

Novartis Research and Development

Clinical Trial Protocol Title:

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

Clinical Trial Protocol Number: CRHH646A12201 / NCT05816395

Version Number: v02 (Clean)

Compound: RHH646

Brief Title: Safety and efficacy of RHH646 for knee osteoarthritis

Study Phase: IIa

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

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Amendment 02 (28-Nov-2023)

Amendment rationale

The protocol was amended to combine updates that were made based on requests received from the U.S. Food and Drug Administration as well as requests for information received from the participating European member states previously documented in local protocol amendments v01-US.01 and v01-EEA.01, respectively. The opportunity was also taken to revise inclusion criterion 7 from joint space width to joint space narrowing and to clarify and correct discrepancies and inconsistencies within the protocol.

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Changes to the protocol

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IRBs/IECs

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

The changes described in this amended protocol require IRB/IEC approval 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 (06-Jan-2023)

Amendment rationale

The primary purpose of this global protocol amendment is to update the number of adverse events reported in study CRHH646A02101. The opportunity was also taken to clarify and correct discrepancies and inconsistencies within the protocol.

Protocol Amendment v01 has been issued before any regulatory submission. The inconsistencies in Original Protocol v00 were noted before the protocol was submitted to any Institutional Review Boards (IRBs)/Independent Ethic Committees (IECs) and Health Authorities.

Changes to the protocol

CCI

1 Protocol summary

1.1 Summary

Protocol Title:

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

Brief Title:

Safety and efficacy of RHH646 for knee osteoarthritis

Purpose

Study CRHH646A12201 is a phase 2a proof-of-concept (POC) study to evaluate the articular cartilage-regenerating capacity of RHH646 in the knee as well as to assess safety and tolerability in patients with knee osteoarthritis (OA) following 1 year of treatment. While the benefits of RHH646 on cartilage regeneration have been demonstrated in pre-clinical studies, this will be the first clinical test of the potential therapeutic effect of RHH646 in patients with knee OA.

Study Indication /Medical Condition:

Knee osteoarthritis

Treatment type

Drug

Study type

Interventional

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To evaluate the articular cartilage-regenerating capacity of RHH646 in the knee following 1 year of treatment	Change from baseline in cartilage volume in the index region of the target knee by MRI at Week 52
To evaluate the safety and tolerability of RHH646 following 1 year of treatment	Adverse Events (AEs) Electrocardiograms (ECGs) Vital signs Hematology, blood chemistry, urinalysis
Secondary	
To evaluate the pharmacokinetics of RHH646 in patients with knee OA	RHH646 plasma concentrations, C _{min,ss} at Week 4, and any other PK parameter as appropriate

Trial Design:

This is a non-confirmatory, randomized, investigator and participant blinded, two-arm, placebo-controlled, phase 2a study to assess safety, tolerability, and efficacy of orally administered RHH646 in male and female adult patients with symptomatic, mild to moderate radiographic knee OA (Kellgren and Lawrence (K&L) grade 2 to 3) in the target knee and with pain requiring analgesic therapy (e.g., n-acetyl-para-aminophenol (APAP) or non-steroidal anti-inflammatory drugs (NSAIDs)). Approximately 78 participants will be enrolled and randomized in the trial and treated for 52 weeks.

Brief Summary:

The purpose of this study is to evaluate the articular cartilage-regenerating capacity of RHH646 in the knee as well as to assess safety and tolerability in participants with knee OA.

- The total study duration for an individual participant will be up to 62 weeks.
- The treatment duration will be up to 52 weeks.
- The on-site visit frequency will be approximately monthly until Week 26 and then quarterly thereafter until Week 52 (End of treatment (EOT)). Phone visits will be scheduled monthly between the quarterly on-site visits.

Treatment of interest

Participants will be treated with either the orally administered RHH646 or the matching placebo treatment for 52 weeks.

Number of Participants:

Approximately 78 male and female participants 35 to 75 years old will be enrolled and randomized in the trial and treated for 52 weeks.

Key Inclusion criteria

- Participant is ≥ 35 and ≤ 75 years old, at time of screening
- Participants must weigh at least 50 kg to participate in the study and must have a body mass index (BMI) ≤ 35 kg/m². BMI = Body weight (kg) / [Height (m)]²
- Diagnosis of tibiofemoral OA in at least one knee by standard American College of Rheumatology clinical and radiographic criteria ([Altman et al 1986](#)) at screening
- K&L grade 2 to 3 OA in the target knee evaluated with X-Ray by the Central Reader at screening.
- Predominantly medial tibiofemoral compartment involvement defined as medial Joint Space Narrowing (medJSN) 1-2 ([Altman et al 1995](#); [Altman, Gold 2007](#)) and medJSN > lateral Joint Space Narrowing (latJSN) in the target knee evaluated with X-Ray by the Central Reader at screening
- Symptomatic disease, defined as having pain in the target knee at least 3 days per week during the last 3 months from screening that is relieved by analgesic therapy (e.g., APAP

or NSAIDs), according to the investigator's evaluation and judgment of the patient's history

Key Exclusion criteria

- 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 at least CCI [REDACTED] after stopping study treatment. In EEA countries, women of child-bearing potential will be excluded from participation in this trial, irrespective of the use of highly effective methods of contraception
- Arthroscopy of the target knee within the 6 months prior to screening or planned arthroscopy during the study
- Previous surgical treatment of the target knee using mosaicplasty, microfracture, meniscectomy >50% or osteotomy; planned surgery for either knee during the study
- Unstable target knee joint (including, but not limited to, post-traumatic or congenital laxity) or insufficiently reconstructed ligaments based on medical history and/or physical examination by the investigator
- Participant has severe malalignment (valgus or varus deformity) in the target knee >7.5° based on X-ray evaluation by the Central Reader at screening.
- K&L grade 4 OA in either knee
- Presence of severe hip OA that either (i) alters lower limb function to a degree that increases or abnormally changes the mechanical forces in the knee while walking, according to investigator's evaluation, or (ii) currently requires or is likely to require specific medical or surgical management during the study period
- Other pathologies affecting the knee, including subchondral insufficiency fractures, bone fracture (acute or subacute within the 6 months prior to screening) or bone bruise, osteonecrosis, malignant bone marrow infiltration, solid tumors, and/or patellofemoral dysplasia based on clinical assessment, or imaging
- Known autoimmune disease with inflammatory arthritis (including but not limited to rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus), crystal-induced arthritides (gout or pseudogout arthritis), active acute or chronic infection of the knee joint, Lyme disease involving the knee, reactive arthritis, systemic cartilage disorders, moderate to severe fibromyalgia, a known systemic connective tissue disease or a widespread pain index >4.
- Inability to undergo MRI (e.g., claustrophobia, body size, leg not fitting in the coil) or contraindications to MRI (e.g., non MRI-compatible metallic implants, metallic foreign bodies, pacemaker, defibrillator)

Treatment Groups:

The study comprises a screening period (up to 6 weeks), a treatment period (CCI [REDACTED]) and a follow up period (CCI [REDACTED]) post last administration of study treatment before the End of Study (EOS) visit. The total duration for each participant will be up to 62 weeks.

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

- RHH646 ^{CCI} mg ^{CCI}
- Matching placebo

In the event that any study participant appears to be not tolerating the study treatment, the investigator will have the discretion to reduce the dose to give the study participant a chance to remain on study treatment.

Data Monitoring/Other Committee:

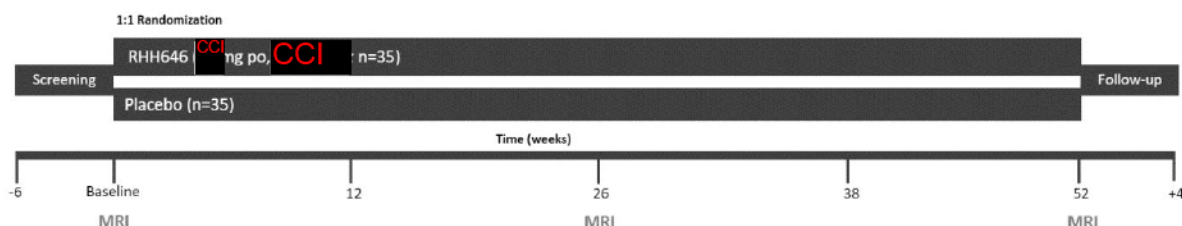
A Data Monitoring Committee (DMC) is not planned for this study

Key words

Tibiofemoral OA, K&L grade 2 to 3 OA in the target knee, Oral RHH646 treatment

1.2 Schema

Figure 1-1 Study design



1.3 Schedule of activities (SoA)

The SoA lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation. 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.

Participants should be seen for all visits/assessments as outlined in the SoA or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Participants who discontinue from study treatment are to complete the EOT visit as soon as possible and attend the follow-up visits as indicated in the SoA.

Participants who discontinue from study should also be scheduled for a final evaluation visit if they agree, as soon as possible, at which time all of the assessments listed for the EOS visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the AEs and concomitant medications not previously reported must be recorded on the Case Report Form (CRF).

Patient reported outcome (PRO) measure(s) must be completed before any assessments are performed at any given visit.

As per [Section 4.5](#), during a public health emergency as declared by local or regional authorities i.e., pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowable by a local health authority, national and local regulations and depending on operational capabilities, phone calls, virtual contacts (e.g., tele consultation) or visits by site staff/ off-site healthcare professional(s) staff to the participant's home, can replace certain protocol assessments, for the duration of the disruption until it is safe for the participant to visit the site again. If the investigator delegates tasks to an off-site healthcare professional, the investigator must ensure the individual(s) is/are qualified and appropriately trained to perform assigned duties. The investigator must oversee their conduct and remain responsible for the evaluation of the data collected.

Table 1-1 Assessment Schedule

Period	Screening	Treatment														Follow-Up	
Visit Name	CCI																
Visit Numbers ¹																	
Days																	
Time (post-dose)																	
Informed consent	X																
Genetic consent ²	X																
Inclusion / Exclusion criteria	X	X															
Demography	X																
Medical history/current medical conditions	X	X															
Smoking/nicotine use history	X																
Concomitant medications	X																
Assessments of fertility	S																
Serum pregnancy test	X	X		X	X	X	X	X	X			X			X	X	
Urine pregnancy test kit dispensation to women of childbearing potential for home testing									S			S					

Period	Screening	Treatment														Follow-Up
Visit Name	CCI															
Visit Numbers ¹																
Days																
Time (post-dose)																
Reporting of urine pregnancy test performed at home										S	S		S	S		
Alcohol Test and Drug Screen	S															
HIV screen	S															
Hepatitis screen	S															
Complete physical examination	S					S			S			S			S	S
Short physical examination		S		S	S		S	S								
Testicular ultrasound ³		X													X	
WPI	X															
Body Height	X															
Body Weight	X	X				X			X			X			X	X
Body Temperature	X	X		X	X	X	X	X	X			X			X	X
Vital Signs	X	X	X	X	X	X	X	X	X			X			X	X
Electrocardiogram (ECG)	X	X		X					X						X	X
Hematology	X	X		X		X			X			X			X	X
Clinical Chemistry	X	X ⁴		X		X			X ⁴			X			X	X ⁴
Urinalysis	X	X		X		X			X			X			X	X

Period	Screening		Treatment												Follow-Up	
Visit Name	CCI															
Visit Numbers ¹																
Days																
Time (post-dose)																
Coagulation Panel	X	X		X		X			X			X			X	X
	CCI															
Thyroid	X	X				X			X			X			X	X
	CCI															
	CCI															
	CCI															
X-ray	X														X	
3T MRI ³		X							X						X	
Randomization		X														
Drug dispensation			X	X	X	X	X	X	X			X				
Study drug administration at study site		X		X												
Participant diary (study treatment) ⁵				X	X	X	X	X	X			X			X	
	CCI															
	CCI															
	CCI															
PK blood collection ⁹		X	X	X	X	X	X	X	X			X			X	X

Period	Screening	Treatment												Follow-Up	
Visit Name	CCI														
Visit Numbers ¹															
Days															
Time (post-dose)															
	CCI														
	CCI														
	CCI														
Adverse Events	X														
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 Visit structure given for internal programming purpose only

² CCI

³ The baseline assessment can be performed up to two weeks before Day 1, during the screening period, after confirmation of clinical, laboratory and X-ray eligibility criteria are met. Assessments for Week 26 and Week 52 may be performed up to 2 weeks before Day 283 and up to 2 weeks before Day 365, respectively.

