment may cause a feeling of claustrophobia in susceptible persons. The presence of metal in the body may also be a safety hazard or affect the MRI image quality. For more information, see Section 5.2 (Exclusion criteria).

4.5.7 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected over a period of 66 weeks, from each participant as part of the study. The approximate volumes are mentioned in the informed consent form (ICF). Additional samples may be required for safety monitoring.

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

The summary blood log, instructions for sample collection, processing, storage and shipment information are available in the Laboratory Manual.

See Section 8.5.3.1 on the potential use of residual samples.

4.5.8 Risks associated with off-site visits

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

4.6 Rationale for planned off-site procedures

The study participants may be offered to perform pre-specified visits in an off-site location (i.e., the participant's house) in order to minimize the burden on participants and to increase flexibility, as described in Section 3 and defined in Section 8. This has the potential to broaden access to the study for both participants and investigators. The hybrid approach will allow participants to maintain contact with investigators, both in person during clinic visits at site and through the telemedicine platform during off-site participation.

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

4.7 Public Health Emergency mitigation procedures

In the event of a Public Health Emergency, as declared by Local or Regional authorities e.g., pandemic, epidemic or natural disaster, additional mitigation procedures to ensure participant safety and trial integrity may be implemented.

Notification of the Public health emergency as declared by local or regional authorities should be discussed among investigators and Novartis. All procedures adapted to the situation must be submitted, if required as per local regulations, through a protocol amendment for approval by Local or Regional Health Authorities and Ethics Committees prior to implementation of mitigation procedures.

5 Study Population

The study population consists of male and female adult patients between 40 and 80 years of age with symptomatic, mild to severe radiographic knee OA (KL grade 2-4).

Approximately 98 participants are planned to be randomized in this study.

The investigator must ensure that a patient meets all of the inclusion and none of the exclusion criteria before enrolling him/her into the trial. No additional criteria should be applied by the investigator when considering a patient's eligibility.

In the case where a safety laboratory assessment at screening meets any of the exclusion criteria but the condition is expected to be transient and resolved prior to first dose, the assessment may be repeated once prior to randomization. If the repeat value remains exclusionary, then the participant will be excluded from the study.

Selection of the target knee: in case of bilateral knee OA, the target knee is defined as the knee that meets the criteria for KL grade 2-4 and the radiologic mJSN 1-2 criteria. In the event that both knees meet these criteria, the target knee will be designated by the highest pain NRS.

5.1 Inclusion criteria

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

1. Written informed consent must be obtained before any assessment is performed.
2. Able to communicate well with the investigator, to understand and comply with the requirements of the study.
3. Male or female participants ≥ 40 and ≤ 80 years of age on the day of informed consent signature.
4. Weight ≥ 50 kg and a body mass index (BMI) between 18 -35 kg/m^2, at Screening 1.
5. Diagnosis of primary tibiofemoral knee OA by standard American College of Rheumatology (ACR) clinical and radiographic criteria (Altman et al 1986) at Screening 1.
6. Kellgren-Lawrence grade 2 to 4 in the tibiofemoral compartment in the target knee confirmed by radiography in standing weight-bearing fixed flexion position and posterior-anterior view, at Screening 1.

7a. mJSN 1-2 (Altman, Gold 2007) in the medial tibiofemoral compartment of the target knee, confirmed with Xray by central reader at Screening 1.

8. Symptomatic OA with moderate to severe pain (corresponding to Pain NRS ≥ 5 to ≤ 9) in the target knee for the majority of days in the last 3 months prior to Screening 1, as per participant's judgement.
9. Symptomatic OA with moderate to severe pain (corresponding to Pain NRS ≥ 5 to ≤ 9) in the target knee at Screening 1 and 2.
10. Moderate to severe OA pain (corresponding to Pain NRS ≥5 to ≤9) in the target knee during the last 7 days prior to Screening 3, confirmed by:
    - Completed pain diary for at least 6 of the last 7 days prior to Screening 3, AND
    - Diary reported Pain NRS ≥5 to ≤9 for at least 6 of the last 7 days prior to Screening 3
11. KOOS pain subscale ≤ 60 in the target knee at Screening 1, Screening 2, and Screening 3
12. Primary source of pain throughout the body is due to OA in the target knee, and a Widespread Pain Index (WPI) score ≤ 4 at Screening 1.
13. In the event the participant has a history of OA in the contralateral hip or knee, pain NRS should be ≤4 at Screening 3.

14a. If the participant is using chronic NSAID or selective COX-2 inhibitors (excluding topical NSAIDs) for any pain indication including OA pain in the target knee, the participant must be willing to switch to the study basic medication: paracetamol/acetaminophen, including combination drugs containing low dose opioids.

5.2 Exclusion criteria

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

1. History of, or planned, following surgical interventions:
   - Knee replacement (partial or total) in either knee.
   - Arthroscopy or lavage of either knee, within 6 months prior to Screening 1 or planned during the study.
   - Mosaicplasty, microfracture, meniscectomy > 50% or osteotomy of the target knee. Any other previous surgical intervention of the target knee needs to be discussed with the clinical team.
   - Hip prosthesis recently implanted (within 1 year prior to Screening 1) or hip replacement on either side planned within the study period.
2. Painful ipsilateral hip OA (corresponding to Pain NRS ≥3) on the majority of days in the last 3 months prior to Screening 1, as reported by the participant.
3. Known autoimmune disease with inflammatory arthritides (including but not limited to rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus), crystal-induced arthritides (gout, pseudogout associated arthritis), active acute or chronic infection or past infection of the knee joint, Lyme disease involving the knee, reactive arthritis, systemic cartilage disorders, moderate to severe fibromyalgia (widespread pain index, WPI >4 out of 19), or a known systemic connective tissue disease.
4. Metabolic or genetically-based abnormalities associated with arthropathy or collagen deficiencies (e.g., arthrogryposis multiplex congenita, hemophilia, neurogenic arthropathy, Ehlers-Danlos syndrome, Marfan's syndrome, osteogenesis imperfecta, hypermobility or hyperelasticity syndromes).
5. Symptomatic, patello-femoral pain in the target knee as per investigator's examination at Screening 1.
6. Severe malalignment > 7.5º in the target knee (either varus or valgus), measured using standardized knee X-ray at Screening 1.
7. Participant is unable or unwilling to undergo MRI or presenting absolute contraindications to MRI (e.g., metallic implants, metallic foreign bodies, pacemaker, defibrillator).
8. 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 which may jeopardize patient safety, pain perception or compliance with study procedures, as judged by the investigator.

9a. Use of the following prohibited medications within the period defined below:

   - Any local i.a. treatment into the target knee, including but not limited to hyaluronic acid, viscosupplementation and corticosteroids (12 weeks prior to planned Day 1).
   - Long-term treatment (> 2 weeks prior to planned Day 1) with oral corticosteroids > 5 mg/day (8 weeks prior to planned Day 1).
   - Any biological drug (26 weeks prior to planned Day 1).

- Glucosamine, chondroitin sulfate (oral), or any other nutraceutical with potential activity on cartilage repair (from Screening 1).
- Diacetylrhein (12 weeks prior to planned Day 1).
- Centrally acting analgesics (6 weeks or 5 half-lives, whichever is shorter, prior to planned Day 1).
- Any live or live-attenuated vaccine (12 weeks prior to planned Day 1).
- Any medications predicted to impact the ST-segment on ECG or drugs with known moderate-high risk of QT prolonging properties (from Screening 1).

10. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or until the expected PD effect has returned to baseline, whichever is longer; or longer if required by local regulations.
11. Previous exposure to any ADAMTS-5 drug, including QUC398.

12a. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the participants' safety in case of participation in the study. The investigator should make this determination in consideration of the participants' medical history and/or clinical or laboratory evidence of any of the following:

- History of or known liver disease or liver injury as indicated by abnormal liver function tests:
  - ALT, AST, GGT or alkaline phosphatase must not exceed 2 x ULN.
  - Serum bilirubin must not exceed 1.4 x ULN (if the subject has known Gilbert syndrome, the total bilirubin level must not exceed 2 x ULN).

    If necessary, laboratory testing may be repeated on one occasion (as soon as possible) prior to randomization, to rule out any laboratory error.
- History or presence of moderate to severe renal impairment (KDIGO 2012), corresponding to eGFR<60 mL/min/1.73 m^2, or impaired renal function as indicated by clinically significantly abnormal creatinine or BUN and/or urea values, or abnormal urinary constituents (e.g., proteinuria).
  - Evidence of urinary obstruction or difficulty in voiding at Screening 1.
- Total WBC count < 3,000/µL, neutrophils < 1,500/µL, hemoglobin < 8.5 g/dL (85 g/L) or platelet count < 100,000/µL at Screening 1.

13. Any known active infections, including skin or knee infections or suspected infections that may compromise the immune system such as chronic Hepatitis B (HBV), Hepatitis C (HCV) infection, or Human Immunodeficiency Virus (HIV) infection.

    A positive HBV surface antigen (HbsAg) test, or if standard local practice, a positive HBV core antigen test, excludes a participant. Participants with positive HbsAb, but with negative HbsAg and negative anti-HBV core, are allowed to participate in the study since these results are compatible with vaccination against HBV. Participants with a positive HCV antibody test should have HCV RNA levels measured. Participants with positive (detectable) HCV RNA should be excluded.

14. Known heart failure classified as New York Heart Association Class III and IV. History of or known unstable angina, myocardial infarction, coronary artery bypass graft surgery, or percutaneous coronary intervention (such as angioplasty or stent placement) within 365 days of screening. Presence or known history of valvular and/or aortic defects, or of blood vessel aneurisms. Uncontrolled hypertension, defined as a systolic blood pressure (SBP) > 160 mmHg or diastolic blood pressure (DBP) > 100 mmHg at Screening 1 and 2.

15a. History or current diagnosis of ECG abnormalities indicating significant safety risk for participants participating in the study, such as signs of myocardial infarction or ischemia, or concomitant clinically significant cardiac arrhythmias (e.g., sustained ventricular tachycardia and clinically significant second- or third-degree AV block without a pacemaker). Participants with QTcF ≥ 450 or < 300 or inability to determine the QTcF interval at Screening 1 and participants with evidence or history/family history of long QT syndrome, history or risk of Torsades de Pointes or long QT syndrome, or other comorbidities which can confound the ECG and assessments.

16a. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years of Screening 1 (except for basal cell carcinoma, squamous cell carcinoma, or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, or carcinoma *in situ* of the cervix or non-invasive malignant colon polyps that have been removed).

17a. History of drug abuse or unhealthy alcohol use within the 12 months prior to expected first dose, or evidence of such abuse as indicated by the laboratory assays conducted during Screening 1. See also Section 8.1.1.3 (Alcohol test, Drug screen, Urine cotinine).

Unhealthy alcohol use is defined as a history of, or current, alcohol misuse/abuse or "Five or more drinks on the same occasion on each of 5 or more days in the past 30 days."

18. Heavy smoker defined as currently smoking > 20 cigarettes per day or equivalent use of tobacco products, at Screening 1. Past history of heavy smoking is allowed.

19a. History of recreational cannabis use within 4 weeks prior to dosing, or evidence of such use as indicated by the laboratory assays conducted during Screening. This exclusion criterion applies even if cannabis use is legalized where the site is located. See also Section 8.1.1.3 (Alcohol test, Drug screen, Urine cotinine).

20. Pregnant or nursing (lactating) women at Screening 1 or 2.

21. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception while taking study treatment and for 3 months after stopping of study drug.

Highly effective contraception methods include:

- Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking study drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
- Male sterilization (at least 6 months prior to Screening 1). For female participants on the study, the vasectomized male partner should be the sole partner for that participant.
- Use of oral (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception, women should be stable on the same pill for a minimum of 3 months before taking study drug.

If local regulations deviate from the contraception methods listed above and require more extensive measures to prevent pregnancy, local regulations apply and will be described in the ICF.

Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of child bearing potential. See also Section 8.4.4 (Pregnancy and Assessments of Fertility).

22. History of hypersensitivity to any of the study treatments or excipients.
23. Signs or symptoms, in the judgment of the investigator, of a clinically significant systemic viral, bacterial or fungal infection within 30 days prior to Screening 1.
24. Aortic diameter of > 40 mm as measured by Echo-Doppler of thoracic and abdominal aorta at Screening 2 or between Screening 2 and Screening 3.

6 Study treatment and concomitant therapy

6.1 Description of study treatment and treatment arms

6.1.1 Investigational and control drugs

In this protocol, the term study drug or study treatment refers to QUC398 or Placebo, while the term investigational drug refers exclusively to QUC398.

Details on the requirements for storage and management of study treatment, and instructions to be followed for participant numbering, prescribing/dispensing, and administering study treatment are outlined in the Pharmacy Manual.

See Section 6.2.4.1 for relevant dietary and smoking restrictions linked to dose administration visits.

Table 6-1 Investigational and control drug

Treatment Title	QUC398 150 mg/mL	Placebo 0 mg/mL
Treatment Description	Solution for injection (1 mL)	Solution for injection (1 mL)
Type	Biologic	Biologic
Dose Formulation	Vial	Vial
Unit Dose Strength(s)	150 mg/mL	0 mg/mL
Dosage Level(s)	300 mg (2 x 1 mL injections, 150 mg each) q4w	Placebo 0 mg/mL (2 x 1 mL injections, 0 mg each) q4w
Route of Administration	Subcutaneous injection	Subcutaneous injection
Use	Experimental	Placebo
IMP	Yes	Yes
Sourcing	Sponsor (global)	Sponsor (global)
Packaging and Labeling	Study treatment will be provided in glass vials. Each vial will be labeled as required per country requirement.	Study treatment will be provided in glass vials. Each vial will be labeled as required per country requirement.

The minimum duration between two dosings of study treatment is three weeks, the maximum is six weeks.

6.1.2 Additional study treatments

It is imperative to standardize and document participants pain medication as it can potentially confound results. Therefore, only the use of paracetamol/acetaminophen, up to 3000 mg/day, alone or in combination with low dose codeine, e.g., co-codamol, is allowed as basic (non-rescue) medication for pain control, regardless of the origin of the pain, until Week 52. This medication is herein referred to as "basic pain medication". Basic pain medication will be used as needed by the participant within the aforementioned margins, and according to the package inserts and investigator instructions. For sites, handling of the basic pain medication (e.g., labelling, storage location/conditions, temperature control, controlled substance measures, resupply (if needed)) is the investigator's responsibility, taking into consideration local regulations and the corresponding package inserts. Basic pain medication is considered to be Auxiliary Medicinal Products (AxMP) under the EU Clinical Trial Regulation 536/2014. AxMP safety reporting requirements will only apply once the trial has been transitioned under EU Clinical Trial Regulation 536/2014.

At each study visit, participants will be provided with a quantity of the basic pain medication, either the paracetamol/acetaminophen or the paracetamol/acetaminophen plus codeine combination product, that is estimated to be sufficient until the next planned study visit, starting at Screening 1 and until Week 52.

Participants who use other pain medications must be switched to the basic pain medication at Screening 1 (inclusion criterion).

The participant should only use the basic pain medication provided by the investigator, even if he/she previously used or can purchase the same compound privately.

The basic pain medication can be taken at any point in the study, also within 48 hours of a study visit. To the extent possible, no other pain medication should be used up until Week 52 (see Section 6.2.3 Rescue medication).

Participants will be provided with a pain diary in which they will document their daily pain and the use of (any) pain medication up to Week 12 (see Section 8.3.1.4). The investigator or delegate must review the pain diary at each visit until Week 12, to ensure the number of returned basic pain medication tablets are reasonable compared to the documented use in the pain diary, and to monitor the potential use of rescue medication as per Section 6.2.3 (drug accountability will be performed on basic pain medication).

Table 6-2 Additional study treatment

Treatment Title	**Paracetamol/acetaminophen 500 mg***	**Paracetamol/acetaminophen in combination with low dose codeine 500/30 mg***
Treatment Description	As needed	As needed
Type	Drug	Drug
Dose Formulation	Tablet	Tablet
Unit Dose Strength(s)	500 mg*	500 mg paracetamol/acetaminophen plus 30 mg codeine*
Dosage Level(s)	Up to 3000 mg per day	Up to 3000 mg paracetamol/acetaminophen plus 180 mg codeine per day
Route of Administration	Oral	Oral
Use	Background intervention	Background intervention
Authorization status of the AxMP in EEA	Yes	Yes
Sourcing	Provided locally by sponsor, or local pharmacy	Provided locally by sponsor, or local pharmacy
Packaging and Labeling	Original packaging, and labeled as per local regulations	Original packaging, and labeled as per local regulations

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

No other treatment beyond investigational drug, placebo and basic pain medication are provided in this trial.

The basic pain medication must be recorded on the concomitant medications Case Report Form (CRF).

6.1.3 Treatment arms/group

Participants will be assigned to one of the following 2 treatment arms in a ratio of 1:1:

- QUC398 300 mg, q4w s.c. injections
- Placebo, q4w s.c. injections

6.2 Other treatment(s)

6.2.1 Concomitant therapy

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

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

Medication entries should be specific to generic name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact Novartis before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, the investigator should contact Novartis to determine if the participant should continue participation in the study.

If a COVID-19 vaccine is available, vaccination of trial participants with non-live vaccines will be permitted during the study duration. The investigator must document their discussion with the participant regarding COVID-19 vaccination in the source documentation, and follow the instructions described above related to the CRF.

6.2.1.1 Permitted concomitant therapy

Topical NSAIDs and topical steroids are allowed during the study.

A daily dose of aspirin of up to 325 mg/day is allowed during the study.

NSAIDs are allowed without restrictions after Week 52 but should still not be taken within 48 hours of a visit where Pain (NRS) or KOOS assessments are conducted (EOS visit).

Non-pharmaceutical therapies, such as electrotherapy, acupuncture, physiotherapy, and chiropractic treatment are allowed during the study.

All permitted concomitant therapy must be reported in the Concomitant medications/Significant non-drug therapies eCRF.

6.2.2 Prohibited medication

Use of the treatments displayed in the table below is NOT allowed in the reported timeframe. If required outside of the definitions of Rescue medication (Section 6.2.3), actions have to be taken as described by Table 6-3 below.