⁴ Assessment of fasting glucose required

⁵ Date and time of the CCI doses of study medication prior to each visit where PK samples are collected will be captured by the participant in a diary.

⁶ CCI

⁷ CCI

⁸ CCI

⁹ At the Baseline visit samples will be collected pre-dose and 4 hours post dose. At the Week 4 visit, a pre-dose PK sample will be collected to determine C_{min,ss}. At subsequent visits, PK samples will be collected at any time point in relation to administration of study drug.

¹⁰ Phone visits

2 Introduction

Osteoarthritis (OA) is the most prevalent form of arthritis and a leading cause of pain and disability. Symptomatic OA affects over 500 million people globally, affecting 1 in 5 people >45 years of age with an incidence that increases with age (Long et al 2022). Due to increases in life expectancy and the prevalence of obesity, knee OA is now the third most rapidly rising condition associated with disability.

Current pharmacologic treatments (e.g., anti-inflammatories, analgesics) offer only symptomatic relief and do not modify or otherwise impact the course of the disease. The only disease-modifying therapy available for OA is arthroplasty (joint replacement), which is used for end-stage disease and is not an option for all types of OA. Therefore, the need for disease-modifying medical treatment options is unmet.

RHH646 is an orally bioavailable small molecule being developed as a novel cartilage regenerating therapy with possible systemic anti-inflammatory and metabolic benefits. Its expected primary effect on repairing and regenerating damaged and lost cartilage has the potential to reverse the course of disease and effectively cure it in some patients. Systemic administration of RHH646 may provide broader clinical utility for the treatment of OA, including patients with multiple joint involvement or those with disease in joints not amenable to local, injectable therapies.

RHH646 has been safely administered CCI [REDACTED]
[REDACTED] No dose-limiting or dose-dependent adverse effects or differences from placebo were apparent. The current study (Study CRHH646A12201) aims to evaluate RHH646 treatment in patients with a diagnosis of tibiofemoral OA.

A more detailed review of the available pre-clinical and clinical information on RHH646 can be found in the Investigator's Brochure (IB).

2.1 Study rationale

Study CRHH646A12201 is a phase 2a POC study to evaluate the articular cartilage-regenerating capacity of RHH646 in the knee as well as to assess safety and tolerability in patients with knee OA following 1 year of treatment. While the benefits of RHH646 on cartilage regeneration have been demonstrated in pre-clinical studies, this study is the first clinical test of the potential therapeutic effect of RHH646 in patients with knee OA.

2.2 Background

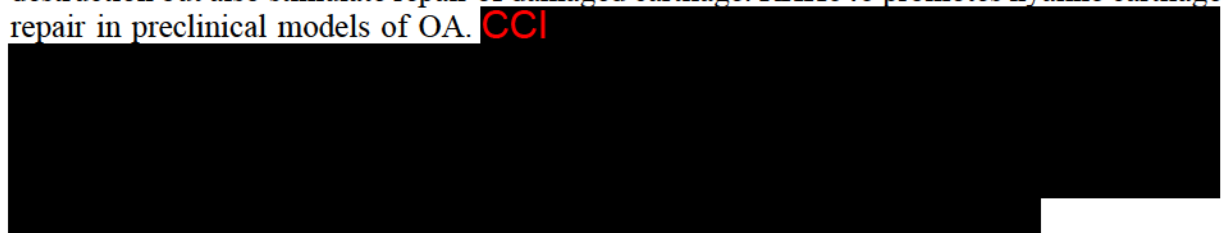
OA affects more than 500 million patients globally with increasing incidence and prevalence (Long et al 2022). The prevalence of OA has increased approximately 113% since 1990 (Long et al 2022). The knees, hands, hips, feet, and spine are most commonly affected. The prevalence of OA is progressively rising in part due to an increase in life expectancy, along with more prevalent predisposing risk factors such as obesity and related metabolic disease. Pain and loss of function due to OA are accompanied by an increased risk of additional comorbidities such as type 2 diabetes and cardiovascular disease (Fernandes, Valdes 2015). The hallmark of OA is joint pain and progressive degradation of articular cartilage, synovitis,

and alterations in subchondral bone and periarticular tissues which ultimately lead to loss of function (Goldring, Otero 2011). Over one million total knee replacements are performed annually in the US alone and are expected to double every decade (Singh et al 2019).


The mainstay of treatment for patients with OA includes non-pharmacological and pharmacological measures to reduce pain (analgesic medication) and improve knee and lower-extremity function (physiotherapy, lifestyle changes, and weight loss) (Kolasinski et al 2020). Current pharmacological treatments are directed only at symptoms with no impact on structure or other modification of disease progression. Therefore, the medical need for non-surgical disease modification of OA remains unmet. Despite major efforts spanning several decades, there are no approved disease-modifying pharmacotherapies for OA.

Clinical demonstration that chondroprotection (i.e., an effect short of cartilage regeneration) can relieve pain may not be possible (Bacon et al 2020). The lack of correlation between the symptoms and structural signs of OA makes the clinical development of novel disease-modifying therapies for OA particularly challenging. A recent approach is the regeneration of hyaline cartilage which involves novel mechanisms and both intra-articular and systemic therapy. The challenge of linking cartilage regeneration to improvements in how the patient feels and functions is similar to that for chondroprotective therapies. While proof of concept for therapeutic cartilage regeneration has been shown (Eckstein et al 2021; Gerwin et al 2022), the clinical findings suggest that symptomatic improvements related to cartilage regeneration (i.e., the patient feeling and functioning better) may take time (Eckstein et al 2021).

Chondrogenic progenitor cells have been identified in human adult cartilage. These cells exhibit stem cell characteristics such as clonogenicity, multipotency, and migratory activity suggesting that, under the proper conditions, cartilage may have intrinsic regenerative capacity (Alsalemeh et al 2004; Koelling et al 2009). Molecules activating the tissue regenerative potential of chondrocyte progenitors thus have the potential to not only prevent cartilage destruction but also stimulate repair of damaged cartilage. RHH646 promotes hyaline cartilage repair in preclinical models of OA. CCI



RHH646 is not genotoxic or phototoxic. It has shown no acute cardiovascular, respiratory, or central nervous system effects in in vivo safety pharmacology studies. The longer term safety of RHH646 has also been investigated in repeat dose in vivo studies of up to 26 weeks duration in rats and 39 weeks duration in dogs. CCI



The most commonly reported adverse events (AEs) in healthy adults were headache (n=5) and COVID-19/SARS-CoV-2 infection (n=3), both of which occurred in the RHH646 and placebo groups. There were no treatment-related changes in vital signs, laboratory tests, or

electrocardiograms after two weeks of dosing. Overall, the available non-clinical and clinical safety data along with the unique combination of potential cartilage-regenerating and anti-inflammatory effects of RHH646 support clinical investigation of RHH646 in patients with OA.

2.3 Benefit/Risk assessment

This study is the first time that RHH646 will be administered to patients with knee OA. Therefore, this study is the first test of the efficacy of RHH646 in humans.

CCI [REDACTED]

[REDACTED] An orally administered therapy also broadens the potential clinical utility of RHH646 to include patients with multiple joint involvement or those with disease in joints not amenable to local/injectable therapies. If RHH646 proves to be effective, it may restore function, reduce reliance on other symptomatic therapies, avoid the need for arthroplasty, and mitigate the impact of secondary complications of impaired function and mobility (for lower extremity OA). No current therapy offers these benefits.

The RHH646 doses/exposures at which toxicities have been found relative to the doses/exposures at which efficacy has been shown in animal models suggest a therapeutic index acceptable for the treatment of OA. The lack of any apparent dose-limiting or dose-dependent adverse effects CCI [REDACTED]

[REDACTED] also supports continued clinical investigation of RHH646. The most common AE reported in healthy adults was headache, which occurred in a total of 5 study participants: 4 who received RHH646 CCI [REDACTED] and one who received placebo. The second most common AE reported in healthy adults was COVID-19, which was diagnosed in two study participants after receiving CCI [REDACTED] of RHH646. An asymptomatic SARS-CoV-2 infection occurred in one participant who received placebo. Aside from the grade 2 symptomatology in the participants who had COVID-19, all AEs were grade 1. There were no evident RHH646-related changes in laboratory tests, vital signs, or ECGs. Therefore, the overall benefit/risk balance for conducting this study is favorable.

The potential risks of participation in the study include risks associated with the administration of study drug and procedural risks (e.g., risks associated with imaging procedures, venipuncture, other assessments). The risk to participants in this trial are minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring and stopping rules.

Risks associated with administration of RHH646

CCI

There may be risks of RHH646 that are unknown and potentially serious.

CCI

CCI

CCI

If there is an RHH646-associated risk of acute epididymitis in males, it is expected to present in a way that is similar to the way acute epididymitis typically presents. This would include new onset scrotal pain, scrotal swelling, scrotal tenderness, urinary or ejaculatory complaints. Study participants with any such complaints should be referred to a urologist for diagnosis and management. Specific monitoring of male participants including external genitalia examinations and urology consultations has been included in the study protocol to ensure safety (see [Section 8.4.6](#) for details).

CCI

CCI

Regular monitoring of the cell counts in circulation is planned.

Other potential risks in this study include changes in laboratory test results (e.g., total cholesterol, fibrinogen, reticulocyte counts) and changes in body weight. CCI

Laboratory tests and body weight will be monitored during the study.

The reproductive toxicity of RHH646 has not been investigated. Therefore, there may be a risk to a developing fetus. In EEA, women of child-bearing potential will be excluded from participation in this trial. Women of child-bearing potential in other regions and sexually active males in all regions 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.

Risks associated with imaging procedures

X-ray views will be required for screening purposes and knee OA assessment at the Week 52/EOT visit. These are often performed during the routine evaluation of patients with knee pain, but not always. Consequently, for the screening assessment of some patients, they will be obtained as described in the Imaging Manual only for research purposes. The total amount of radiation exposure per participant from these X-rays will be about up to 400 μ Sv. This amount of radiation is equivalent to approximately 56 days of background exposure (approx. 0.3 μ Sv per hour at sea level). For effective radiation doses under 3 mSv (300 mrem), the risk is considered "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 RHH646 on cartilage structure and composition. MRI is a non-invasive imaging technique that has no radiation exposure. 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.

Other procedural risks

The risks of venipuncture include pain/discomfort, bruising, and infection. These risks are minimized by employing sterile techniques and using the smallest gauge needles suitable for the study purpose. Leads placed for electrocardiographic monitoring and tapes (e.g., for securing cotton, gauze, or intravenous cannulas, if used) may cause skin irritation.

2.3.1 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected over a period of 14 months, 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 [Section 1.3](#).

3 Objectives, endpoints, and estimands

Table 3-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	Endpoint(s) for primary objective(s)
<ul style="list-style-type: none">To evaluate the articular cartilage-regenerating capacity of RHH646 in the knee following 1 year of treatmentTo evaluate the safety and tolerability of RHH646 following 1 year of treatment	<ul style="list-style-type: none">Change from baseline in cartilage volume in the index region of the target knee by MRI at Week 52AEs Electrocardiograms (ECGs) Vital signs Hematology, blood chemistry, urinalysis
Secondary objective(s)	Endpoint(s) for secondary objective(s)
<ul style="list-style-type: none">To evaluate the pharmacokinetics of RHH646 in patients with knee OA	<ul style="list-style-type: none">RHH646 plasma concentrations, C_{min,ss} at Week 4, and any other PK parameter as appropriate
Exploratory objective(s)	Endpoint(s) for exploratory objective(s)

CCI

Objective(s)	Endpoint(s)
CCI	

3.1 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.

The primary clinical question of interest is:

What is the effect of CCI, orally administered RHH646, with acceptable compliance, on knee cartilage volume after 52 weeks of treatment in patients with symptomatic, mild to moderate knee OA? The primary estimand is described by the following attributes:

1. **Population:** Patients with symptomatic, mild to moderate radiographic knee OA (K&L grade 2 to 3) in the target knee and with pain requiring analgesic therapy. Further details about the population are provided in [Section 5](#).
2. **Primary variable:** change from baseline to Week 52 in cartilage volume in the index region of the knee.
3. **Treatment of interest:** the randomized treatment (RHH646 or placebo) as CCI mg CCI as allowed per protocol ([Section 6.5](#)).

Handling of remaining intercurrent events (ICEs)

Unacceptable non-compliance with treatment: Hypothetical strategy (see [Section 9.3.3](#)).

The summary measure

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

3.2 Secondary estimands

Not applicable.

4 Study design

4.1 Overall design

Refer to [Section 1.2](#) Schema for study design [Figure 1-1](#).

This is a non-confirmatory, randomized, investigator and participant-blinded, two-arm, placebo-controlled, phase 2a study to assess safety, tolerability, and efficacy of RHH646 in male and female adult patients with symptomatic, mild to moderate radiographic knee OA (K&L grade 2 to 3) in the target knee and with pain requiring analgesic therapy (e.g., APAP or NSAIDs). Approximately 78 participants will be enrolled and randomized in the trial and treated for 52 weeks.

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

Screening period

Prior to screening, optional study specific pre-screening assessments may be carried out, including but not limited to X-ray and knee physical examination, to assess participant eligibility for inclusion. Prior to any study specific assessments being carried out, the pre-screening ICF must be signed by the participant. If X-ray is taken during pre-screening according to the protocol imaging criteria, it will not need to be repeated during screening.

After signing informed consent, screening evaluations will take place from Day -42 to Day -1. During this period safety and other assessments must be performed to evaluate eligibility. The target knee for the study should be selected by the investigator based on participant complaints, medical history, careful knee examination along with a local review of the X-ray. The X-ray will require assessment by a central reader. The required assessments may be conducted over several days if it is in the best interest of the participant, or for logistical reasons. During the screening period, any prohibited medication will be washed-out. CCI

as described in [Section 6.8.2](#) Prohibited medication.

Treatment period

The treatment period is 52 weeks (1 year). Study visits are planned approximately monthly during the first 6 months and every 3 months thereafter. In addition, participants will have phone visits at Weeks 30, 34, 43 and 47 where the wellbeing of the participant will be assessed remotely. Participants may be invited for unscheduled assessments at the site if deemed necessary.

Eligible participants will be randomized on Day 1 to receive RHH646 or placebo. MRIs for the primary endpoint are performed at baseline (may be performed up to 2 weeks prior to Day 1 during the screening period), at 6 months, and 12 months.

At scheduled onsite visits, participants will undergo safety, efficacy and functional assessments, various PK, CCI

as indicated in [Section 1.3](#). At Week 4 the participants will take their CCI dose of study treatment during the visit to allow for a collection of a pre-dose sample. CCI

Date and time of intake of the CCI doses of study medication prior to each visit where PK samples are collected will also be captured in a diary. CCI

as indicated in [Section 1.3](#).

Follow-up period

After receipt of last dose and after all safety and efficacy assessments are completed, all participants will begin a 4-week follow-up period to ensure complete washout of the investigational treatment before the EOS visit. At this visit, participants will undergo final assessments as indicated in [Section 1.3](#). Upon completion of this visit, participants will be discharged from the study.

4.2 Scientific rationale for study design

The randomized, blinded, two-arm, placebo-controlled design allows an initial assessment of efficacy (i.e., regeneration of hyaline cartilage measured as cartilage volume by MRI) and safety in patients with knee OA using the most efficient design (optimal power) for the primary endpoint. The blinded 1:1 randomization targets balance across the treatment groups and minimizes potential bias for the evaluation of safety for the first clinical investigation of RHH646 in this patient population with a relatively small sample size and a 52-week duration of treatment. The balanced randomization also ensures a comparably robust assessment of the primary endpoint (cartilage volume by MRI) in both treatment groups, which respects the heterogeneity of OA progression among patients, avoids reliance on non-concurrent control or natural history data, and minimizes the risk of a false negative result.

CCI

The population of patients with symptomatic, K&L grade 2 to 3 knee OA has a stage of disease expected to be responsive to potential disease-modifying therapies and is consistent with the population enrolled in recent studies of other potentially disease-modifying therapies that used MRI to evaluate joint structures. The primary endpoint of cartilage volume by MRI allows the earliest and most precise assessment of any chondroanabolic effect of the treatment.

4.3 Justification for dose

The **CCI** mg **CCI** dose is the highest dose considered safe to administer in this POC study. This dose will maximize the chance for efficacy and minimize the risk of a false negative result (i.e., due to insufficient exposure) because this is the first test of the clinical efficacy of RHH646 in humans. **CCI** may not fully recapitulate human OA and simple scaling of PK (systemic exposures) between species may not translate to clinical efficacy due to differences in disease pathogenesis/pathophysiology, joint size, synovial fluid volume and flow dynamics, cartilage volume, load-bearing characteristics, and other relevant differences between rats and humans, thus making doses in the lower end of the predicted therapeutic range harder to justify in an initial proof-of-concept study with one active treatment arm. The clinical experience includes RHH646 **CCI** **CCI** that were safe and well tolerated in healthy adults without dose-limiting or dose-dependent AEs or differences from placebo.

The PK of RHH646 in humans support **CCI** dosing. **CCI**

CCI

CCI

Human PK at various dose levels was simulated based on human PK in healthy adults after p.o. administration (DMPK R2270344).

Table 4-1 Steady-state exposure multiples by RHH646 dose

CCI

CCI

In those participants for whom a dose modification may be necessary ([Section 6.5](#)), a CCI dose level adjustment (i.e., from CCI mg in those patients receiving active treatment) can be regarded as sufficiently different from a safety or tolerability point of view, while still preserving a chance for efficacy.

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

Since there are no approved disease-modifying drugs for OA and this is the first clinical test of the safety of RHH646 in patients with OA, placebo will be used as a control. Standard of care treatments for knee OA (e.g., analgesics) are allowed throughout the study with limited restrictions, as described in [Section 6.8.1](#).

4.5 Rationale for public health emergency mitigation procedures

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

4.6 Purpose and timing of interim analyses/design adaptations

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

If any adjustments are deemed necessary, such as adjusting the number of participants, the protocol will be amended.

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 ([Section 9.8](#)).

4.7 End of study definition

The EOS is defined as the date of the last visit of the last participant (LPLV) in the study or last scheduled procedure or follow-up shown in [Section 1.3](#) for the last participant in the study globally.

5 Study population

The study population will include males and females 35 to 75 years old with symptomatic, mild to moderate radiographic knee OA (K&L grade 2 to 3) in the target knee and with pain requiring analgesic therapy (e.g., APAP or NSAIDs). Approximately 78 participants will be randomized for an expected 70 participants evaluable for the primary analysis.

5.1 Inclusion criteria

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

1. Signed informed consent must be obtained prior to participation in the study
2. Able to communicate well with the investigator, to understand and comply with the requirements of the study
3. Participant is ≥ 35 and ≤ 75 years old, at time of screening
4. Participants must weigh at least 50 kg to participate in the study and must have a body mass index (BMI) ≤ 35 kg/m². BMI = Body weight (kg) / [Height (m)]²
5. Diagnosis of tibiofemoral OA in at least one knee by standard American College of Rheumatology clinical and radiographic criteria ([Altman et al 1986](#)) at screening
6. K&L grade 2 to 3 OA in the target knee evaluated with X-Ray by the Central Reader at screening
- 7a. Predominantly medial tibiofemoral compartment involvement defined as medial Joint Space Narrowing (medJSN) 1-2 ([Altman and Gold 2007](#)) and medJSN > lateral Joint Space Narrowing (latJSN) in the target knee evaluated with X-Ray by the Central Reader at screening
8. Symptomatic disease, defined as having pain in the target knee at least 3 days per week during the last 3 months from screening that is relieved by analgesic therapy (e.g. APAP or NSAIDs), according to the investigator's evaluation and judgment of the patient's history

5.2 Exclusion criteria

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

General Note: In the case where a safety laboratory assessment at screening is outside of the range specified below, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the participant is excluded from the study. Also the X-ray performed to confirm participant eligibility may be repeated once if the image quality does not allow determination of eligibility. If the repeated X-ray confirms ineligibility, a third X-ray is not allowed, and the participant will be excluded from the study.

1. Use of other investigational drugs within 5 half-lives of enrollment/initiation of study treatment (select as appropriate) within 30 days (e.g., small molecules) / or until the expected pharmacodynamic effect has returned to baseline (e.g., biologics), whichever is longer; or longer if required by local regulations
2. History of hypersensitivity to any of the excipients in the study treatment

3. History of Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS), or a drug-related anaphylaxis
- 4a. 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 CCI [REDACTED] after stopping study treatment.

In EEA, women of child-bearing potential will be excluded from participation in this trial, irrespective of the use of highly effective methods of contraception.

Highly effective contraception methods include:

- Total abstinence (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 bilateral tubal ligation, female sterilization (surgical bilateral oophorectomy, total hysterectomy or salpingectomy) at least six weeks prior to enrollment on study. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant.
- Use of 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 have been stable on the same pill for a minimum of 3 months before taking study treatment.

If local regulations are more stringent than the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age-appropriate history of vasomotor symptoms). Women are considered not of child-bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral salpingectomy at least six weeks prior to enrollment on study. 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 to be not of child-bearing potential.

5. Women who are pregnant, nursing (lactating), or planning to become pregnant during the study
6. Sexually active males unwilling to use a condom during intercourse while taking study treatment and for CCI [REDACTED] after stopping study treatment. A condom is required for **all** sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants must not donate sperm for the time period specified above.