Table 6-3 Prohibited medication

Medication	Prohibition period	Action taken
Local i.a. treatment into the target knee, including but not restricted to hyaluronic acid, viscosupplementation and corticosteroids	12 weeks prior to Day 1 to EOS	Report protocol deviation and discontinue study treatment
Systemic including oral corticosteroid > 5 mg/day for more than 14 consecutive days (topical, intranasal and ophthalmic are permitted)	8 weeks prior to Day 1 to EOS	Report protocol deviation and discontinue study treatment
Any biological drug	26 weeks prior to Day 1 to EOS	Report protocol deviation and discontinue study treatment
Glucosamine, chondroitin sulfate (oral), or any other nutraceutical with potential activity on cartilage repair	From Screening 1 to EOS	Report protocol deviation and discontinue prohibited medication as soon as possible
Diacetylrhein (Diacerein)	12 weeks prior to Day 1 to EOS	Report protocol deviation, discontinue prohibited medication as soon as possible, and reschedule study visit if taken within the last 48 hours*
Centrally acting analgesics, e.g., pregabalin, duloxetine, medical marijuana and CBD oil	6 weeks or 5 half-lives, whichever is shorter, prior to Day 1 to EOS	Report protocol deviation, discontinue prohibited medication as soon as possible, and reschedule study visit if taken within the last 48 hours*
Any live or live-attenuated vaccine	12 weeks prior to Day 1 and until 90 days after the last study treatment	Report protocol deviation and discontinue study treatment
Acetylsalicylic acid > 325 mg/day	Screening 1 to EOS	Report protocol deviation, discontinue or adjust dosing of prohibited medication (as needed) as soon as possible, and reschedule study visit if taken within the last 48 hours*
Paracetamol/acetaminophen > 3000 mg/day	Screening 1 to EOS	Report protocol deviation, discontinue or adjust dosing of prohibited medication (as needed) as soon as possible, and reschedule study visit if taken within the last 48 hours*

Medication	Prohibition period	Action taken
Opioids, including tramadol and transdermal fentanyl patches, except oral low dose codeine combination drugs	Screening 1 to EOS	Report protocol deviation, discontinue prohibited medication as soon as possible, and reschedule study visit if taken within the last 48 hours*
NSAIDs (including combinations with codeine or caffeine, as well as selective COX-2 inhibitors) beyond the use as rescue medication (see Section 6.2.3). Topical NSAIDs are permitted.	Screening 1 to Week 52	Report protocol deviation, discontinue prohibited medication as soon as possible, and reschedule study visit if taken within the last 48 hours*
Any medications predicted to impact the ST-segment on ECG. Drugs with known QT prolonging properties.	Screening 1 to Week 52	Report protocol deviation and discontinue study treatment

* If taken within the last 48 hours before a study visit, the entire visit should be rescheduled to the first possible time point outside the 48-hour limit (after last intake), even if this pushes the visit to outside the visit window specified in Table 8-1. If the rescheduled visit is again compromised by prohibited medication intake within 48 hours, the investigator should contact the sponsor to agree on whether to reschedule the visit further.

All prohibited medication must be reported in the Concomitant medications eCRF.

6.2.3 Rescue medication

If adequate pain control is not achieved with basic pain medication (paracetamol/acetaminophen alone or in combination with low-dose codeine as described in Section 6.1.2), then NSAIDs will be permitted as rescue medication for up to 3 days per week, but must not be taken within 48 hours of a visit where Pain (NRS) or KOOS assessments are conducted, up until Week 52, inclusive.

After Week 52, NSAIDs are allowed without restrictions but should still not be taken within 48 hours from a visit where Pain (NRS) or KOOS assessments are conducted (EOS visit).

In the event that NSAIDs have been taken within 48 hours of a study visit, the entire visit should be rescheduled to the first possible time outside of the 48-hour limit (see Table 6-3).

Rescue medication will not be provided by the sponsor.

Decisions regarding specific NSAIDs to be used as rescue medication should be made by the site's principal investigator, based on local practice and individual patient needs. The maximum dose should not exceed the approved dose in each country. Rescue medication should be used according to the corresponding package insert and investigator instructions while taking into account specific precautions.

Use of rescue medication must be documented by the participant in the pain diary and recorded in the Concomitant medications eCRF.

6.2.4 Restriction for study participants

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

6.2.4.1 Dietary restrictions and smoking

From Screening 1 to EOS, the participant should not smoke > 20 cigarettes per day or use other tobacco products in amounts corresponding to > 20 cigarettes per day. Use of nicotine products is allowed as per package insert.

At visits where ECG measurements are performed, participants must refrain from smoking, consuming alcohol, methylxanthine-containing beverages, citrus-containing fruits or beverages, and tonic water in the 4 hours previous to the ECG collection.

In order to avoid wide variations in urine volumes on PK collection days, participants should be encouraged to have a fluid intake of approximately 240 mL every 4 hours during their waking hours, in addition to the fluid taken with meals (only on PK collection days).

6.2.4.2 Other restrictions

Participants will be required to adhere to the measures and procedures outlined by the study site, to prevent SARS-CoV-2 infections among trial participants and clinical site staff.

6.3 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described in Section 6.1.1.

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

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

The study treatment is blinded and the syringe for s.c. injection must be prepared by adequately trained and qualified personnel, after the investigator or delegate has randomized a participant and information about the assigned treatment arm (kit assignment) has been received from the IRT system. The volume of injection will be the same between participants receiving QUC398 or placebo, i.e., 2 x 1 mL.

Because participants are randomized to a treatment arm only after eligibility has been confirmed at Screening 3, the investigator is responsible for establishing effective communication with the pharmacist, to ensure the study drug is prepared as soon as possible after randomization, and made available on Day 1. It is particularly important to give reasonable notice of an upcoming randomization and dosing visit if the syringe is reconstituted at an external pharmacy and has to be transported to the site.

The investigator site will be provided with a Pharmacy Manual, in which details on all drug handling are described.

For off-site visits by OHPs, where delivery of study medication directly to a participant's secure off-site location (e.g., home) is permitted by national and local governing regulations, the dispatch of study medication directly to the participant may be performed under the accountability of the Investigator. The dispatch of the study treatment from the site to the participant's home remains under the accountability of the investigator. Each shipment will consist of a single dose of study treatment, to be administered at the off-site visit. Regular phone calls or virtual contacts will occur between the site and the participant for instructional purposes, safety monitoring, investigation of any adverse events, and discussion of the participant's health status.

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

6.3.1 Handling of study treatment and other treatment

6.3.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels.

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

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

The investigator or designated site staff (blinded or unblinded, as applicable) must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by field monitors during site or remote monitoring visits, and at the completion of the trial.

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

In the US, the study treatment and all required clinical study supplies will be distributed direct to the participant utilizing an extension of the IND for compliance purposes.

6.3.1.2 Handling of other treatment

Basic pain medication and rescue medication will be handled as described in Section 6.1.2 and Section 6.2.3.

6.3.2 Instruction for prescribing and taking study treatment

Table 6-4 Dose and treatment schedule

Investigational / Control Drug (Name and Strength)	Dose	Frequency and/or Regimen
QUC398 150 mg/mL	300 mg (2 x 1 mL injections, 150 mg each)	q4w
Placebo 0 mg/mL	0 mg (2 x 1 mL injections, 0 mg each)	q4w

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

Study treatment will be administered as 2 injections into a skin fold of the participant's abdomen, by the investigator or delegate. Each injection should be at least 10 cm apart from the previous one. The skin at the injection site must be suitably disinfected before the injection by use of an alcohol wipe to clean the skin. The injection site must not be covered to avoid the possibility of any irritation from the bandaging material and any drops of blood must be carefully dabbed away with a dry cloth until the wound has closed. Participants should be observed for a minimum of 15 minutes after every study treatment administration for any potential hypersensitivity reaction.

The first dose will be administered to participants on Day 1, followed by administrations every 4 weeks (q4w) until Week 48, inclusive.

6.4 Participant numbering, treatment assignment, randomization

6.4.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant’s participation is numbered uniquely across the entire database. Upon signing the ICF, the participant is assigned to the next sequential Participant No. available.

A new ICF will need to be signed if the investigator chooses to re-screen the participant after a participant has screen failed, and the participant will be assigned a new Participant No.

6.4.2 Treatment assignment, randomization

After the Screening 3 phone call (between Day -4 and Day -1), all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the participant.

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

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

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

6.5 Treatment blinding

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

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

Site personnel

All site personnel will be blinded to study treatment throughout the study.

Unblinding a single participant at site for safety reasons (if necessary for participant management) will occur via an emergency system in place at the site (see Section 6.7.3).

Sponsor staff or delegate

The following unblinded sponsor roles are required for this study:

- Unblinded bioanalyst(s) (QUC398 PK)

The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team under blinded conditions. Sample data may be provided to the independent committee/analysis team, if used, under unblinded conditions.

All sponsor staff (study statistician, study programmer, biomarker expert, clinical trial team, decision boards etc.) will stay blinded to treatment assignments (except in the case of a safety event necessitating unblinding) until the Week 12 analysis.