7. Arthroscopy of the target knee within the 6 months prior to screening or planned arthroscopy during the study
8. Previous surgical treatment of the target knee using mosaicplasty, microfracture, meniscectomy >50% or osteotomy; planned surgery for either knee during the study
9. Unstable target knee joint (including, but not limited to, posttraumatic or congenital laxity) or insufficiently reconstructed ligaments based on medical history and/or physical examination by the investigator
10. Participant has severe malalignment (valgus- or varus-deformity) in the target knee >7.5° based on X-ray evaluation by the Central Reader at screening
11. K&L grade 4 OA in either knee
12. Presence of severe hip OA that either (i) alters lower limb function to a degree that increases or abnormally changes the mechanical forces in the knee while walking, according to investigator's evaluation or (ii) currently requires or is likely to require specific medical or surgical management during the study period
13. Other pathologies affecting the knee, including subchondral insufficiency fractures, bone fracture (acute or subacute within the 6 months prior to screening) or bone bruise, osteonecrosis, malignant bone marrow infiltration, solid tumors, and/or patellofemoral dysplasia based on clinical assessment, or imaging
14. Known autoimmune disease with inflammatory arthritis (including but not limited to rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus), crystal-induced arthritides (gout or pseudogout arthritis), active acute or chronic infection of the knee joint, Lyme disease involving the knee, reactive arthritis, systemic cartilage disorders, moderate to severe fibromyalgia, a known systemic connective tissue disease or a widespread pain index (WPI) >4.
15. Inability to undergo MRI (e.g., claustrophobia, body size, leg not fitting in the coil) or contraindications to MRI (e.g., non MRI-compatible metallic implants, metallic foreign bodies, pacemaker, defibrillator)
16. History of testicular disease (males) or ovarian disease (females) unless status post bilateral orchiectomy (males) or bilateral oophorectomy (females). Males who have undergone sub-epididymal orchiectomy are not eligible for participation.
17. History of unstable or untreated mood or anxiety disorders
18. History or evidence of clinically significant or unstable ECG abnormalities including but not necessarily limited to:
 - sustained ventricular tachycardia
 - clinically significant second or third degree AV block without a pacemaker
 - familial long QT syndrome or family history of Torsades de Pointes
 - resting QTcF >450 msec (male) or >470 msec (female) at screening or baseline
 - chronic use of medications with known pro-arrhythmic risks
19. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in-situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases

20. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the participant in case of participation in the study. The investigator should make this determination in consideration of the participant's medical history and/or clinical or laboratory evidence of any of the following:
- Major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection
 - Pancreatic injury or pancreatitis
21. History of or current clinically significant liver disease or liver injury as indicated by abnormal liver function tests such as AST (Aspartate Aminotransferase), ALT (Alanine Aminotransferase), alkaline phosphatase (ALP), or serum bilirubin at screening. The investigator should be guided by the following criteria:
- Any single parameter may not exceed 2× upper limit of normal (ULN)
 - A single parameter elevated up to and including 2× ULN should be re-checked once more as soon as possible, and in all cases, at least prior to enrollment/randomization, to rule out lab error
22. Estimated GFR < 50 mL/min/1.73 m² by the CKD-EPI creatinine equation (2021) at screening
23. History or evidence of immunodeficiency, including a positive HIV (ELISA and Western blot) test result regardless of immune status
24. Chronic infection with Hepatitis B (HBV) or Hepatitis C (HCV). A positive HBV surface antigen (HBsAg) test, or if standard local practice, a positive HBV core antigen (HbcAg) test, excludes a participant. Participants with a positive HCV antibody test should have HCV RNA levels measured. Participants with positive (detectable) HCV RNA should be excluded.
25. Any significant chronic condition that has not been well-controlled for a minimum of 3 months prior to screening (e.g., uncontrolled hypertension, diabetes or chronic heart failure (e.g., patients with New York Heart Association class III or IV)), or poor functional status unable to perform self-care
26. Regular users of nicotine (e.g., smoked tobacco, smokeless tobacco, vaporizers) defined as >10 cigarettes or equivalent use of other forms of tobacco/nicotine per day or former users currently reliant on daily nicotine replacement therapy
27. History of drug abuse or unhealthy alcohol use within the 12 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays conducted during screening. Unhealthy alcohol use is defined as a history of, or current alcohol misuse/abuse, defined as "Five or more drinks on the same occasion on each of 5 or more days in the past 30 days."
28. Taking medications prohibited by the protocol (see [Section 6.8.2](#))
29. Any surgical, medical, psychiatric, or additional physical or social condition that the investigator feels may jeopardize the safety of the participant or may interfere with the conduct of the study and the evaluability of the results

5.3 Lifestyle considerations

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

5.3.1 Meals and dietary restrictions

After signing the informed consent, the study participants should be instructed to refrain from consuming citrus-containing fruits or beverages, and tonic water in the 4 hours prior to the ECG collection.

At Baseline, Week 26, and EOS visits, where fasting glucose will be assessed ([Table 1-1](#)), participants will fast (i.e. no food and liquid except water) for at least 8 hours prior to the assessment.

5.3.2 Caffeine, alcohol, and tobacco

From Screening to EOS, the participant should not smoke >10 cigarettes per day or use other tobacco products in amounts corresponding to >10 cigarettes per day. Use of nicotine replacement therapy is not allowed.

From Screening to EOS, the participant should not consume five or more drinks on the same occasion on each of 5 or more days in a 30-day period.

From Screening to EOS, the participant should not use recreational drugs, even if legal in their location.

After signing the informed consent, the study participants should be instructed to refrain from smoking, consuming alcohol and methylxanthine-containing beverages (i.e., coffee, tea, soda, chocolate) in the 4 hours prior to the ECG collection.

5.3.3 Activity

From Screening to EOS, study participants should refrain from substantial changes in their regular activity or exercise habits. Participation in contact or high impact sports or other activities involving heavy loading, rotation, or pivoting should not begin anew during the study.

5.4 Screen failures

Participants who sign a pre-screening ICF and are subsequently found to be ineligible prior to signing the main ICF will be considered pre-screen failures. Only data related to serious adverse event (SAE) causally related to pre-screening study procedures (e.g., X-ray, knee examination) will be collected (see [Section 8.6.3](#)). All other data related to pre-screening will only be recorded in source documentation.

Participants who sign the main ICF and are subsequently found to be ineligible prior to randomization will be considered as screen failures. The reason for screen failure should be recorded on the appropriate CRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a SAE during the screening period (see [Section 8.6.3](#)). Data and samples collected from participants prior to screen failure may still be analyzed.

If the participant fails to be randomized, the Interactive Response Technology (IRT) must be notified within 2 days of the screen fail that the participant was not randomized.

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Each case must be discussed and agreed with Novartis on a case-by-case basis.

In the case where a safety laboratory assessment at screening is outside of the range specified in the eligibility criteria, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified range, the participant must be excluded from the study.

5.4.1 Replacement policy

Discontinued participants will not be replaced.

5.4.2 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is rescreened. The Participant No. consists of the Site Number (Site 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 rescreen the participant after a participant has screen failed, and the participant will be assigned a new Participant No.

6 Study treatment(s) and concomitant therapy

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

6.1 Study treatment(s)

Table 6-1 Investigational and control drug

Treatment Title	RHH646	Placebo
Treatment Description	RHH646 oral capsule	RHH646 placebo oral capsule
Type	Drug	Drug
Dose Formulation	Capsule	Capsule
Unit Dose Strength(s)	CCI mg	0 mg
Dosage Level(s)	CCI mg, CCI	0 mg, CCI
Route of Administration	Oral	Oral
Use	Experimental	Placebo
IMP	Yes	Yes
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study treatment will be provided in bottles. Each bottle will be labeled as required per country requirement.	Study treatment will be provided in bottles. Each bottle will be labeled as required per country requirement.

6.1.1 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

6.1.2 Treatment arms/group

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

- RHH646 CCI mg CCI
- Placebo CCI

In the event any study participant appears to be not tolerating the study treatment and the only alternative would be to discontinue the study treatment, the investigator will have the option to reduce the dose to give the study participant a chance to remain on study treatment, see [Section 6.5](#).

6.2 Preparation, handling, storage, and accountability

Each study site will be supplied with study treatment in packaging as described under [Table 6-1](#) Investigational and control drugs section.

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

Investigator staff will identify the study medication kits to dispense to the participant by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part

label (base plus tear-off label), immediately before dispensing the medication kit to the participant, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

As per [Section 4.5](#), during a public health emergency as declared by local or regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of Investigational Medicinal Product (IMP) directly to a participant's home may be permitted (if allowed by local or regional health authorities and ethics committees, as appropriate) in the event the investigator has decided that an on-site visit by the participant is no longer appropriate or possible, and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the participant's home remains under the accountability of the investigator. Each shipment/provisioning will be for a maximum of 1-month supply. In this case, regular phone calls or virtual contacts (every 4 weeks or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, investigation of any AEs, ensuring participants continue to benefit from treatment, and discussion of the participant's health status until the participants can resume visits at the study site.

6.2.1 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, the designated person at the site should verify that all study treatment sent per the shipping documentation is received and should verify the condition of the study treatment (e.g., not damaged and no issues, including temperature deviations, during shipment). Once received at site, 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 Country Organization Quality Assurance.

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

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

If study treatment is administered at home, participants will be asked to return all unused study treatment and packaging at each visit or at the time of discontinuation of study treatment.

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

6.2.2 Handling of other treatment

No other treatment will be provided.

6.2.3 Instruction for prescribing and taking study treatment

Table 6-2 Dose and treatment schedule

Investigational / Control Drug (Name and Strength)	Dose	Frequency and/or Regimen
RHH646 CCI mg	CCI mg CCI mg capsules)	CCI
RHH646 Placebo	placebo CCI placebo capsules)	CCI

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

The first dose will be administered at the site on Day 1. Thereafter, participants should take the study treatment CCI with the exception of the dose on visit Week 4 which will be administered in the clinic to allow for a pre-dose sample to be collected. Participants will be provided with individual diary cards to record the date and time of the CCI doses prior to each visit with PK sampling. These will be checked at each visit by site staff.

Participants should take the study treatment without regard to food. Each dose may be taken with a glass of water and participants should be instructed to swallow whole capsules and not to chew or open them.

If vomiting occurs during the course of treatment, participants should not take the study treatment again before the next scheduled dose.

Participants should be instructed not to make up missed doses. CCI and the participant should continue treatment with the next scheduled dose.

6.3 Measures to minimize bias: randomization and blinding

6.3.1 Treatment assignment, randomization

At the Baseline visit, all eligible participants will be randomized via 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 and none of the 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 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.

6.3.2 Treatment blinding

Participants, investigator staff and persons performing the assessments will remain blinded to study treatment from the time of randomization until database lock, except where indicated below. The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Site staff

All site staff (including investigator and study nurse) will be blinded to study treatment throughout the study.

Unblinding a single participant at site for safety reasons (necessary for participant management) will occur via an emergency system in place at the site. As a result, the participant should be discontinued from the study treatment.

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.

Sponsor staff

Unblinding of a single participant for evaluation of a study stopping rule ([Section 7.5](#)) will occur via an emergency system. As a result, the participant should be discontinued from the study treatment.

The following unblinded sponsor roles are required for the duration of the study:

- Unblinded clinical staff managing drug re-supply to site
- Unblinded sample analyst(s) (PK-Bioanalyst)
- Unblinded sample analyst(s) (biomarker)

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

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

In addition, the following unblinded sponsor roles are required for interim analysis:

- Study statistician
- Study programmers and personnel involved in the study data analysis
- Clinical trial team

- Other sponsor staff

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. For example, unblinded summaries and unblinded individual data can be shared with the clinical 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.

Following final database lock all roles may be considered unblinded.

Table 6-3 Blinding and unblinding plan

Role	Time or Event			
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)	Interim Analysis/ dose escalation/ safety review
Participants	B	B	UI	B
Site Staff	B	B	UI	B
Global Clinical Supply	UI	UI	UI	UI
Randomization Office	UI	UI	UI	UI
Statistician/statistical programmer/ data analysts (e.g. biomarker, PK)	B	UI	UI	UI
Unblinded Sponsor staff, e.g. for study treatment re-supply, unblinded monitor(s), sample analyst(s)	B	UI	UI	UI
All other Sponsor staff not identified above (i.e. project team, management & decision boards, support functions)	B	B	UI	UI

B Complete blinded

UI Unblinded to individual participant treatment codes

6.3.3 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
- 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.

As a result of the emergency unblinding, the participant should be discontinued from the study treatment.