The study statistician will be able to access the randomization list for interim analyses and is allowed to share unblinded information with the rest of the clinical team as appropriate for internal decision purposes, as outlined in Table 6-5. For example, unblinded summaries and unblinded individual data can be shared with the team for interim analyses.

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

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

All unblinded sponsor personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure until the Week 12 analysis.

Following final database lock, all roles may be considered unblinded. See the blinding/unblinding table for an overview of the blinding/unblinding plan.

Table 6-5 Blinding and unblinding plan

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

B Remains blinded

UI Allowed to be unblinded on individual patient level

6.6 Dose escalation and dose modification

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

6.7 Additional treatment guidance

6.7.1 Treatment compliance

Compliance to the treatment regimen is ensured by administration of QUC398 300 mg or placebo s.c. injections by the investigator or delegate. Information on the study treatment administration or any deviation from the dose regimen must be recorded in the eCRF. All vials for study treatment and potentially returned vials must be recorded in the Drug Accountability Log. The monitor(s) will review Drug Accountability Logs during site visits.

Dispensed and returned basic pain medication must be recorded in the source documents.

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

6.7.2 Recommended treatment of adverse events

Treatment of AEs should be in line with the investigator site procedures.

For the management of allergic reaction and anaphylaxis, it is recommended to follow the guidelines by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).

In case of any sign of acute reaction, the participant will be managed with treatment as determined by the treating physician on a case-by-case basis, according to local protocols, and depending on severity, using symptomatic treatment such as antihistamines, NSAIDs, acetaminophen, intravenous fluids, corticosteroids, or adrenaline.

Medication or other therapies used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies eCRF.

6.7.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the participant safely.

Most often, discontinuation from study treatment and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

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

- protocol number
- name (if available)
- participant number

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

Novartis will evaluate on a case-by-case basis if a participant will be permitted to continue study participation after an emergency code break.

7 Informed consent procedures

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

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH E6 GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational treatment can be found in the Investigator's Brochure (IB). This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Main study consent, which also included:
  - A subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
  - A subsection that requires a separate signature for the 'Optional Consent for Week 56 Visit' to allow for CCI [redacted]
- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the female partners of any male participants who took study treatment
- CCI [redacted]

Women of child-bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

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

The study includes an CCI [redacted] which requires a separate signature if the participant agrees to participate. It is required as part of this protocol that the Investigator presents this option to the participants, as permitted by local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in these CCI [redacted] and/or Additional Research) will in no way affect the participant's ability to join the main research study.

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

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

As per Section 4.7, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g., telephone, videoconference) if allowable by a local Health Authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g., the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

8 Visit schedule and assessments

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

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

For screening purposes, the following order of assessments is recommended:

1. Clinical eligibility, starting with OA pain in the target knee
2. Laboratory assessments
3. X-ray
4. Other (e.g., pain diary, CCI)

After eligibility has been confirmed at Screening 3, the following order of assessments is recommended:

1. Assessment of rescue and/or prohibited medication use
2. Pain assessments, in the order KOOS, Pain NRS, PGA
3. Pain diary review and basic pain medication review/dispensation
4. Vital signs, ECG
5. Blood sampling
6. CCI [redacted].

Other orders of priority to consider are:

Randomization must occur after eligibility has been confirmed at Screening 3.

The preferred sequence of data collection during study visits is ECG recording, vital signs, blood sampling and then CCI [redacted]

MRI can be performed before or after other clinical assessments at a visit, also on a different day if needed for logistical reasons, but should always be done within the visit window.

Participants who discontinue from study treatment are to return for the EOT visit as soon as possible, and return for safety follow-up assessments 8 weeks later (EOS visit).

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

The “X” in the table denotes the assessments to be recorded in the clinical database or received electronically from a vendor. The “S” in the table denotes the assessments that are only in the participant’s source documentation and do not need to be recorded in the clinical database.

Table 8-1 Assessment Schedule

Period	Screening			Treatment										Post-Treatment Follow-Up		
Visit Name	Screening 1	Screening 2	Screening 3 (Randomi-zation)[1]	Day 1	Day 5	Week 4	Week 8	Week 12	Week 16 / Week 20 / Week 24[2]	Week 28	Week 32 / Week 36[2]	Week 40	Week 44 / Week 48[2]	EOT - Week 52	Week 56[2,3]	EOS - Week 60
Days	-40 to -21	-20 to -9	-4 to -1	1	5 ±2	29 ±3	57 ±3	85 ±3	113 ±3 / 141 ±3 / 169 ±3	197 ±3	225 ±3 / 253 ±3	281 ±3	309 ±3 / 337 ±3	365 ±3	393 ±3	421 ±7
Informed consent	X															
Inclusion / Exclusion criteria	X	X	X													
Demography	X															
Genetic consent	X															
Medical history/current medical conditions	X															
Hepatitis screen	S															
HIV screen	S															
Alcohol Test and Drug Screen	S															
Smoking history	S															
Body Height	X															
Body Weight	X			X				X						X		
Vital Signs[4]	X	X		X	X	X	X	X	X	X	X	X	X	X		X

Period	Screening			Treatment										Post-Treatment Follow-Up		
Visit Name	**Screening 1**	**Screening 2**	**Screening 3 (Randomi-zation)[1]**	**Day 1**	**Day 5**	**Week 4**	**Week 8**	**Week 12**	**Week 16 / Week 20 / Week 24[2]**	**Week 28**	**Week 32 / Week 36[2]**	**Week 40**	**Week 44 / Week 48[2]**	**EOT - Week 52**	**Week 56[2,3]**	**EOS - Week 60**
Days	**-40 to -21**	**-20 to -9**	**-4 to -1**	**1**	**5 ±2**	**29 ±3**	**57 ±3**	**85 ±3**	**113 ±3 / 141 ±3 / 169 ±3**	**197 ±3**	**225 ±3 / 253 ±3**	**281 ±3**	**309 ±3 / 337 ±3**	**365 ±3**	**393 ±3**	**421 ±7**
Physical Examination	S			S	S			S		S		S		S		S
Electrocardiogram (ECG)[5]	X			X	X			X		X		X		X		X
Hematology	X			X	X	X		X	X	X		X		X		X
Clinical Chemistry	X			X	X	X	X	X	X	X		X		X		X
Coagulation Panel	X			X	X	X		X	X	X		X		X		X
CCI																
Urinalysis	X			X	X	X	X	X	X[6]	X	X	X	X	X		X
Pregnancy and assessments of fertility[7]	X	X		X		X	X	X	X	X	X	X	X	X	X	X
WPI	X															
KOOS	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Patient's Global Assessment				X	X	X	X	X	X	X	X	X	X	X		X
Pain NRS	X	X	X[8]	X	X	X	X	X	X	X	X	X	X	X		X
CCI																
X-ray target knee	X															

Period	Screening			Treatment										Post-Treatment Follow-Up		
Visit Name	**Screening 1**	**Screening 2**	**Screening 3 (Randomi-zation)[1]**	**Day 1**	**Day 5**	**Week 4**	**Week 8**	**Week 12**	**Week 16 / Week 20 / Week 24[2]**	**Week 28**	**Week 32 / Week 36[2]**	**Week 40**	**Week 44 / Week 48[2]**	**EOT - Week 52**	**Week 56[2,3]**	**EOS - Week 60**
Days	**-40 to -21**	**-20 to -9**	**-4 to -1**	**1**	**5 ±2**	**29 ±3**	**57 ±3**	**85 ±3**	**113 ±3 / 141 ±3 / 169 ±3**	**197 ±3**	**225 ±3 / 253 ±3**	**281 ±3**	**309 ±3 / 337 ±3**	**365 ±3**	**393 ±3**	**421 ±7**
CCI																
MRI target knee				X[10]						X				X		
CCI																
Randomization			X													
Study drug administration				X[11]		X	X	X	X	X	X	X	X			
CCI																

Period	Screening			Treatment										Post-Treatment Follow-Up		
Visit Name	**Screening 1**	**Screening 2**	**Screening 3 (Randomi-zation)[1]**	**Day 1**	**Day 5**	**Week 4**	**Week 8**	**Week 12**	**Week 16 / Week 20 / Week 24[2]**	**Week 28**	**Week 32 / Week 36[2]**	**Week 40**	**Week 44 / Week 48[2]**	**EOT - Week 52**	**Week 56[2,3]**	**EOS - Week 60**
Days	**-40 to -21**	**-20 to -9**	**-4 to -1**	**1**	**5 ±2**	**29 ±3**	**57 ±3**	**85 ±3**	**113 ±3 / 141 ±3 / 169 ±3**	**197 ±3**	**225 ±3 / 253 ±3**	**281 ±3**	**309 ±3 / 337 ±3**	**365 ±3**	**393 ±3**	**421 ±7**
CCI																
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Echo-Doppler of thoracic and abdominal aorta		X[20]												X[21]		