6.4 Study treatment compliance

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

6.4.1 Recommended treatment of adverse events

AEs requiring treatment should be treated according to current standards of care. Due to the limited clinical experience with RHH646, there is insufficient information to provide specific recommendations regarding treatment of AEs. AEs in individual participants may be managed at the discretion of the investigator and/or sub-investigator(s) providing medical oversight. The risk of a consequential drug-drug interaction between RHH646 and other drugs used to treat an AE is considered low and outweighed by the benefits of treating the AE.

CCI

If necessary, study treatment may be temporarily withheld to manage certain AEs (Section 6.5).

Details of medication(s) and/or other intervention(s) used to treat AEs must be recorded in the source documents and the CRF.

6.5 Dose modification

Downward dose adjustment from CCI [REDACTED] and/or temporary interruptions are permissible in individual participants if the participant is not tolerating study treatment or medically requires a temporary interruption in order to give the participant a chance to remain in the study. A CCI dose level adjustment (i.e., from CCI mg in those patients receiving active treatment) can be regarded as sufficiently different from a safety or tolerability point of view while still preserving a chance for efficacy.

Adjustments or temporary interruptions may occur at the discretion of the investigator in consultation with the medical monitor when the only alternative would be discontinuation of study treatment. Examples of events or situations that may warrant dose adjustment include but are not limited to persistent gastrointestinal complaints (e.g., nausea, diarrhea), persistent laboratory abnormalities, persistent rash, or persistent increases in blood pressure. Examples of events or situations that may warrant a temporary interruption of study treatment include but are not limited to medical/surgical procedures that are either unexpected or cannot be postponed. Dose adjustments or temporary interruptions are not permissible for circumstances that would not otherwise warrant consideration of study treatment discontinuation (e.g., relatively low intensity, transient, manageable AEs) or events that fulfil the criteria for discontinuation of study treatment ([Section 7.1](#)).

A downward dose adjustment shall persist for the remainder of the study (i.e., the participant should not resume the higher dose). A temporary interruption of study treatment may be for no more than CCI [REDACTED] of RHH646. If the interruption of study treatment is required for circumstances unrelated to the study or study treatment, the participant should resume the dose of study treatment that was being taken prior to the interruption. If the interruption of study treatment is required for safety or tolerability reasons possibly related to the study treatment, then the participant should resume study treatment at the lower dose.

The date of the downward dose adjustment and/or the dates of the temporary treatment interruption, along with the reasons, including AEs, other treatments, and other circumstances that were relevant to the decision to reduce the dose or temporarily interrupt study treatment should be documented by the site in the source documents and as applicable in the electronic case report form (eCRF).

6.6 Continued access to study treatment after the end of the study

Since this is an exploratory study, no further study treatment will be made available to the participants after study completion.

6.6.1 Post trial access

Not applicable.

6.7 Treatment of overdose

In the event of a confirmed or suspected overdose, the investigator should:

- Contact the medical monitor immediately.
- Evaluate the participant to determine, in consultation with the medical monitor, whether study treatment should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities at least until RHH646 can no longer be detected systemically (at least CCI). Similar to any other AE or SAE, overdose-related AEs must be followed until its resolution or until it is judged to be not recovered/not resolved (Section 8.6).
- Obtain a plasma sample for PK analysis within three days from the date of the last dose of study treatment if requested by the medical monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose.

6.7.1 Reporting of study treatment errors including misuse/abuse

Study treatment errors are unintentional errors in the prescribing, dispensing, and administration of study treatment.

Study treatment misuse refers to situations where the study treatment is intentionally and inappropriately used not in accordance with the protocol.

Study treatment abuse corresponds to the persistent or sporadic, intentional excessive use of study treatment, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol, including misuse or abuse, must be reported on the AE (or SAE, if the event meets the definition of an SAE) CRF.

6.8 Concomitant and other therapy

6.8.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including but not limited to physical therapy, diet for weight loss, insole wedges and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate eCRFs.

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

6.8.1.1 Permitted concomitant therapy requiring caution and/or action

Participants undergoing physical or occupational therapy (e.g., diet for weight loss, insole wedges) and/or taking NSAIDs, COX-2 inhibitors, low potency opioids or APAP can continue to do so in the study as long as they are on a stable regimen in the opinion of the investigator for at least 4 weeks prior to screening. Participants can continue taking these medications during the trial but will need to CCI as

described in [Section 6.8.2](#) Prohibited medication. Investigators are encouraged to minimize changes to concomitant therapies including physical and occupational therapies during the study unless changes are otherwise specifically indicated for an individual participant.

In addition to the above and with specific respect to permitted concomitant drug therapies for the symptoms of OA, investigators should consider:

- The potential gastrointestinal, liver and cardio-renal toxicities of NSAIDs including COX-2 inhibitors, when adjudicating AEs or contemplating new therapy. It is recommended to initiate oral NSAIDs/COX-2 inhibitors at the lowest effective dose for the shortest period of time with additional protective medication (e.g. misoprostol, proton pump inhibitors), if judged necessary by the treating physician. It is also advised that a need for new analgesic therapy in patients who require low-dose aspirin or other anticoagulant therapy be addressed by non-NSAID treatments or topical NSAIDs, if possible.
- The possible role of acetaminophen (paracetamol, APAP) as a cause or contributor to laboratory evidence of potential hepatotoxicity, especially in patients who regularly rely on total daily doses between 3 and 4 grams.
- The potential impact of pain in other joints or elsewhere and its management on the assessment of pain in the target knee for this study. Clinical histories should be taken carefully when the protocol-specified assessments of pain in the target knee are performed.

CCI

(see [Section 6.8.2](#) Prohibited medication).

6.8.2 Prohibited medication

Use of the treatments displayed in [Table 6-4](#) are not allowed for the duration indicated. Any actions taken in individual cases if a prohibited medication is taken will be discussed and agreed between the investigator and sponsor.

Table 6-4 Prohibited medication

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6.8.3 Rescue medicine

Not applicable.

7 Discontinuation of study treatment and participant discontinuation/withdrawal

7.1 Discontinuation of 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 treatment administration, if any) and 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
- Following emergency unblinding
- Diagnosis of non-infectious epididymitis or development of a new scrotal mass (in male participants)
- Hypersensitivity reaction occurs, corresponding to CTCAE grade 2 or higher, including any of the following: anaphylaxis, fever, chills, urticaria, dyspnea, headache, myalgia, hypotension
- An AE of severe intensity (corresponding to CTCAE grade 3 or higher) considered possibly related to RHH646 treatment
- Any laboratory abnormalities or other situation, that in the judgment of the investigator, taking into consideration the participant's overall status, might result in a safety risk or otherwise prevents the participant from continuing participation in the study

If a liver or renal event occurs, follow guidelines outlined in [Section 10.5](#) and [Section 10.6](#) 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 or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw consent (see [Section 7.3](#)). Where possible, participants should be asked if they agree to return for the EOT and EOS visits indicated in [Section 1.3](#).

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
- AEs / SAEs

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

7.2 Participant discontinuation from the study

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

If the participant agrees, a final evaluation at the time of the participant's study discontinuation should be performed as detailed in [Section 1.3](#).

7.3 Withdrawal of informed consent and exercise of participants' data privacy rights

Withdrawal of consent/opposition to use of data and/or biological samples occurs in countries where the legal justification to collect and process the data is consent and when a participant:

- Explicitly requests to stop use of their data

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 as per local regulations (e.g., in writing) and recorded in the source documentation.

Withdrawal of consent impacts ability to further contact the participant, collect follow-up data (e.g., to respond to data queries) and potentially other country-specific restrictions. It is therefore very important to ensure accurate recording of withdrawal vs. discontinuation based on the protocol definitions of these terms.

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/exercise data privacy rights and record this information. The investigator shall clearly document if the participant has withdrawn his/her consent for the use of data in addition to a study discontinuation.

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 should be made at the time of the participant's withdrawal of consent/exercise of data privacy rights, as detailed in [Section 1.3](#).

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

7.4 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits or fail to respond to any site attempts to contact them without stating an intention to discontinue from study treatment or discontinue from study or withdraw consent (or exercise other participants' data privacy rights), the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until EOS.

7.5 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 (CTCAE Grade 4 or higher) considered possibly related to RHH646 treatment;
- Two or more participants experience a similar SAE (other than death or life-threatening events) considered possibly related to the study treatment;
- Two or more participants are diagnosed with non-infectious epididymitis or develop a new scrotal mass (detected by palpation or ultrasound) while receiving RHH646;
- Two or more participants experience a similar AE which was assessed as CTCAE grade 3 or higher in intensity and are considered as possibly related to the study treatment;
- Novartis considers that the number and/or severity of AEs, abnormal safety monitoring tests, or abnormal laboratory findings justify putting the study on hold.

The study may resume following the safety review if the investigator and Novartis agree it is safe to proceed. Dependent on regional guidance, any restart following a temporary hold due to stopping rules being met will require prior submission and approval of a substantial CTA amendment to the competent authorities.

7.6 Early study termination by the Sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination (but not limited to):

- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study treatment 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. 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 Novartis depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Study Assessments and Procedures

Study procedures and their timing are summarized in [Section 1.3](#). Protocol waivers or exemptions are not allowed. Adherence to the study design requirements, including those specified in [Section 1.3](#), is essential and required for study conduct.

Immediate safety concerns should be discussed with Novartis upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Screening

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 [Section 1.3](#), 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.

8.1.1.1 Pre-screening

Prior to the Screening visit, optional study specific pre-screening assessments may be carried out, including but not limited to collection of medical history, concomitant medication, height and weight, X-ray ([Section 8.1.1.4](#)) and knee physical examination (e.g., assessment of knee OA laterality) ([Section 8.4.1](#)), to assess participant eligibility for inclusion. Prior to any study specific assessments being carried out, the pre-screening ICF must be signed by the participant.

Data from the pre-screening will not be entered into the clinical database, unless the participant either experiences an SAE causally related to pre-screening study procedures (X-ray, knee examination), in which case the SAE will be collected (see [Section 8.6.3](#)), or the participant signs the main consent and is screened within 3 months, in which case the pre-screening X-ray can replace the screening X-ray. All other data related to pre-screening will only be recorded in source documentation.

8.1.1.2 Widespread Pain Index (WPI)

WPI will be assessed at Screening only, to exclude participants with substantial pain due to unknown illness ([Wolfe et al 2016](#)).

8.1.1.3 Hepatitis screen, HIV screen

All participants will be screened for HBsAg or HBcAg (per standard local practice). Screening for Hepatitis C will be based in HCV antibodies and if positive, HCV RNA levels should be determined.

Evaluation for HIV seropositivity will be performed, and, if positive, confirmation by a second technique available at the laboratory site, e.g., ELISA, 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. Results will be recorded in source data only.

8.1.1.4 Alcohol test, drug screen, urine cotinine

Participants will be tested for substances of abuse (e.g., alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates). A positive result for alcohol and/or cannabinoids use may not be exclusionary. However, consumption habits for participants should be clarified by the investigator. Cotinine in urine will not be analyzed at screening. However, the investigator should clarify tobacco use habits for participants who use tobacco as per [Section 5.2](#). Results will be recorded in source data only.

8.2 Participant demographics/other baseline characteristics

Participant demographics: full date (only if required and permitted) or year of birth or age, biologic sex, race/predominant ethnicity (if permitted per local regulations) and relevant medical history/current medical conditions (until date of signature of main informed consent) will be recorded in the eCRF. Participant race/ethnicity data are collected and analyzed to identify any differences in the safety and/or efficacy profile of the treatment due to these characteristics. In addition, these data are necessary to assess the diversity of the study population as required by health authorities.

All prescription medications, over-the-counter drugs and significant non-drug therapies prior to the start of the study must be documented. See the protocol [Section 6.8.1](#) Concomitant Therapy for further details on what information must be recorded on the appropriate page of the eCRF.

Smoking and/or nicotine use histories (e.g., former user, current user, never used) and estimates of current or past use, if applicable, will also be collected.

8.3 Efficacy assessments

Planned time points for all efficacy assessments are provided in [Section 1.3](#).

8.3.1 Knee MRI

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

The index region is defined as the union of the femoral medial anterior (FMA), central (FMC) and posterior (FMP) cartilage sub-regions in the knee.

CCI

CCI



Image collection

MRI acquisition will be performed by a trained MRI professional at the imaging facility. Imaging facilities for the study should be trained and qualified by the central imaging laboratory prior to the first image is taken for the study assessment. The MRI radiologist will be blinded to the treatment received by the participant. All participants will be imaged using a clinical MRI 3T scanner and a multi-channel knee coil. For each MRI session, images will be acquired as described in the MRI Participant Scanning Guide to assess over the course of the study the extent of cartilage loss or regeneration in the index region as well as other potentially relevant knee OA structures as mentioned above.

MR images will be acquired at the imaging site(s) and sent for independent central review by the imaging core laboratories. The reviewers will be blinded to the treatment received by the participant. MRI analysis results will not be shared with the investigators to maintain the blind.

If the MRI quality does not allow central reader analysis, the MRI acquisition must be repeated as soon as possible.

Image processing

The image analysis will be performed centrally, as defined in the Independent Review Charter for MRI, 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 other knee structures as described above.

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 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 posteriorFMP, medial central-FMC, medial anterior-FMA, trochlea medial-FTM, trochlea centralFTC, trochlea lateral-FTC, lateral posterior-FLP, lateral central-FLC and lateral anterior-FLA; lateral posteriorTLP, lateral central-TLC, lateral anterior-TLA, medial posterior-TPM, medial anteriorTMA; lateral inferior-PLI, lateral central-PLC, lateral superior-PLS, medial inferiorPMI, 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.

CCI



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 well-being of the participant, as well as compliance with local ethical regulations.

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 related to the area of research that this study covers.

8.3.2 Knee X-ray

A bilateral posterior-anterior (PA) fixed flexion knee X-ray will be performed to confirm participant eligibility CCI to evaluate the K&L grade and medial JSN using a nonfluoro, standardized and quality-controlled method, as described in the Imaging Manual. In addition, a bilateral weight bearing anterior-posterior (AP) full length lower extremity X-ray will be acquired for the malalignment eligibility criterion. If a site does not have a long cassette, a bilateral AP knees with collimation to include as much of the femurs and tibias as possible may be acquired instead. The local radiologist and/or investigator should review the images for determination of the target knee and incidental findings relevant to the participant's safety. Thereafter, a central reader will analyze the images as described in the Independent Review Charter for X-ray.


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

The X-ray performed to confirm participant eligibility may be repeated once, if the image quality does not allow determination of eligibility by the central reader. If the repeat X-ray confirms ineligibility, a third X-ray is not allowed, and the participant will be excluded from the study.

8.3.3 Appropriateness of efficacy assessments

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. CCI



8.4 Safety assessments

Safety assessments are specified below with [Section 1.3](#) detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to [Section 8.6](#).

As per [Section 4.5](#), during a public health emergency as declared by local or regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 4 weeks or more frequently if needed) for safety monitoring and discussion of the participant's health status until it is safe for the participant to visit the site again.

8.4.1 Physical examinations

A complete or a short physical examination will be performed at each visit.

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, neurological and testicular/external genitalia exams ([Section 8.4.6](#)). If indicated based on medical history and/or symptoms, rectal, breast, and pelvic exams will be performed. In addition, a careful examination of the target knee will be performed by assessing redness, warmth, swelling, pain, range of motion, stability, and bulge sign, crepitus, flexion contracture, varus/valgus laxity, antero-post laxity, maximum extension, and maximum flexion should be recorded.

A short physical exam will include the examination of general appearance as well as target knee and symptom-oriented examination.

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) without shoes) will be measured as specified in the [Section 1.3](#). Body weight shall be measured in the same condition (e.g., clothed or unclothed wearing a clinic gown) throughout the study.

BMI will be calculated using the following formula (rounding to the nearest tenth):
$$\text{BMI} = \text{Body weight (kg)} / [\text{Height (m)}]^2$$

The Screening visit height measurement will be used for BMI calculations throughout the study.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

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 CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an AE must be recorded as an AE.

8.4.2 Vital signs

Vital signs will include the collection of body temperature (recorded in °C), blood pressure (BP) and pulse measurements. The method of measurement of body temperature (e.g., oral, otic, transdermal) shall be recorded in the source documents and the eCRF. The method of measurement shall remain the same throughout the study if possible.

After the participant has been sitting for 3 minutes, with back supported and both feet placed on the floor, systolic and diastolic BP will be measured using an automated validated device, e.g., OMRON with an appropriately sized cuff. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

8.4.3 Electrocardiograms

ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, blood sampling, and any remaining assessments for that visit (Figure 8-1).

Figure 8-1 **Timing of study procedures**



The Fridericia QT correction formula (QTcF) must be used for clinical decisions, e.g., at the Screening and Baseline visits to assess eligibility. The investigator must calculate QTcF if it is not auto-calculated by the ECG machine.

Single 12 lead ECGs will be locally collected and evaluated. Interpretation of the tracing must be made by a qualified physician and documented on the appropriate CRF. Each ECG tracing should be labeled with the study number, participant initials (where regulations permit), participant number, date, and kept in the source documents at the study site.

Clinically significant abnormalities present at screening should be reported on the appropriate CRF. Clinically significant findings must be discussed with Novartis prior to enrolling the participant in the study. New or worsened clinically significant findings occurring after informed consent must be recorded as AEs.

The original ECGs on non-heat-sensitive paper or a certified copy on non-heat sensitive paper, appropriately signed, must be archived at the study site.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the investigator at any time during the study as clinically indicated. For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. ECG safety monitoring, or a review process, should be in place for clinically significant ECG findings at baseline before administration of study treatment and during the study.

If an ECG abnormality is suspected to being related to potential ECG-altering activities/beverages, ECG should be repeated under conditions that exclude potentially interfering factors (such as smoking, consuming alcohol and methylxanthine-containing beverages [i.e., coffee, tea, soda, chocolate] citrus-containing fruits or beverages, and tonic water).

Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or AEs as appropriate.

8.4.4 Clinical safety laboratory tests

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.

Clinically significant abnormalities must be recorded as either medical history/current medical conditions or AEs as appropriate. All abnormal lab results must be evaluated for criteria defining an AE and reported as such if the criteria are met. For those lab AEs, repeated evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant.


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.

As per [Section 4.5](#), during a public health emergency as declared by local or regional authorities' i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if participants cannot visit the site for protocol-specified safety lab assessments, an alternative lab (local) collection site may be used.

Urinalysis

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

Table 8-1 Laboratory evaluations

Test Category	Test Name
Hematology	Erythrocyte Mean Corpuscular Hemoglobin, Erythrocyte Mean Corpuscular HGB Concentration, Erythrocyte Mean Corpuscular Volume, Erythrocyte Cell Morphology, Erythrocytes, Hematocrit, Hemoglobin, Leukocytes, Platelets, Differential Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands, Other (absolute value preferred, %s are acceptable)
Chemistry	Albumin, Alkaline phosphatase (ALP), ALT, Amylase, AST, Bicarbonate, Calcium, Chloride, Creatine kinase (CK), Creatinine, Direct Bilirubin, Gamma-glutamyl-transferase (GGT), Non-fasting and Fasting Glucose ¹ , HDL Cholesterol, Indirect Bilirubin, Lactate dehydrogenase (LDH), LDL Cholesterol, Lipase, Magnesium, Phosphate, Potassium, Sodium, Total Bilirubin, Total Cholesterol, Total Protein, Triglycerides, Urea Nitrogen or Urea, Uric Acid The central lab will use the CKD-EPI Creatinine Equation (2021) to estimate GFR.
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)
Coagulation	Prothrombin time (PT), International normalized ratio (INR), Activated partial thromboplastin time (APTT)
Thyroid	Thyrotropin, Thyroxine, Free
Hepatitis markers	HBsAg (or HBcAg), HCV Antibody, Hepatitis C Virus RNA
Liver Event Testing and Liver Follow-Up Testing	Albumin, ALP, ALT, AST, CK, GGT, GLDH, INR, PT, and Total Bilirubin (TBIL). Test for hemolysis (haptoglobin, reticulocytes, unconjugated [indirect] bilirubin). These tests are in addition to routine testing, to be performed only in follow-up to safety events when indicated in Section 10.5 Liver safety monitoring
Renal follow-up	Urine Albumin and Albumin (for Albumin:creatinine ratio (ACR)), Serum Creatinine. Repeat standard chemistry testing and standard urinalysis (Microscopic Panel (Casts, Crystals, Bacteria, Epithelial cells, Erythrocytes, Leukocytes.) and Macroscopic panel (Dipstick) (Color, Bilirubin, Glucose, Ketones, Leukocytes esterase, Macroscopic Blood, Nitrite Occult Blood, pH, Protein, Specific Gravity, Urobilinogen)) These tests are in addition to routine testing, to be performed only in follow-up to safety events when indicated in Section 10.6 , Renal safety monitoring
Additional tests	

Test Category	Test Name
Pregnancy Test and Assessments of Fertility	Serum pregnancy test Urine pregnancy test Confirmatory serum pregnancy required in case of positive urine pregnancy test Follicle Stimulating Hormone, Luteinizing Hormone Refer to Section 8.4.5 Pregnancy testing.
Inclusion/Exclusion	For inclusion or exclusion criteria testing not already included above, please refer to Section 5.1 and Section 5.2 .

¹ Fasting glucose is required at Baseline, Week 26 and EoS visits only. Non-fasting glucose will be collected at all other visits, see [Table 1-1](#).

8.4.5 Pregnancy testing

Pregnancy testing

All women of child-bearing potential will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements. In EEA women of child-bearing potential are excluded from the study.

A central laboratory will be used for analysis of the serum pregnancy tests 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. In addition, participants will be provided with urine pregnancy test kits at Week 26 and 38 to use at home at Weeks 30, 34, 43, and 47. The participant will be instructed to report the results to the site during the scheduled safety follow-up phone visits. The date and the result of the home testing will be captured in source documents only. Any positive urine pregnancy test should be confirmed with a serum pregnancy test.

As per [Section 4.5](#), during a public health emergency as declared by local or regional authorities' i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, if participants cannot visit the site to have serum pregnancy tests, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first and only if the test result is negative proceed with the administration of the study treatment. A communication process should be established with the participant so that the site is informed and can verify the pregnancy test results (e.g., following country specific measures).

Assessments of fertility

A woman is considered of childbearing potential from menarche and until becoming post menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Medical documentation of permanent method of sterilization must be retained as source documents. 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 to be not of child-bearing potential.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause and an appropriate clinical profile.

In absence of the medical documentation confirming permanent sterilization, or if the post-menopausal status is not clear, the investigator should use his medical judgment to appropriately evaluate the fertility state of the woman and document it in the source document.

8.4.6 Other safety evaluations

Testicular ultrasounds will be performed at screening and at the end-of-treatment evaluation. Information for the testicular ultrasounds must be included in the source documentation at the study site and in the eCRF. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an AE must be recorded as an AE.

External genitalia examinations of male participants will be performed approximately every three months during study treatment ([Section 8.4.1](#)). If there are findings on the external genitalia examinations of male participants or new complaints of testicular pain, tenderness, redness, inflammation, painful urination or ejaculation, urinary frequency, abnormal discharge from the penis, blood in the semen, or lower abdominal pain or discomfort, the study participant should be referred to a urologist to confirm the diagnosis and treatment plan in consultation with the principal investigator and the medical monitor.