Period	Screening			Treatment										Post-Treatment Follow-Up		
Visit Name	Screening 1	Screening 2	Screening 3 (Randomi-zation)[1]	Day 1	Day 5	Week 4	Week 8	Week 12	Week 16 / Week 20 / Week 24[2]	Week 28	Week 32 / Week 36[2]	Week 40	Week 44 / Week 48[2]	EOT - Week 52	Week 56[2,3]	EOS - Week 60
Days	-40 to -21	-20 to -9	-4 to -1	1	5 ±2	29 ±3	57 ±3	85 ±3	113 ±3 / 141 ±3 / 169 ±3	197 ±3	225 ±3 / 253 ±3	281 ±3	309 ±3 / 337 ±3	365 ±3	393 ±3	421 ±7
Study completion information																X

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
1 Phone call visit.
2 May be performed at an off-site location, if allowed by local laws and regulations and as agreed with the Investigator.
3 Optional visit: only for participants who consented to optional PK and PD samples
4 Pre- and post-dose BP, body temperature, and pulse rate measurements will be performed.
5 Triplicate ECGs except single 12-lead ECG at Screening 1.
6 Only at Week 20
7 Only for women of childbearing potential: Serum pregnancy test at Screening 1, Screening 2, and Week 60 (EOS) visits, urine pregnancy test at all other visits except Screening 3 (phone call) and Day 5 visits.
8 Only for NRS pain in the contralateral hip or knee, if applicable to the participant.
CCI
10 MRI assessment is allowed from Day 1 to Day 10.
11 Study drug to be administrated after all scheduled pre-dose assessments in Day 1 completed.
CCI
13
CCI
CCI
17 CCI This optional sample can be collected anytime during Day 1 or thereafter
CCI
Echo-Doppler of thoracic and abdominal aorta is to be performed at Screening 2 or between Screening 2 and Screening 3.
21 Echo-Doppler of thoracic and abdominal aorta is to be performed at Week 52 (EOT) or between Week 52 (EOT) and Week 60 (EOS).

8.1 Screening

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

Re-screening is permitted if the reason(s) for failing the initial screening were unrelated to the knee X-ray. The participant will not need to undergo another knee X-ray and the initial one may be used for re-screening purposes, if re-screening occurs within 6 months of the X-ray date. The objective of this measure is to avoid unnecessary radiation exposure, given that meaningful radiologic changes are not likely to occur during the period of re-screening.

Echo-Doppler of the thoracic and abdominal aorta does not have to be repeated if re-screening occurs within 6 months of the Echo-Doppler date.

Participants can repeat the KOOS once without being screen failed if the pain subscale score was > 60 and < 70 at Screening 1, Screening 2, or Screening 3. Participants can be re-screened once if KOOS pain at Screening 1, Screening 2, or Screening 3 is not within the permitted range despite its repetition, provided that the other pain criteria listed in inclusion criterion 8 and 9 were within the permitted range.

8.1.1 Eligibility screening

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

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

In the case where a safety laboratory assessment at screening meets any of the exclusion criteria but where the condition is expected to be transient and resolved prior to first dose, or if a laboratory error is suspected, the assessment may be repeated once prior to randomization. If the repeat value still meets the exclusion criterion, the patient does not qualify for the study.

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

8.1.1.1 Pain

Widespread Pain Index (WPI) (Wolfe et al 2016) will be assessed at Screening 1 only, to exclude participants with substantial pain from undiagnosed diseases.

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

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

8.1.1.2 Hepatitis screen, HIV screen

All participants will be screened for Hepatitis B surface antigen antibody (HBsAb), Hepatitis B surface antigen (HBsAg), and Hepatitis B core antibody (HBcAb).

If HBsAg or HBcAb is positive the participant will be excluded.

Screening for Hepatitis C will be based on HCV antibodies (HCVAb) and if positive, HCV RNA levels should be determined.

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

8.1.1.3 Alcohol test, Drug screen, Urine cotinine

Participants will be tested for substances of abuse (e.g., alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine and opiates) with a urine sample as they may interfere with the participants' perception of pain, which is the primary endpoint of the study, and with safe adherence to this protocol (e.g., unknown interaction effects with study treatment, proper conduct of assessments). Positive tests for opioids such as codeine and/or benzodiazepines are not considered exclusionary if ongoing at study start and recorded on the Concomitant Medication page in the eCRF. If the initial drug screen was failed, one re-test for cannabinoids is allowed.

Cotinine in urine will not be analyzed at screening. However, the investigator should clarify tobacco use habits for participants who use tobacco since heavy smokers, defined as smoking > 20 cigarettes/day, are excluded from the study as described in Section 6.2.4.1. Nicotine replacement therapies are allowed.

8.1.1.4 Knee X-ray

A standardized flexion knee X-ray will be performed at Screening 1 to evaluate the KL, mJSN and malalignment eligibility criteria, using a non-fluoro, standardized and quality-controlled method, as described in the Imaging Manual. The local radiologist and/or investigator should review the images for incidental findings relevant to the participant's safety. A central reader will analyze the images as described in the Imaging Manual.

If a participant has been screened for a similar Novartis trial with the same conventional X-ray projections, these images can be used within six months of the X-ray date, provided the participant confirms there are no significant changes in local symptoms since the initial image was taken.

8.1.2 Information to be collected on screening failures

A screen failure occurs when a participant who consents to participate in the clinical study is subsequently found to be ineligible and therefore not dosed with randomly assigned study treatment. In this situation, the investigator must provide minimal set of screen failure information. Data and samples collected from participants prior to screen failure may still be analyzed.

The reason for screen failure should be recorded on the appropriate eCRF. The protocol version log, subject status, disposition, visit dates, demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will need to be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event or an adverse event related to AxMPs during the screening phase (see Section 10.1.3 for SAE reporting details).

Participants who are randomized and fail to start treatment, e.g., participants randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate eCRF.

The IRT must be notified within 2 days of the screen failure/early termination.

8.2 Participant demographics/other baseline characteristics

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

Participant race/ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors, as well as to assess the diversity of the study population as required by Health Authorities.

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

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

8.3 Efficacy

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

Pain (primary endpoint) will be assessed by KOOS, as described in Section 8.3.1.

Cartilage volume (secondary endpoint) as well as other structure components (e.g., bone marrow lesions) will be evaluated by MRI as described in Section 8.3.2.

PD samples will be obtained and evaluated in all participants, including the placebo group.

The samples will be collected at the time points defined in the assessment schedule (Table 8-1). Instructions are outlined in the Laboratory Manual regarding sample collection, numbering, processing, and shipment.

8.3.1 Patient Reported Outcomes (PROs)

The PROs used in this study are KOOS, Pain (NRS), PGA (NRS), a Pain diary (to record pain intensity and pain medication; described in this Section 8.3.1), and WPI (described in Section 8.1.1.1).

To assess the presence of pain in joints other than the index knee, the participant will be asked to mark the painful joints in the CCI and score the pain in each of these joints using a pain NRS.

The participant must complete the PRO assessments at the scheduled visit before any other clinical assessments are conducted, either at the site or in an off-site visit, when permitted by local regulations and agreed by the investigator and the participant.

The questionnaires should be completed in the language most familiar to the participant. The participant should be given sufficient space and time to complete the PRO measures. A participant's refusal to complete all or any part of a PRO measure should be documented in the eCRF.

The site personnel or delegated person should check the PRO measures collected for completeness and ask the participant to complete any missing responses.

The investigator is asked to review the KOOS pain subscale and the concomitant medication recorded in the diary for responses which may indicate potential AEs or SAEs before any clinical study examinations. If AEs or SAEs are confirmed, study investigators should not encourage the participant to change responses reported in the completed questionnaires. Study investigators must follow reporting instructions outlined in Section 10.

8.3.1.1 Knee Injury and Osteoarthritis Outcomes Score (KOOS)

Knee-related symptoms and function will be assessed by means of the KOOS measure (Roos et al 2011) collected at regular intervals. The KOOS has a recall period of seven days and includes 42 items grouped into 5 subscales: Pain, Other symptoms, Activities of Daily Living (ADL), Function in Sport and Recreation (Sport/Rec), and Knee related Quality of Life (QoL). Standardized answer options are given (5 Likert boxes) and each question gets a score from 0-4. A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale (KOOS User Guide 2003).

8.3.1.2 Pain Numerical Rating Scale (NRS)

The participant's pain in the target knee using NRS (Hawker et al 2011) is assessed to confirm eligibility and at regular intervals throughout the study.

The Pain NRS utilizes an 11-point scale from 0 – 10, has a recall period of 24 hours, and the participants will be asked to rate the pain intensity at its worst.

For the assessment of painful joints other than the index knee, the participants will be asked to score the pain at each joint marked in the CCI [redacted] with the same recall period and anchor questions as for the target knee.

8.3.1.3 Patient's Global Assessment (PGA)

The PGA of OA disease activity will be performed using a NRS (11-point scale from 0 – 10) with a recall period of 24 hours, and it is completed by the participant prior to drug administration at visits specified in the assessment schedule.

8.3.1.4 Pain diary

Daily assessments of pain intensity (NRS) in the target knee, as well as any pain medication intake will be recorded by the participant in the study-specific pain diary, from Screening 2 until Week 12. Use of prescribed or OTC pain medications will still need to be documented as Concomitant Medications according to Section 6.2.1.

The participant may choose when but should assess the pain intensity at approximately the same time on every day, also on study visit days. The Pain (NRS) assessment in the diary and the Pain (NRS) assessment performed at site during study visits are done at different time points and therefore documented separately in the eCRF.

From Screening 2 to Week 12, participants will either be provided with a new pain diary that covers at least the period until the next planned visit, or will be completed via an electronic device where all visits are available.

8.3.2 Knee Magnetic resonance imaging (MRI)

The baseline MRI will only be performed after randomization of the participant.

MRI can be performed before or after the application of the study drug, and even on a different day if needed for logistical reasons, but should always be done within the visit window.

MRI will be obtained from the target knee. Specific MRI pulse sequences will be used to quantify changes in volume and thickness of cartilage; CCI [redacted] The index region is defined as the union of the femoral medial anterior (FMA), central (FMC) and posterior (FMP) cartilage subregions in the knee.

CCI [redacted]

8.3.2.1 Image collection

The MRI acquisition will be performed by a trained MRI professional at each site. The MRI radiologist will be blinded to the treatment received by the participant. All MRI acquisitions will be done using a clinical MRI 3T scanner and a multi-channel knee coil. For each MRI session, images will be acquired as described in the scanning guide manual to assess cartilage structure and texture as well as bone marrow lesions. Both 2D and 3D non-contrast MRI pulse sequences will be used to these ends.

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

8.3.2.2 Image processing

The image analysis will be performed centrally, as defined in the Imaging Manual, in order to assess changes in cartilage volume, thickness, T2 and texture both in the index region and the rest of the joint as well as changes in CCI volume.

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

Segmentation of knee articular cartilage will be performed for the measurement of cartilage volume and thickness by using a CE marked and FDA approved (510(k) number K231351) automated segmentation software (Chondral Quant, Siemens, Erlangen, Germany). The software allows a robust automated segmentation of the femoral, tibial and patellar cartilage as well as the Region-of-Interest analysis. It uses 3D active shape models, the extraction of the expected bone–cartilage interface, and cartilage segmentation using a graph-based method. As a result, the complete set of parameters is provided (volumetry and descriptive statistics of quantitative MR parameters). These include volumes (in milliliters) and cartilage thickness (in millimeters) separately for 21 regions (femur: medial posterior-FMP, medial central-FMC, medial anterior-FMA, trochlea medial-FTM, trochlea central-FTC, trochlea lateral-FTC, lateral posterior-FLP, lateral central-FLC and lateral anterior-FLA; lateral posterior-TLP, lateral central-TLC, lateral anterior-TLA, medial posterior-TPM, medial anterior-TMA; lateral inferior-PLI, lateral central-PLC, lateral superior-PLS, medial inferior-PMI, medial central-PMC, medial superior-PMS). This definition of the subfields is based on a modified ICRS score as published before (Surowiec et al 2014). This subdivision of the knee joint is more accurate than the subdivision provided by the MOAKS classification. The automated software will calculate cartilage volume and cartilage thickness within each of these subfields.

Structural MR images will also be analyzed for the determination of CCI volume.

CCI

CCI analysis will be performed on CCI As previously shown CCI seem to correlate with the CCI and therefore, this method may help to improve the quantification of degenerated cartilage tissue. The main CCI that will be considered are: CCI

8.3.3 Appropriateness of efficacy assessments

The PRO KOOS score is an expanded version of the Western Ontario and McMaster Universities Arthritis Index (WOMAC) score, which traditionally has been used in OA trials (KOOS User Guide 2003). KOOS includes WOMAC OA index LK 3.0 in its complete and original format, allowing WOMAC scores to be derived from the KOOS instrument. Compared to WOMAC, the KOOS score gives a more comprehensive picture because it also includes "Function in sport and recreation" and "Knee related QoL". KOOS has a 7-day recall period.

The Pain (NRS) score is traditionally used to assess pain.

KOOS, with a 7-day recall period, and pain NRS, with a 24-hour recall period, are used in combination to guarantee a full understanding of pain behavior.

The PGA (NRS) score is traditionally used to evaluate the overall OA disease status of the patient.

Imaging techniques including X-rays and MRI are standard measures used for assessing joint structure in participants with OA (Hayashi et al 2019).

The use of an automated segmentation software will make it possible to overcome the inherent limitations in the manual segmentation of MR images, i.e., a time-consuming process, possible measurement inaccuracies related to the subjectivity of the radiologist and incomplete knee coverage. In addition, a unique feature of the chosen software (i.e., MR Chondral Quant) will allow CCI for a comprehensive assessment of cartilage, covering both structural (volume and thickness) and qualitative (CCI aspects.

8.4 Safety/Tolerability

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

For details on AE collection and reporting, refer to Section 10.1.

Table 8-2 Assessments and specifications

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

Assessment	Specification
	A knee joint examination will also be performed as part of the physical examination at all time points specified in Table 8-1, and includes examination for warmth, swelling/bulge sign and patellar tap sign as well as for patellofemoral pain. Targeted physical examinations to elaborate self-reported symptoms, complaints, injection site reactions or post-injection flares as applicable, can be done at any visit. An injection site exam will be performed at every visit. Participants should be observed for a minimum of 15 minutes after every study treatment administration for any potential hypersensitivity reaction. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs will include the collection of (pre-and post-dose) otic, oral or armpit body temperature (recorded in °C), blood pressure (BP) and pulse measurements. The same method for measuring the body temperature should be used throughout the study. Systolic and diastolic blood pressure will be measured (pre- and post-dose) after the participant has been sitting for five minutes, with back supported and both feet placed on the floor, three times at 3-minute intervals using an automated validated device, e.g., OMRON, with an appropriately sized arm cuff. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. The mean of the three measurements will be used for evaluations and entered in the eCRF. If the blood pressure is out-of-range at Screening 1 or 2 or on Day 1, three additional readings can be obtained after approximately 30 minutes, in the manner described above. The mean of the last three readings must be within the ranges provided in the eligibility criteria in order for the patient to qualify. Pulse rate will be measured (pre- and post-dose) by palpation of radial pulse during 60 seconds after each measurement of blood pressure. The mean of the three measurements will be registered in the eCRF. If radial pulse cannot be measured, femoral pulse can be used. In case of repeated blood pressure assessments, the mean value from both set of measurements (initial and repeat) should be entered in the eCRF.
Height and weight	Height in centimeters (cm) (Screening 1) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured as per assessment schedule. At screening 1 body mass index (BMI) will be calculated to one decimal using the following formula: BMI = Body weight (kg) / [Height (m)]^2

8.4.1 Laboratory evaluations

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

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

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

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

Urinalysis

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

Special clinical laboratory evaluations

All abnormal laboratory results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met (see Section 10.1). For laboratory related adverse events, follow-up evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant.

Table 8-3 Laboratory evaluations

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Erythrocytes, Erythrocytes Mean Corpuscular Hemoglobin, Erythrocytes Mean Corpuscular Hemoglobin Concentration, Erythrocytes Mean Corpuscular Volume, Platelets, Leukocytes, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Chemistry	Clinical chemistry: Albumin, Bicarbonate, BUN (Urea Nitrogen/Urea), Calcium, Chloride, Creatinine, Creatine kinase, Cystatine C, Potassium, Sodium, Total Protein, Uric Acid, Liver function tests: Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Total Bilirubin (if Total Bilirubin is above 1.5 times the upper limit of normal, direct and indirect reacting Bilirubin should be performed). Lipids and glucose: Total Cholesterol, HDL, LDL, Triglycerides, Glucose, HbA1c.

Test Category	Test Name
CCI [redacted]	CCI [redacted]
Urinalysis	Microscopic Panel (Erythrocytes, Leukocytes, Casts, Crystals, Bacteria, Epithelial cells). Macroscopic Panel (Dipstick) (Color, Bilirubin, Occult Blood, Macroscopic Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen). Chemistry Panel (protein, creatinine, protein-creatinine ratio).
Coagulation	Prothrombin time (PT), International Normalized Ratio (INR)
Hepatitis markers	HbsAg, HbsAb, HbcAb, HCVAb HBV-DNA and HCV RNA, as per Section 8.1.1.2
Pregnancy Test	Serum / Urine pregnancy test, see Section 8.4.3

8.4.2 Electrocardiogram (ECG)

Single 12-lead ECG at Screening 1, and triplicate 12-lead ECGs from Day 1 onwards, will be performed as outlined in the assessment schedule (Table 8-1), and will undergo central reading.

Full details of all procedures relating to the ECG collection and reporting are contained in the technical manual provided to the site by the ECG vendor.

ECGs must be recorded after at least 10 minutes rest in the supine position to ensure a stable baseline. Psychological stimuli with effect on autonomic nerve tone should be kept to a minimum. This includes watching television, using the cell phone, or listening to music before and during the ECG collection.

Participants must refrain from smoking, consuming alcohol, methylxanthine-containing beverages, citrus-containing fruits or beverages, and tonic water in the 4 hours prior to the ECG collection.

The preferred sequence of cardiovascular data collection during study visits is (pre-dose) ECG collection first, followed by vital signs, blood sampling, and any remaining assessments for that visit (refer to flow diagram below).

Figure 8-1 Timing of study procedures

Triplicate 12-lead ECGs are to be recorded 2 minutes apart.