If there are new, non-specific complaints from female participants of lower abdominal pain or discomfort, pelvic pain or fullness, pain during vaginal intercourse, urinary frequency, or change in bowel habits, the study participant may be referred to a gynecologist to confirm the diagnosis and treatment plan in consultation with the principal investigator and the medical monitor.

All AEs (diagnoses), treatments and other courses of action, and outcomes shall be documented.

8.4.7 Appropriateness of safety measurements

The safety assessments and monitoring plan are appropriate for the patient population and the potential risks of the study treatment as informed by the non-clinical safety studies and the limited clinical experience with the study treatment to date.

8.5 Additional assessments

8.5.1

CCI

CCI

8.5.1.1 CCI

CCI

8.5.1.1.1 CCI

CCI

8.5.1.1.2 CCI

CCI

8.5.1.2 CCI

CCI

8.5.1.2.1 CCI

CCI

8.5.1.2.2 CCI

CCI

8.5.2 Other assessments

8.5.2.1 CCI

CCI

8.6 Adverse events (AEs), serious adverse events (SAEs), and other safety reporting

The definitions of AEs and SAEs can be found in [Section 8.6](#).

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in [Section 8.6.3](#).

8.6.1 Adverse events

An 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.

The investigator has the responsibility for managing the safety of individual participant and identifying AEs.

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

For participants who sign the pre-screening ICF, AEs which occur after signature of this consent will only be captured if they meet the definition of serious as outlined in [Section 8.6.2](#) and are reported to be causally related with study procedures (e.g. the X-ray). Once the main study ICF is signed, all AEs per the descriptions below will be captured as adverse events.

The occurrence of AEs must be sought by non-directive questioning of the participant at each visit during the study. AEs 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 (PROs are considered as other assessments to detect AEs, See [Section 8.5.1](#)).

AEs 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 8.6.2](#)):

1. The Common Toxicity Criteria (CTC) AE grade (version 5 or higher). 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 between the study treatment 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 that 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. The causality assessment is one of the criteria used when determining regulatory reporting requirements. If the event is due to lack of efficacy or progression of underlying illness (i.e., progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant.

3. Its duration (start and end dates or ongoing) and the outcome must be reported.
4. Whether it constitutes a SAE (see [Section 8.6.2](#) for definition of SAE) and which seriousness criteria have been met.
5. Action taken regarding with study treatment. All AEs must be treated appropriately. Treatment may include one or more of the following:
 - Dose not changed
 - Dose Reduced
 - 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.

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

AE monitoring should be continued until the EOS visit.

Once an AE is detected, it must be followed until its resolution or until it is judged to be not recovered/not resolved (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 for the investigational drug can be found in the IB.

Abnormal laboratory values or test results constitute AEs 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 [Section 10.5](#) and [Section 10.6](#). For a complete list of reference ranges, please refer to the Laboratory Manual.

8.6.2 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 condition(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, fetal death or a congenital abnormality or birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
 - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
 - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
 - social reasons and respite care in the absence of any deterioration in the participant's general condition
 - treatment on an emergency 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.

All reports of intentional misuse and abuse of the product are also considered SAEs irrespective of whether a clinical event has occurred.

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

Treatment-emergent elevations in AST or ALT ($>3\times$ ULN) in combination with total bilirubin $>2\times$ 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.

8.6.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until the EOS visit must be reported to Novartis safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events. Note: If more stringent, local regulations regarding reporting timelines prevail. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded on the electronic SAE 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 30 days after the participant has discontinued from study treatment (or longer, depending on the elimination half-life of the specific compound).

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.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety (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 EU Clinical Trial Regulation 536/2014 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the EOS 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.

8.6.4 Pregnancy

In EEA countries, female trial participants must be physiologically incapable of becoming pregnant.

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study treatment and until the EOS visit.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

Any post study pregnancy-related SAE considered reasonably related to the study treatment by the investigator will be reported to Novartis as described in [Section 8.6.3](#). While the investigator is not obligated to actively seek this information in former study participants/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

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 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 for any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

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

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

8.6.5 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not applicable.

8.6.6 Adverse events of special interest

Not applicable.

8.7 Pharmacokinetics

PK samples will be collected at the visits defined in [Section 1.3](#).

At the Baseline visit, a pre-dose and 4-hour post dose PK sample will be collected. At the Week 4 visit, a pre-dose PK sample will be drawn to determine $C_{min,ss}$. At subsequent visits, PK samples will be drawn at any time point. Participants will record the date and time of the **CCI** doses of study treatment prior to each visit after the Baseline visit in a diary as described in [Section 6.2.3](#).

Follow instructions outlined in the Laboratory Manual regarding sample collection, numbering, processing and shipment. See [Section 8.8](#) for the potential use of residual samples for more information. PK samples will be obtained in all participants and evaluated in all participants except the placebo group.

RHH646 will be determined by a validated LC-MS/MS method; the anticipated Lower Limit of Quantification (LLOQ) is 2 ng/mL.

Concentrations will be expressed in mass per volume units and will refer to the free base. Concentrations below the LLOQ will be reported as “zero” and missing data will be labeled as such in the Bioanalytical Data Report.

$C_{min,ss}$ collected at Week 4 will be the only PK parameter determined in this study and will be determined using the actual recorded sampling times with Phoenix WinNonlin (Version 6.4 or higher). All PK data from this study, in combination with rich PK data from the FIH trial, will be used to develop a population PK model in OA patients. Results from the population PK model will be reported separately.

For standard pharmacokinetic abbreviations and definitions see the list provided in the appendices of this protocol.

8.8 Biomarkers

CCI

CCI

CCI

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CCI

CCI

CCI

8.9 Immunogenicity assessments

Immunogenicity is not being evaluated in this study. There is no *a priori* reason to believe that RHH646 is immunogenic. However, if a participant experiences an apparent hypersensitivity reaction or other event suggesting immunogenicity of the study treatment, management of the event may include collection of blood/plasma/serum or other samples that may aid in the diagnosis and understanding of the event.

8.10 Medical resource utilization and health economics

Medical resource utilization and health economics is not being evaluated in this study.

9 Statistical considerations

The analyses will be conducted on all participant data at the time when interim analysis occurs and when the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

9.1 Analysis sets

Participants will be analyzed according to the treatment assigned.

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

The **Safety Analysis Set** will include all participants who received any study treatment.

For this study, the FAS and the Safety Analysis set are identical.

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

9.2 Statistical analyses

9.2.1 General considerations

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

Study day

Study day 1 for all assessments is taken to be the start of investigational treatment. The study day for all assessments will be calculated as follows:

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

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

Baseline

For safety evaluations, the last available assessment on or before the date of start of investigational treatment is taken as 'baseline' assessment. In case time of assessment and time of treatment start is captured, the last available assessment before the treatment start date/time is used for baseline.

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

For ECG, study Day 1 scheduled pre-dose ECGs will be considered to have been obtained prior to start of investigational treatment if dosing time or ECG time is missing and used in the calculation of the baseline value. If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be treated and analyzed similar to an unscheduled post-dose measurement.

Regarding MRI, baseline is defined as the scan performed between Day -14 and Day 1.

On-treatment assessment/event

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

1. **pre-treatment period:** from day of participant's informed consent to before date of first administration of investigational treatment
2. **on-treatment period:** from date of first administration of investigational treatment to 28 days after date of last administration of investigational treatment (including start and stop date)

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

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

9.2.2 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.

9.2.3 Treatments

The Safety Analysis Set will be used for the analyses below.

Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in days to RHH646 will be summarized by means of descriptive statistics 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.

9.3 Primary endpoint(s)/estimand(s) analysis

The primary aim of this study is to evaluate the efficacy of RHH646 administered CCI CCI. A statistical analysis will be performed to compare the change from baseline in cartilage volume in the index region of the knee for participants receiving RHH646 versus those receiving placebo.

In addition, the study aims to evaluate the safety and tolerability of RHH646 CCI of treatment. AEs, ECGs, vital signs, and clinical laboratory assessments such as hematology, blood chemistry, urinalysis will be the endpoints used to assess this objective.

9.3.1 Definition of primary endpoint(s)

The primary efficacy endpoint of the study is change from baseline in cartilage volume in the index region of the knee.

The primary safety endpoint of the study is evaluation of AEs, ECGs, vital signs, and clinical laboratory assessments.

9.3.2 Statistical model, hypothesis, and method of analysis

The aim is to estimate the treatment effect of the RHH646 compared to placebo, for the target population, in the change from baseline in cartilage volume. The definition of the corresponding primary estimand is detailed in [Section 3.1](#).

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

9.3.3 Handling of intercurrent events of primary estimand

Handling of the ICE will follow a hypothetical strategy. Assessments impacted by an ICE will be considered missing and implicitly imputed by the MMRM under the missing at random (MAR) assumption (i.e., assuming that participants with missing data would have efficacy outcomes like those of similar participants in their treatment group who continue their randomized treatment).

The assumptions underlying the hypothetical strategy might be revised and/or the SAP may be amended prior to database lock if:

- An unexpectedly high number of participants show poor compliance with study treatment,
- Other events with potential impact on the interpretation of the treatment effect occur at a relevant frequency.

The definition of "unacceptable non-compliance with treatment" and the impact on the interpretability of the subsequent MRI assessments will happen prior the database lock before unblinding.

9.3.4 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.

9.3.5 Sensitivity analyses

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

9.3.6 Supplementary analysis

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

9.3.7 Safety analysis

For all safety analyses, the Safety Analysis Set will be used. All listings and tables will be presented by treatment group.

Safety summaries (tables, figures) include only data from the on-treatment period 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 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 AEs will be displayed by treatment group and participant.

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

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

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.

9.4 Secondary endpoint(s)/estimand(s) analysis

9.4.1 Pharmacokinetics

Descriptive summary statistics of RHH646 C_{min,ss} at Week 4 will be provided by treatment and visit/sampling time point, including the frequency of concentrations below the LLOQ, which will be reported as zero.

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

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

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

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

9.5 Exploratory endpoint(s) analysis

The statistical analysis for exploratory endpoints will be described in detail in the SAP or in dedicated stand-alone exploratory SAPs.

9.5.1 CCI

CCI

9.5.2 CCI

CCI

9.5.3 CCI

CCI

CCI

9.6 Other Safety analyses

Not applicable.

9.7 Other analyses

Not applicable.

9.8 Interim analysis

An interim analysis with efficacy evaluation (see [Section 4.6](#)) is planned to be conducted. The data will be examined as a preliminary evaluation of therapeutic effect CCI

Additional interim analyses may be conducted CCI or in case of any safety concerns.

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.

9.9 Sample size determination

9.9.1 Primary endpoint(s)

A positive treatment effect is indicated by an increase in cartilage volume at Week 52. A standard deviation of approximately CCI of change from baseline to Week 52 was observed on the preliminary data from OA patients CCI

Under this assumption, a sample size of 35 evaluable participants per arm, i.e., 70 participants in total (randomization ratio 1:1), will provide at least 80% power that the primary analysis will be statistically significant at one-sided 5% significance level for a true effect size of CCI and at least 90% power for a true effect size greater than CCI

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

10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with 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 Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations

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.

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

Protocols and any substantial amendments/modifications to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Signing 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
- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- Inform Novartis immediately if an inspection of the clinical site is requested by a regulatory authority

This clinical study was designed and shall be implemented, executed, and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Clinical Trial Regulation 536/2014, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

10.1.2 Informed consent process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

Informed consent must be obtained before conducting any study-specific procedures (e.g., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

A copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional additional research. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for additional research. Participants who decline to participate in this optional additional research will document this.

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

Information about common side effects already known about the investigational treatment can be found in the IB. This information will be included in the participant informed consent and should be discussed with the participant upon obtaining consent and also 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:

- Pre-screening ICF
- 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
 - Optional consent for activities that may be done outside of the study site
- As applicable, Pregnancy Outcomes Reporting Consent for female participants or the female partners of any male participants who took study treatment

- Patient information sheet for female partners of any male participants who took study treatment
- CCI [REDACTED]

As applicable by local regulation:

- Site Training Consent for Digital Sensors for volunteers wearing a digital sensor for the purpose of collecting data used to confirm that this site meets the qualification requirements for using the digital sensor in this study.
- Site Training Consent for Imaging Devices for volunteers undergoing MRI for the purpose of collecting data used to confirm that this site meets the qualification requirements for collection of MRI in this study.

The study includes an optional sub studies/CCI component 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 optional assessments (CCI [REDACTED]) 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.

As per [Section 4.5](#), 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.).

10.1.3 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.

10.1.4 Committees structure

Not applicable.

10.1.5 Data quality assurance

Monitoring details describing strategy, including 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), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the monitoring plan.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a minimum of 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.

Efforts should be made to collect all data that are relevant to support a statistical analysis aligned with the estimands of interest. If the estimands that are required to support regulatory decision making do not require the collection of the variable after an intercurrent event, then the benefits of collecting such data for other estimands should be weighed against any complications and potential drawbacks of the collection.

10.1.5.1 Data collection

Designated investigator staff will enter the data required by the protocol into the 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.

10.1.5.2 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 AEs 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 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 or statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

10.1.6 Source documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. The investigator must also keep the original ICF signed by the participant (a signed copy is given to the participant). Definition of what constitutes source data and its origin can be found in the source data acknowledgment form.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

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 organization. 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.

10.1.7 Publication policy

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

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

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

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

10.1.8 Protocol adherence and protocol amendments

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.

10.1.8.1 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.

10.2 Appendix 2: Abbreviations and definitions

10.2.1 List of abbreviations

ACR	Albumin:creatinine ratio
ADL	Activities of Daily Living
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AP	Anterior-posterior
APAP	n-Acetyl-Para-Aminophenol
APTT	Activated partial thromboplastin time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
BML	Bone Marrow Lesion
BP	Blood Pressure
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine Kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
cm	centimeter(s)
C _{max}	Maximum concentration
C _{min,ss}	Minimum (trough) concentration, steady state
CMO&PS	Chief Medical Office and Patient Safety
COA	Clinical Outcome Assessment
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
CTA	Clinical Trial Application
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trials Information System
CV	Coefficient of variation
DMC	Data Monitoring Committee
DRESS	Drug Rash with Eosinophilia and Systemic Symptoms
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EOS	End of Study
EOT	End of Treatment
FAS	Full Analysis Set
FIH	First in Human

FLA/C/P	Femur Lateral Anterior/Central/Posterior
FMA/C/P	Femur Medial Anterior/Central/Posterior
FTM	Femur Trochlea Medial/Central/Posterior
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GLCM	Grey Level Co-occurrence Matrix
GLDH	Glutamate Dehydrogenase
GLP	Good Laboratory Practice
HBcAg	Hepatitis B virus core antigen
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDL	High-Density Lipoprotein
HGB	Hemoglobin
HIV	Human immunodeficiency virus
HO-1	Heme Oxygenase-1
CCI	
i.v.	intravenous
IB	Investigator's Brochure
ICE	Intercurrent Events
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IN	Investigator Notification
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine System
JSW	Joint Space Width
K&L	Kellgren and Lawrence
KDIGO	Kidney Disease Improving Global Outcomes
kg	kilogram
CCI	
latJSN	Lateral Joint Space Narrowing
LDH	Lactate dehydrogenase
LDL	Low-Density Lipoprotein
LFT	Liver function test

LLOQ	Lower limit of quantification
MAR	Missing at Random
MedDRA	Medical dictionary for regulatory activities
medJSN	Medial Joint Space Narrowing
mg	milligram(s)
mL	milliliter(s)
MMRM	Mixed Effect Model for Repeated Measures
MOAKS	MRI Osteoarthritis Knee Score
mrem	millirem
MRI	Magnetic Resonance Imaging
mSv	millisieverts
NOAEL	No observed adverse effect level
CCI	
NSAID	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
OHP	Off-site Healthcare Professional
PA	Posterior-anterior
p.o.	Oral(ly)
PCR	Protein-creatinine ratio
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PoC	Proof of Concept
PRO	Patient Reported Outcomes
PT	Prothrombin time
PTOA	Post-Traumatic OA
QD	Once a day
QoL	Quality of Life
QTcF	QT interval corrected by Fridericia's formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
sCr	Serum creatinine
SD	Standard deviation
SJS	Stevens-Johnson Syndrome
SMQ	Standardized MedDRA Query
SoA	Schedule of Activities
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBIL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
TEN	Toxic Epidermal Necrolysis
TLP/C/A	Trochlea Lateral Posterior/Central/Anterior
TMA	Trochlea Medial Anterior
TPM	Trochlea Medial Posterior

ULN	Upper limit of normal
ULOQ	Upper limit of quantification
UTI	Urinary Tract Infection
WHO	World Health Organization
WPI	Widespread Pain Index
μSv	microsieverts

10.2.2 Definitions

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Auxiliary medicinal product	Medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. rescue medication, challenge agents, background treatment or medicinal products used to assess end-points in the clinical trial). Concomitant therapy is not considered as AMP.
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 intervention (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g. q28 days)
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 intervention 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
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 Novartis 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.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational 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, 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 participant about the status of a participant's health condition without amendment or interpretation of the participant'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
Remote	Describes any trial activities performed at a location that is not the investigative site.
Rescreening	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
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 device	Study device is a medical device (marketed or investigational) that is used in a circumstance that makes it part of the investigation.
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
Target knee	Participants left or right knee, selected by the investigator based on patient complaints, medical history, careful knee examination along with a local review of the X-ray. For example, if a similar stage of radiographic disease exists in both knees and the level of pain is similar in both knees, then either knee can be chosen as the target knee. If a similar stage of radiographic disease exists in both knees but the patient acknowledges that one of the knees gives him/her more trouble than the other, the more troublesome knee should be chosen as the target knee.

Tele-visit	Procedures or communications conducted using technology such as telephone or video-conference, whereby the participant is not at the investigative site where the Investigator will conduct the trial.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of consent	<p>Withdrawal of consent from the study occurs when the participant explicitly requests to stop use of their data and/or 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.</p> <p>This request should be distinguished from a request to discontinue the study. Other study participant's privacy rights are described in the corresponding informed consent form.</p>

10.3 Appendix 3: Clinical laboratory tests

10.3.1 Clinically notable laboratory values and vital signs

Please refer to the Laboratory Manual for details.

10.4 Appendix 4: 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
- Participant visit guide
- Individual treatment information - after database lock
- Plain language trial summary - after CSR publication

10.5 Appendix 5: 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 10-1](#) for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in [Table 10-1](#) 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 10-2](#). 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 investigational drug (refer to the Discontinuation of study treatment [Section 7.1](#)), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
 - These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

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

10.5.1 Liver event and laboratory trigger definitions & follow-up requirements

Table 10-1 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	<ul style="list-style-type: none"> • 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:	<ul style="list-style-type: none"> • ALT or AST > 3x baseline AND > 5x ULN

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; non-infectious hepatitis; benign, malignant and unspecified liver neoplasms ULN: upper limit of normal

Table 10-2 Follow up requirements for liver laboratory triggers - ALT, AST, TBL

	ALT	TBL	Liver Symptoms	Action
ALT increase without bilirubin increase:				<ul style="list-style-type: none">• Interrupt study treatment• Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours.• Follow-up for symptoms.• Initiate close monitoring and workup for competing etiologies.• Study treatment can be restarted if liver enzymes return to baseline..
	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	
	If elevated at baseline: ALT > 3 x baseline AND > 5x ULN for more than two weeks OR ALT ≥ 5x baseline AND ≥ 8x ULN			
ALT increase with bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN	TBL > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
	If elevated at baseline: ALT > 2 x baseline AND > 3x ULN			
	If normal at baseline: ALT > 3 x ULN	Normal or elevated*	Severe fatigue, nausea, vomiting, right upper quadrant pain*	
	If elevated at baseline: ALT > 2 x baseline AND > 3x ULN			

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

Table 10-3 Follow up requirements for liver laboratory triggers - Isolated Hyperbilirubinemia

Criteria	Actions required	Follow-up monitoring
Total Bilirubin (isolated)		
>1.5 – 3.0 ULN	<ul style="list-style-type: none"> • 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)	<ul style="list-style-type: none"> • 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 	<p>Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT)</p> <p>Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)</p>
> 10 x ULN	<ul style="list-style-type: none"> • Discontinue the study treatment immediately • Hospitalize the participant • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF 	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution (frequency at Investigator discretion)
Any AE potentially indicative of a liver toxicity	<ul style="list-style-type: none"> • 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 	

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.

10.6 Appendix 6: 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 $\geq 25\%$ compared to baseline during normal hydration status
- Any one of the following:
 - Urine protein-creatinine ratio (PCR) $\geq 1\text{g/g}$ or $\geq 100\text{ mg/mmol}$, OR
 - New onset dipstick proteinuria $\geq 3+$, OR
 - New onset dipstick hematuria $\geq 3+$ (after excluding menstruation, UTI, extreme exercise, or trauma)

Abnormal renal event findings must be confirmed within 24-48 hours after the first assessment.

Once a participant is exposed to study treatment, renal laboratory alerts or renal safety events, as defined in [Table 10-4](#), should be monitored and followed up by the investigator or designated trial staff as summarized in [Table 10-5](#).

10.6.1 Specific Renal Alert Criteria and Actions and Event Follow-up

Table 10-4 Specific renal alert criteria and actions

Renal Event	Actions
Confirmed serum creatinine (SCr) increase 25 – 49%	<ul style="list-style-type: none"> • Consider causes and possible interventions • Follow up within 2-5 days
(SCr) increase 50 % ⁺	<ul style="list-style-type: none"> • Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider participant hospitalization and specialized treatment
New onset dipstick proteinuria $\geq 3+$ OR Protein-creatinine ratio (PCR) $\geq 1\text{g/g Cr}$ (or mg/mmol equivalent as converted by the measuring laboratory)	<ul style="list-style-type: none"> • Consider causes and possible interventions • Assess serum albumin & serum total protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria $\geq 3+$ on urine dipstick	<ul style="list-style-type: none"> • Repeat assessment to confirm • Distinguish hemoglobinuria from hematuria • Urine sediment microscopy • Assess sCr • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

Renal Event	Actions
New evidence of crystals on microscopy	<ul style="list-style-type: none"> • Repeat assessment to confirm • Assess (SCr), urea and electrolytes • Consider causes and possible interventions • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected

* Corresponds to Kidney Disease Improving Global Outcomes (KDIGO) criteria for Acute Kidney Injury

Table 10-5 Renal Event Follow Up

<ul style="list-style-type: none"> • Urine dipstick and sediment microscopy evidence of DIN: crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells • Blood pressure and body weight • (SCr), BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output
Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the eCRF
<ul style="list-style-type: none"> • Event resolution: (sCr within 10% of baseline or PCR < 1 g/g Cr, or ACR <300 mg/g Cr) or • Event stabilization: sCr level with $\pm 10\%$ variability over last 6 months or protein-creatinine ratio stabilization at a new level with $\pm 50\%$ variability over last 6 months. • Analysis of urine markers in samples collected over the course of the DIN event

11 References

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