The Fridericia QT correction formula (QTcF) must be used for clinical decisions. The mean QTcF value for each visit will be calculated from the triplicate ECGs for each participant. PR interval, QRS duration, heart rate, RR, QT, QTcF (Fridericia QT) will be collected. Clinically significant abnormalities must be reported as AE in the CRF.

Clinically significant ECG findings at baseline must be discussed with the sponsor before administration of study treatment.

In order to enable ECG evaluation by the central ECG laboratory for eligibility assessment, ECGs should be submitted to the central ECG laboratory prior to the planned randomization date, within the timeframe detailed in the technical manual provided by the central ECG laboratory. In the event that a QTcF value of > 450 ms (males) or > 460 ms (females) is observed or if an unscheduled ECG is performed for safety reasons, it is recommended to collect a time-matched PK sample and record the time and date of the last study drug intake to determine the drug exposure.

In the event that a clinically significant ECG abnormality is identified at the site (e.g., severe arrhythmia, conduction abnormality of QTcF ≥ 450 ms or < 300 ms and/or an increase > 60 ms, a copy of the assessment is sent to the central ECG laboratory for expedited review and the ECG is repeated to confirm the diagnosis. If the participant is hemodynamically compromised, the investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example cardioversion).

All ECGs, including unscheduled safety ECGs with clinically relevant findings collected during the study needs to be transmitted to the central ECG laboratory for review.

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

8.4.3 CCI

CCI

8.4.4 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing.

Central serum pregnancy testing is required at Screening 1, Screening 2, and at EOS. Local urine pregnancy tests will be performed at all other visits except Screening 3 (phone call) and Day 5, and if applicable, before administration of the study treatment. A positive local urine

test needs to be confirmed with central serum test. If positive, the participant will be discontinued from study treatment.

Local pregnancy test and associated results will be collected on the eCRF.

Assessments of fertility

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

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

In the absence of the above medical documentation, FSH testing is required of any female participant regardless of reported reproductive/menopausal status at Screening.

8.4.5 Appropriateness of safety measurements

Cardiovascular effects (blood pressure increases, ECG changes and correlated histological cardiac lesions) were reported in cynomolgus monkeys in published studies (Larkin et al 2014, Larkin et al 2015) of an ADAMTS-5 targeting monoclonal antibody (GSK2394002). This finding was not observed for QUC398, neither in pre-clinical investigations (4-week, 13-week and 39-week repeat-dose studies in cynomolgus monkeys), nor in clinical investigations (SAD and MAD phase 1 studies).

In order to fully evaluate the cardiovascular safety of QUC398 and to rule out a possible class effect, ECGs will be performed predose, at Cmax and at steady state, as well as throughout the study.

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

8.5 Additional assessments

8.5.1 CCI [redacted]

8.5.1.1 CCI [redacted]

CCI [redacted]

8.5.1.2 CCI [redacted]

CCI [redacted]

CCI

8.5.1.2.1 CCI

CCI

8.5.1.2.2 CCI

CCI

8.5.1.2.3 CCI

CCI

8.5.1.2.4 CCI

CCI

8.5.2 CCI

CCI

8.5.3 CCI

- CCI

CCI

CCI

8.5.3.1 Use of residual biological samples

Residual serum, plasma and urine samples may be used for another protocol specified endpoint.

Any residual samples remaining after the protocol-defined analysis has been performed may be used for additional exploratory analysis related to the purpose of this study. CCI Given the exploratory nature of the work, the analytical method used for those assessments will not be validated. As such, the results from this exploratory analysis will not be included in the clinical study report.

8.5.4 Imaging

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

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

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

8.5.5 CCI

9 Discontinuation and completion

9.1 Discontinuation from study treatment and from study

9.1.1 Discontinuation from study treatment

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

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

Discontinuation from study treatment is required under the following circumstances:

- Participant decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the Prohibited medication section (see Section 6.2.2)
- Any situation in which continued study participation might result in a safety risk to the participant
- Following emergency unblinding
- Emergence of the following adverse events:
  - A life-threatening adverse event (corresponding to NCI-CTCAE grade 4 or higher) considered at least possibly related to QUC398 treatment
  - An AE of severe intensity (corresponding to NCI-CTCAE grade 3 or higher) considered at least possibly related to QUC398 treatment
  - Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the participant's overall status, prevents the participant from continuing participation in the study
  - If a liver or renal event occurs, follow guidelines outlined in Section 16.2 and Section 16.3 regarding discontinuation of study treatment

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

Participants who discontinue from study treatment agree to return for the EOT and follow-up visits indicated in the assessment schedule (refer to Section 8).

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

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

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

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

9.1.2 Discontinuation from study

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

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

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent/oppose to the use of their data/biological samples, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g., dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed.

9.2 Withdrawal of informed consent/Opposition to use data/biological samples

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

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

and

- No longer wishes to receive study treatment

and

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

This request should be in writing (depending on local regulations) and recorded in the source documentation.

In this situation, the investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw their consent/opposition to use data/biological samples and record this information.

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

Study treatment must be discontinued, and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

If the participant agrees, a final evaluation at the time of the participant's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table (refer to Section 8).

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

9.3 Study stopping rules

Overall study stopping rules

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

- Any death or life-threatening event (corresponding to NCI-CTCAE grade 4 or higher) considered to at least possibly related to QUC398 treatment
- Two (2) or more SAEs of a similar type (other than death or life-threatening event, corresponding to (NCI-CTCAE grade 3 or higher) considered to at least possibly related to QUC398 treatment
- An acute allergic reaction of grade 3 severity or greater, or if one (1) or more participants develop a life-threatening (grade 4) or fatal acute allergic reaction according to the NCI-CTCAE, within 24 hours following QUC398 administration (i.e., active drug), unless clearly caused by exposure to a known allergen (e.g., peanut allergy).
- Two (2) or more participants are discontinued due to a liver event as defined in Section 16.2
- Two (2) or more participants are discontinued due to a renal event as defined in Section 16.3
- Number and/or severity of AEs, abnormal safety monitoring tests, or abnormal laboratory findings justify putting the study on hold

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

9.4 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their End of Study visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

No further study treatment will be made available to the participants after study completion.

9.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination can be:

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of investigational drug development

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a participant who discontinued from study treatment: instructions for contacting the participant, when the participant should stop taking drug, when the participant should come in for a final visit, will be provided at that time. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

10 Safety monitoring, reporting and committees

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

For medical devices, an adverse event (AE) is any untoward medical, unintended disease or injury or untoward clinical signs, including an abnormal laboratory finding, in participants, users or other persons, in the context of a clinical investigation, whether or not related to the device.

The Investigator and any qualified designees are responsible for managing the safety of individual participants. They are also responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and for following up all AEs and SAEs. Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments (Patient-Reported Outcomes are considered as other assessments to detect adverse events, see Section 8.3.1).

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The Common Toxicity Criteria (CTC)

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

2. The causality

   The investigator is obligated to assess the relationship to any treatment used in the study (two different study treatments, and two AxMPs) and each occurrence of each AE.
   The investigator will use clinical judgment to determine the relationship. A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
   Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

   For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.

   The causality assessment is one of the criteria used when determining regulatory reporting requirements.
3. Its duration (start and end dates or ongoing) and the outcome must be reported.
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met.
5. Action taken regarding with study treatment.

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

   - Dose not changed
   - Drug interrupted/permanently discontinued
6. Its outcome (i.e., recovery status or whether it was fatal)

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

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

Adverse event monitoring should be continued for at least 60 days following the last dose of study treatment or end of study visit, whichever is longer. The end of study visit for early discontinuation is defined in Section 8.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g., continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions can be found in the Investigator's Brochure (IB) for the investigational drug, or in the product information for marketed products.

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

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

Reporting of AEs related to AxMP(s)

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

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

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

AxMP safety reporting requirements will only apply once the trial has been transitioned under EU Clinical Trial Regulation 536/2014.

10.1.2 Serious adverse events

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

- fatal
- life-threatening

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

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the participant's general condition
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g., defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might

require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met

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

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

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

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and for at least 60 days following the last dose of study treatment or end of study visit, whichever is longer must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: if more stringent, local regulations regarding reporting timelines prevail). The end of study visit for early discontinuation is defined in Section 8. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded on the electronic Serious Adverse Event Report Form (with paper backup, if needed); all applicable sections of the form must be completed in order to provide a clinically thorough report.

Screen Failures: SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.

Randomized Participants: SAEs collected between time participant signs ICF until at least 60 days following the end of study visit, whichever is longer. The end of study visit for early discontinuation is defined in Section 8.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the investigator receiving the follow-up information (Note: if more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Any SAEs experienced after the 60 day-period following the last study visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

Reporting of SAEs related to AxMP(s)

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

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

Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with national regulatory requirements in participating countries, including EU Clinical Trial Regulation 536/2014.

10.1.4 Pregnancy reporting

Pregnancies

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

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

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

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

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

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

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

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Table 16-1 in Appendix 2 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-2 and

Table 16-3. Repeat liver chemistry tests (i.e., ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the study drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include, based on investigator's discretion:
  - serology tests, imaging and pathology assessments, hepatologist's consultancy
  - obtaining a more detailed history of symptoms and prior or concurrent diseases
  - obtaining a history of concomitant drug use, alcohol use, recreational drug use, and special diets
  - exclusion of underlying liver disease, as specified in Table 16-2 and Table 16-3
  - imaging such as abdominal US, CT or MRI, as appropriate
  - obtaining a history of exposure to environmental chemical agents
  - considering gastroenterology or hepatology consultations

All follow-up information and procedures performed must be recorded as appropriate in the CRF.

10.2.2 Renal safety monitoring

Once a participant is exposed to study treatment, the following two categories of abnormal renal laboratory alert values should be assessed during the study period:

- Serum creatinine increase or eGRF ≥ 25% compared to baseline during normal hydration status
- Any one of the following:
  - Urine protein-creatinine ratio ≥1g/g or ≥100 mg/mmol, OR
  - New onset dipstick proteinuria ≥ 2+, OR
  - New onset dipstick hematuria ≥ 3+ (after excluding menstruation, UTI, extreme exercise, or trauma)

Abnormal renal event findings must be confirmed within 48 hours after the first assessment (when results become available).

Every renal laboratory trigger or renal event as defined in Section 16.3 should be followed up by the investigator or designated personnel at the trial site as summarized in Section 16.3.

10.3 Committees

Not applicable.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

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

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

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

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

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e., eSource DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

The primary analysis will be conducted after all participants have completed Week 12 or discontinued treatment prior to Week 12. The final analysis will be conducted on all participants' data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The 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.

12.2 Participant demographics and other baseline characteristics

All data for background and demographic variables 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.

12.3 Treatments

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

The duration of exposure in days to QUC398 will be summarized by means of descriptive statistics using the safety set.

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

12.4 Analysis supporting primary objectives

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.

12.4.1 Definition of primary endpoint(s)

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

12.4.2 Statistical model, hypothesis, 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] A two sided 90%

confidence interval for the treatment effect (i.e., QUC398 minus placebo) at Week 12 will be reported.

12.4.3 Handling of intercurrent events of primary estimand

As described in Section 2.1, handling of ICEs will follow a hypothetical strategy. Data collected post-ICE 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 group who continue their randomized treatment). In case of an unexpectedly high number of discontinuations (in particular due to a similar reason) from the study treatment are observed, the assumptions underlying the strategy considered might be revised and modified as appropriate. Potential changes would be detailed in the SAP.

12.4.4 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.

12.4.5 Sensitivity analyses

The robustness of conclusions from the primary analysis to the assumptions that missing data arise from, and MAR mechanism may be stress-tested via a delta adjustment tipping-point analysis, and/or performing sensitivity analysis considering a jump-to-reference imputation.

12.4.6 Supplementary analysis

The average amount of concomitant and rescue medications will be presented by treatment group. In case a substantial difference between treatment groups is observed on average amount of concomitant and/or rescue medications, its inclusion as a covariate may be considered in the MMRM. Other approaches may be also explored.

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. The same MMRM model as for the primary estimation will be adopted.

12.5 Analysis supporting secondary objectives

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

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 an 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 fixed covariate, treatment, time-point, treatment by time-points as fixed effects and participant as random effect. 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 facilitate analysis. The model will include baseline as fixed covariate, treatment, time-point, treatment by time-points as fixed effects and participant as random effect. A two sided 90% confidence interval for the treatment effect (i.e., QUC398 minus placebo) will be reported.

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).

12.5.2 Safety endpoints

For all safety analyses, the Safety 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 with the exception of 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 adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

Adverse events

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

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

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

Vital signs

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

12-lead ECG

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

Clinical laboratory evaluations

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

12.5.3 Patient reported outcomes

Please see Section 12.5.1 for details.

12.6 CCI

12.6.2 Other efficacy assessments

12.6.3 CCI

12.6.4 CCI

CCI

12.6.5 CCI

CCI

12.7 Interim analyses

The analysis of the primary endpoint will be performed after all participants have completed Week 12, or have discontinued prior to 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).

A final analysis will be performed after all participants have completed Week 60 (or discontinued prior to Week 60). Formal testing of the primary endpoint with full level alpha will be performed at the primary analysis time point.

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.

Unblinded interim analysis results will be reviewed by the clinical team.

The clinical team may communicate interim results (e.g., evaluation of PoC criteria or 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. This would typically require investigator input to abstract preparation. Every attempt will be made to assure that the investigator will not have access to individual participants' data, but rather will review aggregate, summary data.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

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 approximatively 98.

CCI [redacted]

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable ICH Tripartite Guidelines for Good Clinical Practice (GCP)
- Applicable local regulations (including European Directive 2001/20/EC or European Clinical Trial Regulation 536/2014, US CFR 21)

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated at that specific site.

Any amendments to the protocol will require IRB/IEC and Health Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is

requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.2.1 Data protection

Participants will be assigned a unique identifier by Novartis. Any participant records or datasets that are transferred to Novartis will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by Novartis in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Novartis, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Novartis has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws.

13.2.2 Data quality assurance

Monitoring strategy, methods, responsibilities, and requirements, are provided in the monitoring plan, contracts. Details may include definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring).

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

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT or Clinical Trials Information System (CTIS) public website. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g., Clinicaltrials.gov, EudraCT, CTIS public website, etc.).

Summary results of primary and secondary endpoints will be disclosed based upon the global Last Participant Last Visit (LPLV) date, since multinational studies are locked and reported based upon the global LPLV.

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

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

13.4 Quality Control and Quality Assurance

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

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

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

13.5 Participant Engagement

The following participant engagement initiatives are included in this study and will be provided, as available, for distribution to study participants at the time-points indicated. If compliance is impacted by cultural norms or local laws and regulations, sites may discuss modifications to these requirements with Novartis.

- Thank You letter
- Plain language trial summary - after CSR publication

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case-by-case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

Please refer to the Laboratory Manual for details.

16.2 Appendix 2: Liver event and laboratory trigger definitions & follow-up requirements

Abnormal liver chemistry and a liver event as per table below must be followed up by repeat testing within 48 to 72 hours of ALT, AST, ALP, GGT, total bilirubin (direct and indirect if total bilirubin is increased > 2 x ULN), INR, albumin, CK and GLDH.

Table 16-1 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity
If ALT or AST abnormal at baseline:	• ALT or AST > 3 x baseline or > 200 U/L (whichever occurs first)

Table 16-2 Follow up requirements for liver laboratory triggers - ALT, AST, TBL

	ALT	**TBL**	**Liver Symptoms**	**Action**
ALT increase without bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	• **No change to study treatment** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH within 48-72 hours. • Follow-up for symptoms.
	If elevated at baseline: ALT > 3 x baseline or > 200 U/L (whichever occurs first)			

	ALT	TBL	Liver Symptoms	Action
	If normal at baseline: ALT > 5 x ULN for more than two weeks OR ALT > 8 x ULN	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	• **Interrupt study drug** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH within 48-72 hours. • Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies. • Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
	If elevated at baseline: ALT > 3 x baseline AND 5 x ULN for more than two weeks OR ALT ≥ 5 x baseline AND ≥ 8 x ULN			
ALT increase with bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN	TBL > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
	If elevated at baseline: ALT > 2 x baseline AND > 3 x ULN			
	If normal at baseline: ALT > 3 x ULN	Normal or elevated*	Severe fatigue, nausea, vomiting, right upper quadrant pain*	
	If elevated at baseline: ALT > 2 x baseline AND > 3 x ULN			

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

Table 16-3 Follow up requirements for liver laboratory triggers - Isolated Hyperbilirubinemia

Criteria	Actions required	Follow-up monitoring
Total Bilirubin (isolated)		
>1.5 – 3.0 ULN	• Maintain treatment • Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	• Interrupt treatment • Repeat LFT within 48-72 hours • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	• Discontinue the study treatment immediately • Hospitalize the participant • Establish causality • Record the AE and contributing factors (e.g., concomitant medications, medical history, laboratory and imaging investigations) in the appropriate CRF	Monitor LFTs until resolution to ≤ Grade 1 or to baseline (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab)in the appropriate CRF	Investigator discretion

Based on investigator's discretion, investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

16.3 Appendix 3: Specific Renal Alert Criteria and Actions and Event Follow-up

Renal Event	Actions
eGFR decrease 25 – 49%	• Consider causes and possible interventions • Repeat laboratory values within 48 hrs of receipt of abnormal test results. Assess patient for signs and symptoms of illness, AKI, etc.
eGFR decrease ≥ 50 % * OR if <18 years old, eGFR < 35 mL/min/1.73 m^2	• Consider causes and possible interventions • Repeat laboratory values within 48 hrs of receipt of abnormal test results. Assess patient for signs and symptoms of illness, AKI, etc. • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider referral to nephrologist for diagnosis and management • Consider patient hospitalization and specialized treatment
New onset dipstick proteinuria ≥3+ OR Protein-creatinine **ratio** ≥1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)	• Repeat assessment to confirm • Confirm presence of true proteinuria by quantification: protein:creatinine on first morning void • Assess serum albumin & serum total protein • Consider causes and possible interventions • Consider referral to nephrologist • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria ≥3+ on urine dipstick	• Assess & document • Obtain urine microscopy to distinguish hemoglobinuria or myoglobinuria from hematuria • Assess sCr • Exclude infection, trauma, calculi, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder