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Novartis Research and Development

LRX712

Clinical Trial Protocol CLRX712A12201 / NCT04097379

A randomized, placebo-controlled, subject and investigator blinded study investigating the safety, tolerability and preliminary efficacy of 8-week treatment with intra-articular LRX712 to regenerate articular cartilage in patients with mild/moderate knee osteoarthritis

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study procedures. Note: The SOM will not be a part of the Clinical Study Report.

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List of abbreviations

ADE	Adverse Device Effect
ADLs	Activities of Daily Living
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CCPD	Calcium Pyrophosphate Dihydrate Crystal Deposition Disease)
CMO&PS	Chief Medical Office & Patient Safety
COA	Clinical Outcome Assessments
CRO	Contract Research Organization
CSPC	Cartilage Stem Progenitor Cells
CSR	Clinical Study Report
CTC	Common Toxicity Criteria
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked Immunosorbent Assay
EoT	End-of-Treatment
EoS	End-of-Study
eSAE	Electronic Serious Adverse Event
eSource	Electronic Source
FDA	Food and Drug Administration
FIH	First In Human
fmJSW	Fixed Medial Joint Space Width
FSH	Follicle Stimulating Hormone
GAG	Glycosaminoglycans
GCP	Good Clinical Practice
GGT	Gamma-glutamyl Transferase
GLCM	Grey Level Co-Occurrence Matrix
h	Hour
HbsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
hsCRP	High Sensitivity C-Reactive Protein
i.a.	Intra-articular
i.v.	Intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form

ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICRS	International Cartilage Repair Society
IEC	Independent Ethics Committee
IMU	Inertial Measurement Unit
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
JSW	Joint space width
KAM	Knee adduction moment
KCF	Knee contact forces
KLG	Kellgren & Lawrence Grade
CCI	[redacted]
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
mL	Milliliter(s)
MMRM	Mixed effect Model Repeat Measurement
CCI	[redacted]
MRI	Magnetic Resonance Imaging
NCDS	Novartis Clinical Data Standards
OA	Osteoarthritis
PA	Posteroanterior
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic(s)
PerfO	Performance Outcomes
PK	Pharmacokinetic(s)
PoM	Proof-of-Mechanism
CCI	[redacted]
PT	Prothrombin Time
q4w	Every 4 Weeks
QD	Once a Day
QMS	Quality Management System
QTcF	QT Interval Corrected by Fridericia's Formula
R Value	ALT/ALP x ULN
RBC	Red Blood Cell(s)
RoW	Rest of World
s.c.	Subcutaneous

SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
sCR	Serum Creatinine
SD	Standard Deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SLE	Systemic Lupus Erythematosus
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
ULN	Upper Limit of Normal
ULQ	Upper Limit of Quantification
WBC	White Blood Cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent
WPI	Widespread Pain Index

Amendment 4 (July 2021)

Amendment rationale

The main purpose of this amendment is to:

1) Restart the study following an investigation to ensure subject safety, after a temporary hold had been placed on the study by Novartis in February 2021 due to tolerability concerns;
2) Integrate new tolerability and safety data from the current Proof-of-Mechanism (PoM) (LRX712A12201) and completed First-in-Human (FIH) (LRX712X2101) studies;
3) Align the study design with these recent safety and tolerability data, and the efficacy endpoints with the more standard MRI endpoints for this population;
4) Reduce subject and site burden where possible.

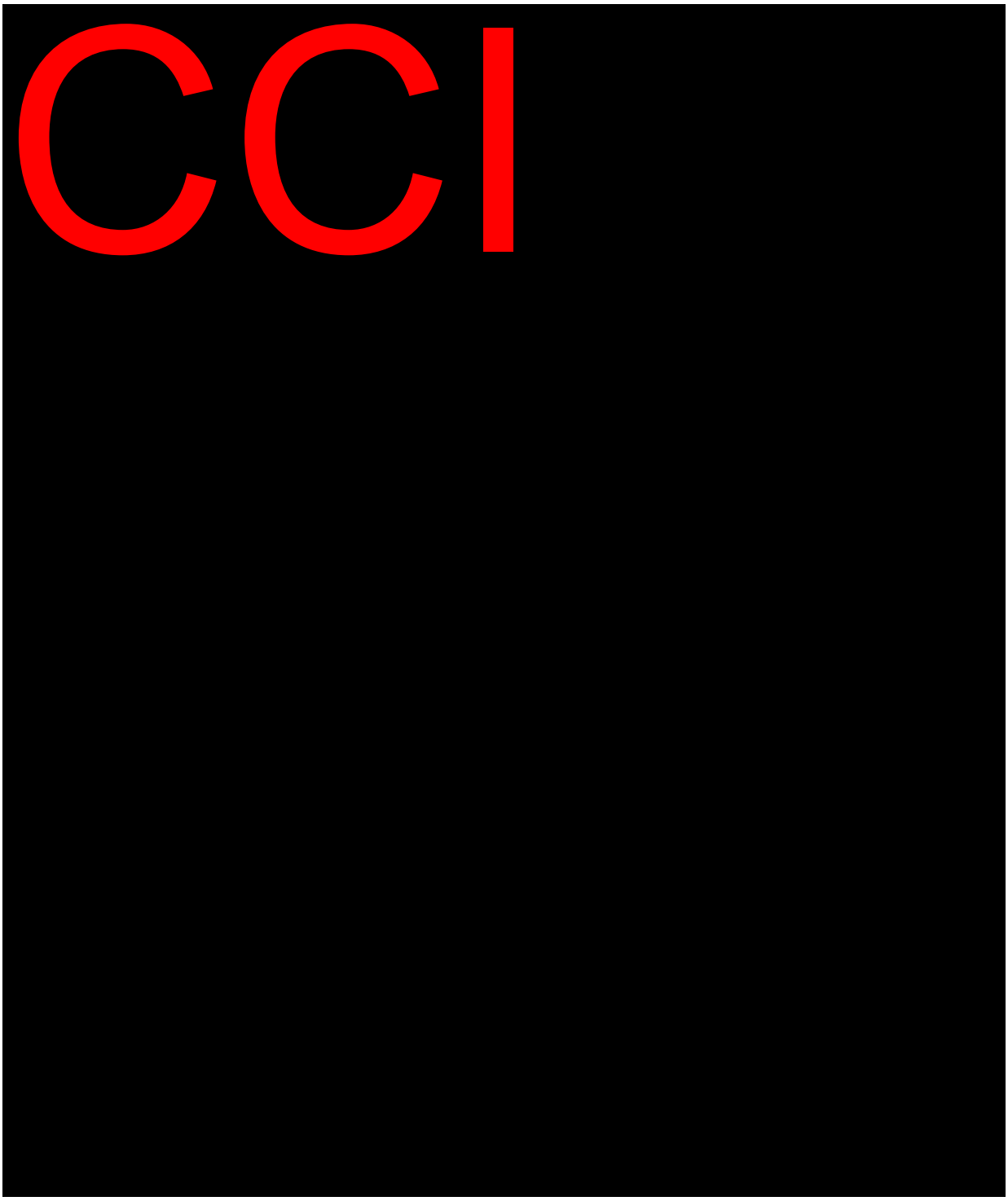
This amendment is characterized by two key design changes: change in LRX712 dose level, and change in the primary endpoint. The change in cartilage volume and thickness will replace the assessment of the cartilage composition (based on [^{23}Na]) as the primary endpoint, and cartilage composition [^{23}Na] will become a secondary endpoint.

- *Change in dose level*: Preliminary data from the first six subjects enrolled in LRX712A12201 identified injection site adverse events, including but not limited to joint warmth and/or swelling, CCI [redacted], following dose administration in subjects (n=3) receiving active drug. As a result, Novartis put the study on temporary hold in February 2021 while further investigations were initiated. CCI [redacted] from the FIH study also identified a pattern of transient elevations in high sensitivity C-Reactive Protein (hsCRP) post-administration, primarily at LRX712 dose levels > 15 mg. In addition, the estimated probability of local tolerability AEs rose with LRX712 dose from 15 mg (5% higher than placebo) to 25 mg (10% higher than placebo) to 75 mg (45% higher than placebo). Therefore, based on available preclinical efficacy data, and on the available safety and tolerability data from human studies, two dose levels of LRX712 are warranted in the revised study design. The original two-arm study design (75 mg LRX712 vs. placebo) has been modified to a three-arm design, with two lower doses of LRX712 (15 mg and 25 mg) vs. placebo.
- *Change in primary endpoint*: The primary endpoint is being changed from [^{23}Na] content to cartilage volume, based on recent data describing an increase in cartilage volume at week 28 in response to another chondro-anabolic investigational drug (Novartis LNA043) administration (Trattnig et al. 2021). The timeframe of this observed chondro-anabolic effect coincides with the timing of efficacy assessments in the present PoM study, suggesting a high likelihood of being able to detect a relevant treatment effect of LRX712 based on this endpoint, if one exists.

Exploratory endpoints and assessments: CCI [redacted] In addition, the baseline visit has been removed and activities originally scheduled for that visit, shifted to the Day 1 visit, pre-dose administration.

At the time of this amendment, six subjects have been enrolled in the study and have completed their treatment period, who will continue on the treatment arm to which they were randomized (all the dosing completed prior to temporary hold), but will be switched to the new assessment schedule at their next study visit.

Changes to the protocol




CCI

Minor editorial changes have been made throughout the protocol for increased clarity and consistency.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions. A copy of this amended protocol will be sent to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and Health Authorities (HAs).

The changes described in this amended protocol require IRB/IEC and HA approval prior to implementation.

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

Amendment 3 (November 2020)

Amendment rationale

The main purpose of this amendment is to include flexible language for participating countries to follow their national regulatory requirements or guidelines related to the COVID-19 pandemic and SARS-CoV-2 testing. The study was initially set up as a single site study but now it is expanding into new countries, and therefore the protocol requires some adaptations to add flexibility and accommodate country-specific procedures. The sponsor's recommendation for SARS-CoV-2 testing and minimum requirements are outlined, as well as the potential use of a COVID-19 vaccine in the future.

The protocol is also amended to simplify and clarify eligibility criteria (BMI, age, radiographic criteria) to better match the population expected to benefit from LRX712, to update requirements for condom use for sexually active males according to internal safety guidelines, and to update the safety reporting with the addition of rules for reporting "adverse device effect" and "serious adverse device effect".

Changes to the protocol


CCI

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Amendment 2 (June 2020)

Amendment rationale

The main purpose of this amendment is to update the language of essential protocol sections, such as Eligibility criteria and Prohibited medication among others, in order to better align them, correct inconsistencies that may have contributed to errors, and improve overall clarity. Timelines for use of Prohibited medication and Eligibility criteria have also been adjusted. CCI

The protocol is also amended to include measures taken in line with the guidance document for restart of clinical research during the COVID-19 pandemic issued by the competent authority in the Netherlands (CCMO).

Changes to the protocol


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Amendment 1 (January 2020)

Amendment rationale

The main purpose of this amendment is to update the study duration and the sample size calculation, among other details explained below, in response to suggestions of the Ethics Committee following review of the protocol in October 2019.

In response to a request to change the statistical plan to include a 95% confidence interval instead of 90% and a 2-sided p-value. Using 80% power for a test two-sided alpha level 0.05, demonstrating a minimum 20% difference in the primary endpoint between the two treatment arms of the study, requires an increase in the sample size from 26 to 34 subjects (17 completers at week 28 per treatment arm). Sections discussing sample size have been updated throughout the protocol.

This amendment also reflects on the suggestion of the Committee to follow the pharmacodynamic effect of LRX712 for a longer period, which will enable better understanding of the evolution of structural effects of the drug. In this amendment, we introduce a W52 visit with a 4-week window to capture the long-term effects of the treatment, first and foremost on a structural level including both compositional and morphometric effects on cartilage.

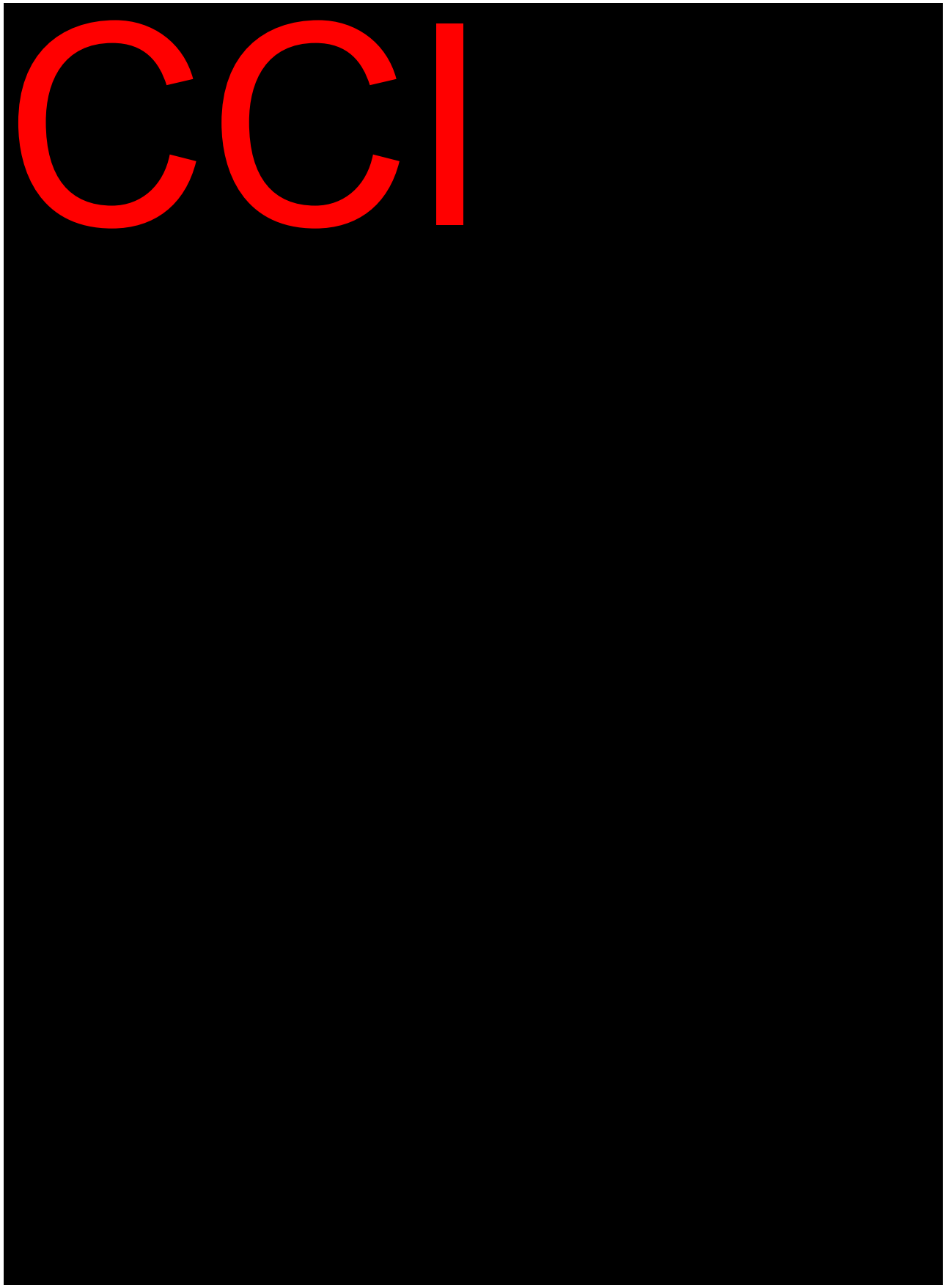
Several adjustments regarded the list of eligibility criteria are listed below in the Changes to the protocol, among which are the following key changes or updates:

- Reduction of the age range to 35 to 65 years
- Updating the definition of symptomatic knee OA, while emphasizing exclusively or predominantly one-sided clinical disease in the index knee
- Removal of unilateral knee OA as structural requirement
- Inclusion of two exclusion criteria on analgesic medication use

The rescue medication section has also been modified to be in line with the overall context of the trial (primary focus on cartilage structure) and provide some guidelines to the use of NSAIDs during the study period. Since there are studies supporting the notion that chronic use of certain NSAIDs can promote cartilage degradation and thereby interfere with the beneficial effects of chondrogenic therapy, use of these medications will be carefully monitored and documented.

Finally, as part of the extended monitoring, we introduced two follow-up calls in addition to the W52 study visit. During these calls, information on AEs of special interest with focus on events, complications, procedures related to the index knee (Section 10.1.1).

Changes to the protocol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Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
Dosage	Dose of the study treatment given to the subject 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 paper source forms 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 subject or at a later point in time as defined by the protocol.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
eSource	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
Investigational drug/treatment	The drug whose properties are being tested in the study
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Run in Failure	A subject who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to subject's medications or other intervention)
Screen Failure	A subject who is screened but is not treated or randomized
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
Study treatment	Any drug or combination of drugs administered to the study subjects as part of the required study procedures; includes investigational drug(s), control(s) or background therapy

Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Protocol summary

Protocol number	CLRX712A12201
Full Title	A randomized, placebo-controlled, subject and investigator blinded study investigating the safety, tolerability and preliminary efficacy of 8-week treatment with intra-articular LRX712 to regenerate articular cartilage in patients with mild/moderate knee osteoarthritis.
Brief title	Safety, tolerability and preliminary efficacy of LRX712 in knee OA.
Sponsor and Clinical Phase	Novartis, Phase II.
Investigation type	Drug
Study type	Interventional
Purpose and rationale	This study aims for exploring the preliminary efficacy of LRX712 when administered as 3 consecutive i.a. injections at monthly intervals (i.e. 8-week treatment period) by evaluating the ability of the drug to restore structural integrity of articular cartilage. Efficacy will be evaluated in the context of systemic safety and local tolerability of the investigational drug.
Primary Objective(s)	To assess the efficacy of multiple i.a. injections of LRX712 in improving the morphometric characteristics of articular cartilage in the medial femoral condyle.
Secondary Objectives	To assess the efficacy of multiple i.a. injections of LRX712 in regenerating the composition of articular hyaline cartilage in the medial femoral condyle. To evaluate LRX712 and metabolite MAE344 pharmacokinetics in plasma. To assess safety and local tolerability of multiple i.a. injections of LRX712.
Study design	This is a 52 week, randomized, double-blind, placebo-controlled, parallel-group, clinical study.
Population	Subjects with mild/moderate knee OA (KLG 2 or 3) in the medial tibio-femoral compartment, joint space width fixed medial (JSW) gender specific 1.5-4 mm without significant malalignment, joint effusion, meniscal damage, and with a widespread pain index (WPI) ≤ 4. Up to 45 patients will be randomized in the study, to ensure that at least 39 patients will complete the Week 28 assessments, assuming a 13% drop out rate until this time point.
Key Inclusion criteria	Patients are 35 to 75 years old at Screening. At least 50 kg, BMI 18 - 35 kg/m^2 at Screening. Symptomatic knee OA (i.e. KLG of 2 or 3). Fixed medial JSW (fmJSW) between 1.5 and 3.5 (females), or 2 and 4 mm (males) at the X=0.225 fixed point in the medial tibio-femoral compartment. Patient must be ambulatory (able to walk without assistive devices).

Key Exclusion criteria	Patient has a known autoimmune disease, inflammatory arthropathy (including but not limited to rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, SLE, CPPD, gout and fibromyalgia), active acute or chronic infection of the joint, Lyme disease involving the knee, systemic cartilage disorder, or a known systemic connective tissue disease. Patient has had surgical treatment of the target knee using mosaicplasty, microfracture, or resecting more than 50% of meniscal tissue. Patient has symptomatic, isolated patello-femoral pain in the index knee as per the Investigator's examination. Patient has malalignment (valgus- or varus-deformity) in the index knee ≥ 7.5° as per anatomic PA axis measured by weight-bearing short knee radiography. Effusion in the index knee that clinically required aspiration in the past 12 weeks prior to Screening, or that is clinically relevant in the index knee as per physical examination (bulge sign, patellar tap) at Screening or Day 1. Any local i.a. treatment to the knee, including but not restricted to visco-supplementation and corticosteroids, within 12 weeks prior to Screening. Patient has widespread pain index ≥4.
Study treatment	Three treatment arms are planned to test repeated dosing with three consecutive i.a. injections of either LRX712 15 mg, LRX712 25 mg, or placebo.
Key Efficacy assessments	Change from baseline in cartilage morphometrics (volume) in the medial femoral condyle evaluated with 7T MRI. Change in articular cartilage [^{23}Na] content from baseline compared to placebo measured with 7T MRI.
Pharmacokinetic assessments	To evaluate LRX712 and metabolite MAE344 pharmacokinetics in plasma and synovial fluid.
Key safety assessments	Hematology, blood chemistry, urinalysis. Vital signs. Local and Systemic Adverse Events (CTC-AE) and 12-lead digitized ECG parameters (PR, QRS, heart rate, RR, QT, QTc).
Other assessments	CCI [redacted]

Data analysis	It is hypothesized that LRX712 treatment can increase the cartilage volume of the impacted compartment from its baseline level, and that this change can be measured by 7T MRI. For the primary analysis, the signal intensity (measured as an absolute change from baseline) will be analyzed, at week 28, using a Mixed effect Model Repeat Measurement (MMRM) with an unstructured covariance matrix. The secondary PD endpoints (i.e., cartilage [^{23}Na] content (weeks 16, 28 and 52) and volume at weeks 16 and 52) will be analyzed in the same manner as the primary endpoint. For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group. LRX712 and MAE344 plasma concentration data will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.
Key words	knee osteoarthritis, chondroanabolic drug, articular cartilage, magnetic resonance imaging, CCI

1 Introduction

1.1 Background

Approximately 10-12% of the adult population has symptomatic knee OA with a worldwide estimate of 250 million people affected in 2012 (Vos 2012; Valdes and Stocks 2018). The prevalence of OA is progressively rising due to an increase in life expectancy and population aging, along with rising prevalence of predisposing risk factors such as obesity and related metabolic conditions.

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 (Piva et al 2015). The hallmark of OA is joint pain and progressive degradation of articular cartilage, synovitis, and alterations in subchondral bone and peri-articular tissues (Goldring et al 2011).

The mainstay of OA treatment includes non-pharmacological and pharmacological measures to reduce pain (analgesic medication) and improve knee and lower-extremity function (physiotherapy). Current pharmacological treatments for knee OA are directed only at symptoms without addressing structural alterations, posing an unmet medical need for patients.

Despite major efforts in the past decades, disease-modifying OA drugs remain to be developed. None of the tested drug candidates has restored the degenerated articular cartilage and thereby the structural integrity and function of the knee joint. Therefore, the quest for novel compounds that can potentially halt or reverse the structural changes associated with OA continues.

LRX712 is a synthetic, small molecular entity that was identified via phenotypic screening. The drug is intended for intra-articular (i.a.) administration. The direct molecular target of LRX712 has not been identified yet, but the compound is known to trigger cartilage stem/progenitor cells (CSPCs) to undergo differentiation into chondrocytes and facilitate hyaline cartilage repair, while avoiding any influence on molecules that are involved in tissue fibrosis and tissue hypertrophy/ossification. LRX712 induces restoration of hyaline articular cartilage in preclinical models. Treatment with LRX712 might also delay surgical interventions (e.g., knee arthroplasty) in patients with OA, by promoting hyaline cartilage regeneration with subsequent clinical benefits in terms of pain reduction and improved knee function.

LRX712 has been evaluated in a single ascending dose-escalation (First-in-Human) study to explore and document the safety and tolerability of the compound in the 0.5 to 75 mg dose range administered to patients with OA (KLG 1 to KLG3) as an intra-articular injection. This protocol is prepared based on the results of the previous study and adapted according to a safety analysis of data from subjects enrolled in this ongoing study.

1.2 Nonclinical data

1.2.1 Physical, chemical and pharmaceutical properties

LRX712 drug substance is a crystalline solid with CCI [redacted]

LRX712 drug product consists of 25 mg/mL microcrystals suspension for injection. The solution is a whitish suspension intended for i.a. administration.

Standard syringes and needles will be used for diluting and dosing of LRX712 25 mg/mL suspension for injection and are described in the SOM.

For further information, please refer to the Investigator's Brochure, Section 3.

1.2.2 Pharmacology

In healthy cartilage, it has been demonstrated that approximately 4% of cells display mesenchymal progenitor cell markers. These cartilage stem progenitor cells (CSPCs) increase in number after articular cartilage degeneration, and are capable of multi-lineage differentiation, including into chondrocytes, when exposed to an appropriate signaling environment. It is thought that these cells are involved in regeneration of damaged cartilage. However, they may also be abnormally activated in affected joints and directly contribute to osteophyte formation and cartilage degradation.

LRX712 is a small molecule that directly promote chondrogenesis *in vitro* in human CSPCs and in human articular chondrocytes. It is intended for i.a. administration. It was identified utilizing a non-biased high throughput phenotypic screen for identification of small, drug-like compounds capable of selectively directing the differentiation of human CSPCs to chondrocytes. Although LRX712 promotes cartilage regeneration in animal models, no preclinical data indicate growth/overgrowth of cartilage at any other anatomic location. LRX712 has not been observed to promote *in vitro* cell proliferation in any cell type examined to date.

Using qPCR, 1 µM LRX712 was found to significantly increase Sox9, collagen II, aggrecan, and lubricin at 24 hours after dosing. The increase in chondrogenic differentiation was not associated with a significant increase in proliferation, suggesting a different mechanism of action than for growth factors, such as FGF18. CCI [redacted]

To evaluate LRX712 *in vivo* as a cartilage repair therapeutic, a rat meniscal tear model was utilized (Gerwin et al 2010). In this model, medial femoral cartilage repair of 70% and 92% was observed after a single i.a. administration of 250 µg (25 µL of a 10 mg/mL suspension) and 1250 µg (25 µL of a 50 mg/mL suspension) LRX712, respectively. Safranin O staining has confirmed the synthesis of glycosaminoglycans (GAGs) as the early event in cartilage regeneration.

When dosed directly into the synovial cavity in the undamaged knee joint of naive rats, no evident histological changes in the articular cartilage, the meniscal fibrocartilage, nor the synovial tissues were observed. CCI [redacted]

1.2.3 Non-clinical pharmacokinetics and metabolism

LRX712 was assessed in pharmacokinetic and toxicokinetic studies. The parent drug and its inactive major metabolite, N-oxide MAE344, were determined by LC-MS/MS.

CCI [redacted]

[redacted]

[redacted]

[redacted]. LRX712 half-life in human synovial fluid is unknown.

The bioavailability in man after i.a. administration is expected to be 100%. A single i.a. dose of 100 ng, administered as an immediate release formulation, achieved cartilage repair (approx.70%) in a rat meniscal tear model; at 5 minutes post-dose, the synovial fluid was 293 ng/mL and declined rapidly thereafter with a half-life of <1 hr. LRX712 concentrations in human synovial fluid obtained at 72 hours post-dose in the FIH study were in the range between 54.4 and 202 ng/mL after single doses of either 15 or 25 mg (as extended release formulations). Local synovial fluid concentrations were most likely higher at earlier time points than 72 hours post dose. Therefore, dose levels of 15 and 25 mg/knee, given as q4w x3 doses are predicted to be in the efficacious range.

CCI [redacted]

For the calculation of animal exposure multiples, the plasma exposure at NOAEL in animals after i.v. administration was compared to the human plasma exposure at single intra-articular doses of 0.5 mg, and 75 mg, which were starting dose and evaluated top dose, respectively. With the starting dose of 0.5 mg, exposure multiples ≥ 3500 were calculated, whereas for the dose of 75 mg, an exposure multiple of 18 (based on AUCinf) is obtained. Exposure multiples are higher at 15 mg and 25 mg (see Section 4.2).

1.2.4 Toxicology summary

CCI [redacted]

When administered i.a. in dogs, treatment with the microcrystal formulation at the highest dose of 25 mg/knee/injection resulted in mild to moderate granulomatous inflammation of the knee joint synovium, which recovered partially after 5 weeks of the treatment-free recovery period. This effect is adverse and reflects an overloading of the joint with microcrystal particle, rather than a sign of LRX712 toxicity. The NOAEL could be established at 2.5 mg/knee/injection after 13 weeks of treatment with the ER formulation.

1.2.5 Teratogenicity and reproductive toxicity data

Formal studies to assess effects of LRX712 on the reproductive functions have not yet been conducted. Potential effects on male fertility have been assessed by careful histopathologic examination of the testes and the accessory organs in the rodent and non-rodent 2-week toxicity studies.CCI [redacted]

1.3 Clinical data

1.3.1 Human safety and tolerability data

The completed first-in-human study enrolling 42 subjects with early to moderate OA (KLG 1-3) evaluated the safety, tolerability and pharmacokinetic profile of single injections of LRX712 microcrystals (at doses from 0.5 to 75 mg, 7 groups of 6 subjects each, with randomization ratio 4:2 between LRX712 and placebo) into the knee. Two sentinel subjects (LRX712: placebo = 1:1) were dosed first in each cohort, and their safety data were reviewed before dosing the remaining 4 subjects. LRX712 was safe up to single 75 mg i.a. injection in subjects with OA. Injection site tolerability reactions were less frequent and milder in lower dose groups compared to the 40 and 75 mg dose groups, where 75% and 100% of subjects, respectively, reported any adverse injection site reaction. Of those, (3/4 subjects reported moderate reactions in the 40 mg group and 2/4 in the 75 mg group). A total of 29 subjects (69.0%) consisting of more than 75% of subjects in the LRX712 treatment groups (25subjects) and 4 subjects (28.6 %) in the placebo group had AEs suspected to be related to the study drug by the Investigator. All subjects in the treatment groups LRX712 7.5 mg, LRX712 25 mg, LRX712 40 mg, LRX712 75 mg had AEs suspected to be related to the study drug by the Investigator. The most frequent AEs were injection site warmth, discomfort or pain, or related terms. . CCI [redacted]

All subjects exposed to LRX712 reported at least one AE. However, there were no SAEs, AE-related discontinuations, or death. None of the AEs posed a systemic safety signal.

CCI [redacted] As a result, the study was put on temporary hold while further investigations were initiated. CCI [redacted] from the FIH study also identified a pattern of transient (< 5 days duration) elevations in hsCRP post-administration, increasing with LRX712 dose levels > 15 mg, consistent with observed during acute respiratory illness, for example, hsCRP elevations Pathologic values ranged from 5-57.5 mg/L (mean 12.8 mg/L, median 8.4 mg/L).

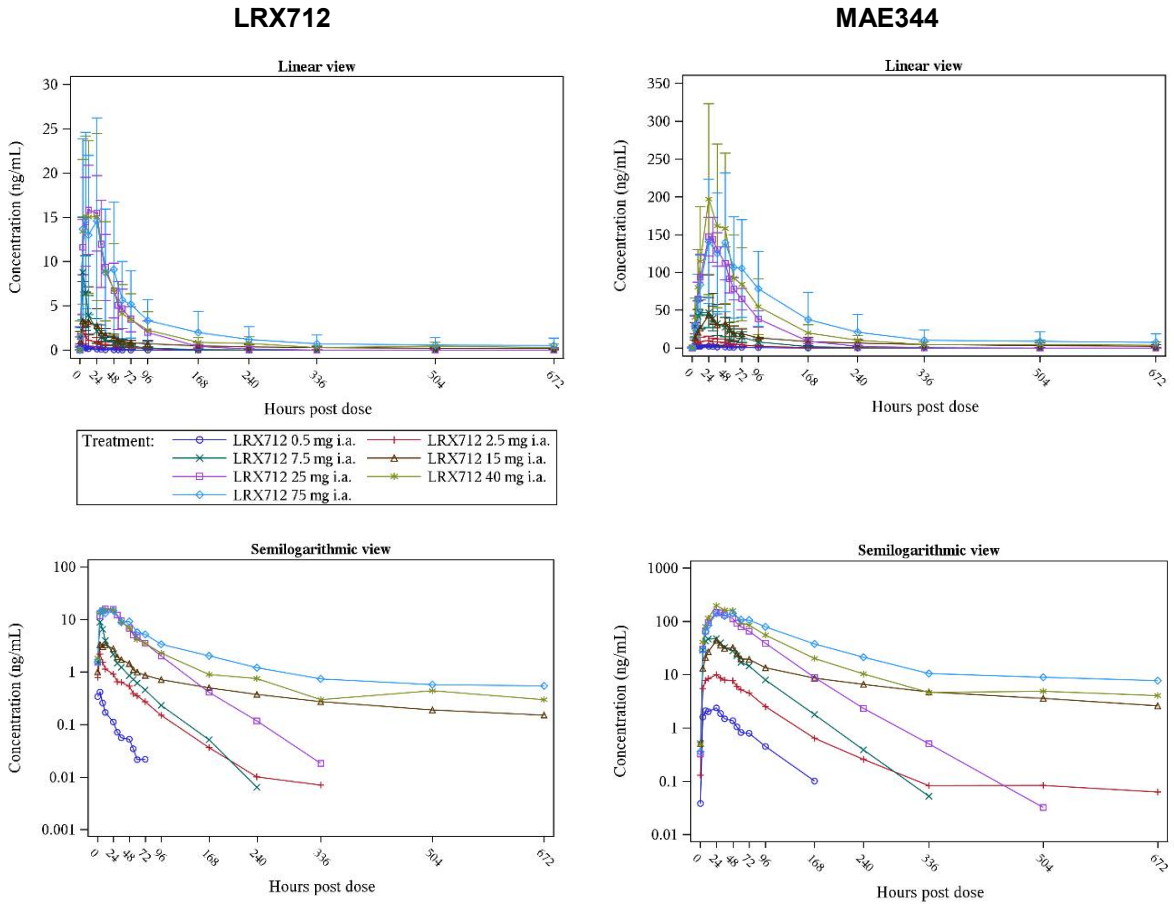
1.3.2 Human pharmacokinetic data

Following intra-articular administration, measurable plasma concentrations were already obtained at the starting dose of 0.5 mg. After single doses, the plasma concentration of LRX712 peaked between 4 and 6 hours post dose (median) at doses between 0.5 and 7.5 mg (Figure 1-1). At doses greater than or equal to 15 mg, the median Tmax increased to 14 to 24 hours and plasma concentrations remained measurable for several weeks. T1/2 increased from less than 43 hours at the three lowest dose levels to 239 hours at 15 mg. This suggests a slower release of LRX712 from synovial fluid into the systemic circulation at higher doses, starting at 15 mg, in line with predictions from semi-physiological modeling. Plasma exposure increased approximately dose-proportionally up to 40 mg, with a less than dose-proportional further increase from 40 to 75 mg. In approximately half of subjects, plasma concentrations were

measurable for the complete 4-week sampling period at doses greater than or equal to 15 mg. Cmax levels did not show any further increase with doses that were greater than or equal to 25 mg. In the dose range between 7.5 and 75 mg, synovial fluid concentrations were measured in 9 out of 20 subjects. Concentrations at 72 hours post-dose in 8 out of these 9 subjects were much higher than in plasma and ranged between 54.4 and 1900 ng/mL. In one subject, the synovial fluid level was <BLQ at 72 h post dose. No obvious dose to local exposure relationship could be established.

MAE344 is an N-oxide metabolite of LRX712 and was measured in plasma in all patients in all cohorts. The plasma exposure of MAE344 exceeded the exposure of the parent drug by far. Depending on the dose level, Cmax and AUCinf were 5- to 12-fold and 12- to 18-fold higher than for LRX712, respectively.

Figure 1-1 Mean time - plasma concentration profiles of LRX712 and MAE344 following single intra-articular doses of 0.5 to 75 mg



Preliminary PK results from the 3 out of 6 subjects randomized to the LRX712 75 mg arm showed time-concentration profiles which are in line with PK from the FIH study, except for one subject who showed a higher plasma Cmax after the second and third i.a. injection, i.e 49.3 and 46.4 ng/mL, respectively.

1.3.3 Human pharmacodynamic data

Pharmacodynamic data are not yet available.

1.4 Purpose

This study will explore the preliminary efficacy of LRX712 when administered as 3 consecutive i.a. injections at monthly intervals (i.e., an 8-week treatment period) by evaluating the ability of the drug to regenerate articular cartilage. Efficacy will be evaluated in the context of systemic safety and local tolerability. The primary endpoint will be measured by high-resolution 7T Magnetic Resonance Imaging (MRI), which is the gold standard for non-invasive quantification of the composition and morphometrics of articular cartilage. Clarifying the structural benefits triggered by LRX712 relative to its tolerability and/or safety profile will inform about the benefit-risk profile of the drug as well as its further development for the treatment of knee OA.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the efficacy of q4w x3 i.a. injections of LRX712 in restoring the morphometrics of articular cartilage in the medial femoral condyle	• Change in the medial femoral condyle cartilage volume in the index region measured by 7T MRI from baseline to week 28 in LRX712- vs. placebo-treated patients
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate LRX712 and metabolite MAE344 pharmacokinetics in plasma and synovial fluid	• PK parameters in plasma: Tmax, Cmax, Cmin in plasma (as per time-points defined in PK blood collection Table 8-2) Synovial fluid: concentration at Day 1, Week 4, Week 8
• To assess safety and local tolerability of multiple i.a. injections of LRX712	• Vital signs (blood pressure, heart rate, temperature) as per assessment schedule • Hematology, blood chemistry and urinalysis as per assessment schedule • Local and Systemic Adverse Events • ECG parameters (PR, QRS, heart rate, RR, QT, QTc) as per assessment schedule
• To assess the efficacy of q4w x3 i.a. injections of LRX712 in regenerating the articular hyaline cartilage composition in the medial femoral condyle	• Change in articular cartilage [^{23}Na] content measured by 7T MRI from baseline to weeks 16, 28 and 52 in LRX712- vs. placebo-treated patients
• To assess the efficacy of q4w x3 i.a. injections of LRX712 in restoring the morphometrics of articular cartilage in the medial femoral condyle	• Change in the medial femoral condyle cartilage volume measured by 7T MRI from baseline to Weeks 16 and 52
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**

Objective(s)	Endpoint(s)
CCI	

Objective(s)	Endpoint(s)
CCI	

3 Study design

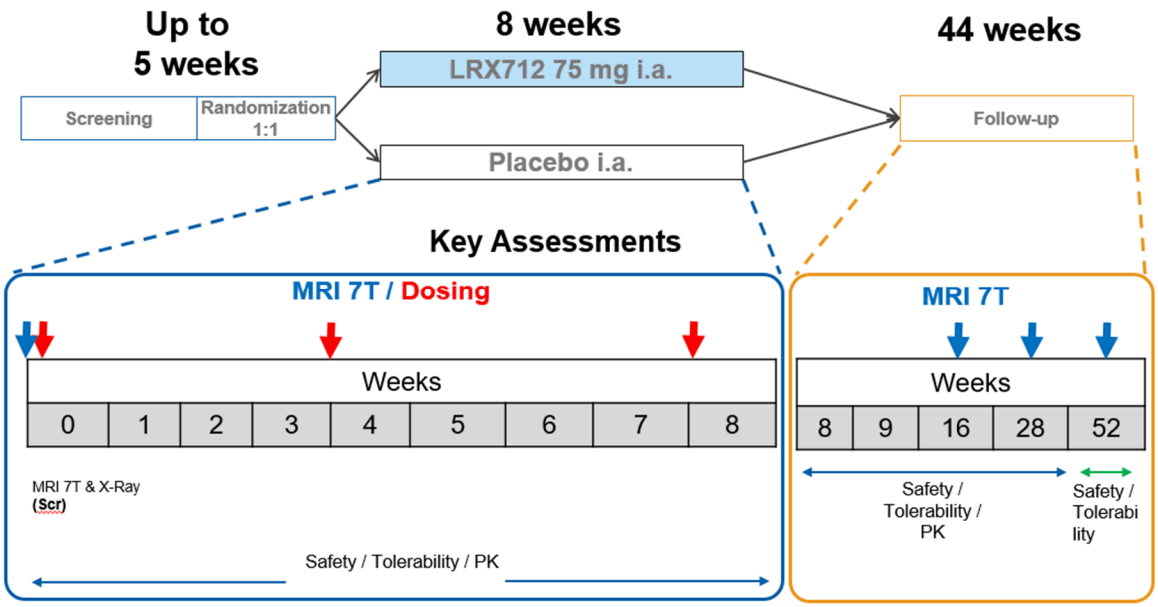
3.1 Protocol amendment 3

In this section, we describe the study design that was in place for the first six (6) subjects, up until the time when the study was temporarily halted in February 2021:

- 75 mg LRX712 q4 weeks x 3 doses (n=3)
- Placebo q4 weeks x 3 doses (n=3)

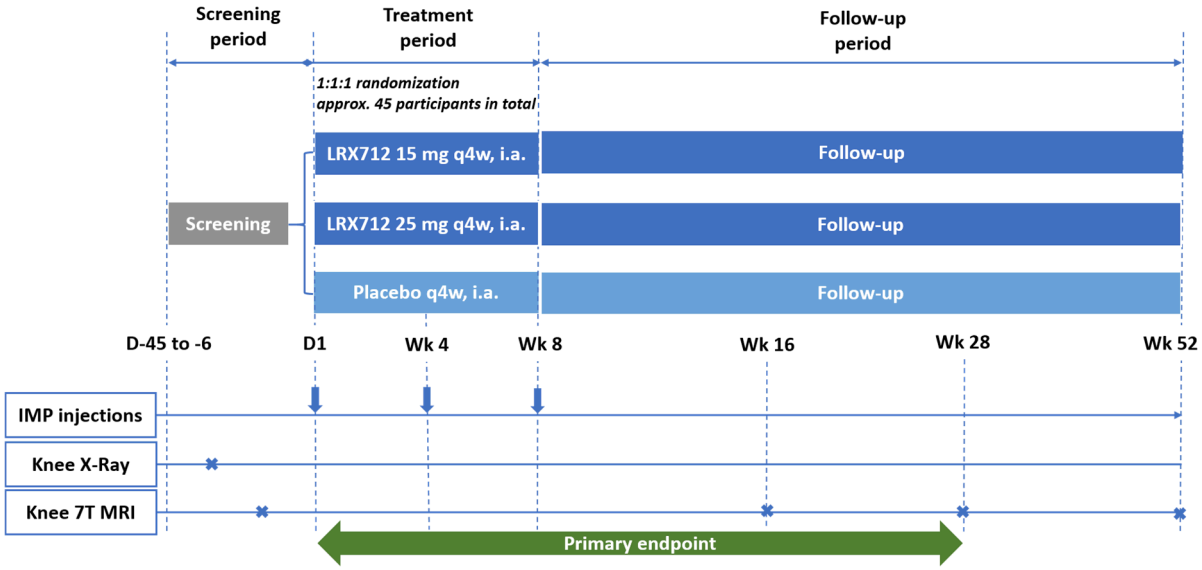
CCI , and data from the 3 subjects who completed dosing with placebo will be pooled, with the data from subjects enrolled after the implementation of protocol amendment 4 (see Section 3.2)

Figure 3-1 Study design protocol amendment 3



3.2 Protocol amendment 4

Figure 3-2 Study design protocol amendment 4



This section describes the study design as amended in July 2021. In this revised protocol the word baseline refers to data collected at Screening for the imaging assessments (X-Ray and 7T MRI), and at Day 1 (-1.5 h pre-dose) for the non-imaging assessments (as per assessment schedule).

This is an exploratory study, with 7-week screening, 8-week treatment and 44-week follow-up periods, using a 3-treatment arm, parallel-group, randomized, double-blind, placebo-controlled clinical study design (Figure 3-1). Approximately 45 patients will be randomized in the study to ensure that at least 39 patients will complete the Week 28 assessments, assuming a 15% drop out rate. Additional subjects may be enrolled if the dropout rate exceeds 13%.

Selected key study assessments include knee X-ray, 7T MRI, triplicate 12-lead digitized ECGs, laboratory measures (e.g., systemic inflammatory markers), PK blood and synovial fluid collection CCI . Please see Table 8-1 for further information.

All MRI assessments at Screening, Week 16, Week 28 and Week 52 (EOS) will be performed at the specific site called investigational site for medical device (subsequently in the protocol referred to as imaging site, for simplicity).

Subjects who meet the eligibility criteria at screening will be admitted for Day 1 evaluations. Study sites may choose to admit subjects overnight on Day -1 and from Day 1 to Day 2, due to the extensive assessment schedule and organizational purposes.

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

The study consists of 3 periods:

Screening (Day -45 to Day -6)

Informed consent will be obtained prior to undertaking any study specific procedures. The Screening epoch begins at Day -45 and ends with randomization between Day -5 to Day -1.

All entry criteria must be fulfilled before randomization (and latest on Day -6). In the case where a safety laboratory assessment at Screening is outside of the range specified in the exclusion criteria, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the subject must be excluded from the study.

It is recommended to perform simple Screening assessments first (e.g., medical history, 12-lead digitized ECG, vital signs, age, body mass index, etc.) to identify non-eligible subjects early, followed by laboratory samples, which require shipping and analysis. Finally, the X-ray examination should confirm the radiographic presence of OA and fmJSW in the 1.5-3.5 mm range for females, and 2-4 mm range for males (based on normative values of 4.1-5.5 for women and 4.9-6.5 for men (Beattie et al 2008) at the x=0.225 fixed point of the medial tibio-femoral compartment (Neumann et al 2009).

MRI examination is performed during the Screening period after verifying that none of the previous Screening tests precludes study eligibility.

Due to the extensive preparation of study medication, the randomization may be performed the days before study drug administration on Day 1 (Day -5 to Day -1), once eligibility is confirmed and as near to Day 1 as possible. The reference for visit scheduling throughout the study will be Day 1. Eligible subjects will be randomized in a 1:1:1 ratio to either i.a. LRX712 15 mg, LRX712 25 mg, or placebo.

Please see the SOM for further details on Screening assessments.

Treatment (8 weeks)

First dose of investigational treatment will be administered on Day 1. Each subject will receive 3 i.a. doses, one every 4 weeks. The third and last dose will be administered at the Week 8 visit, which will thus correspond to the End of Treatment (EoT) visit.

Post treatment Follow-up (44 weeks)

After completing the EoT visit, subjects will enter a post-treatment follow-up period consisting of five visits at Week 8 + 1 day, Week 9, 16, 28 and 52, the latter being the End of Study visit.

Following their study participation, subjects will be further followed by their treating physician, if required, according to the local standard of care.

4 Rationale

4.1 Rationale for study design

The design of this study addresses the primary objective of cartilage regeneration in subjects with mild/moderate OA of the knee and considers (i) the clinical need; (ii) clinical and preclinical data on LRX712; (iii) current practice with intra-articular injectable drugs; and (iv) the burden on patients with knee OA. The combination of frequent clinical and laboratory safety monitoring, as well as MRI with cartilage-specific pulse sequences (Juras et al 2016), performed at multiple time-points, CCI [redacted] will ensure appropriate evaluation of LRX712 safety, tolerability and efficacy, from both a morphological and a functional standpoint.

The parallel design ensures comparison of potential dose-dependent adverse events and distinguishes them from potential procedure (i.a. injection)-related AEs.

The study has been designed as subject- and investigator-blinded in order to ensure that both investigators and subjects remain in a state of equipoise, so that a putative difference between the treated and control groups can be interpreted as an effect of study treatment.

The study duration of 8 weeks of treatment with 11 months of monitoring after the last administration of study drug is considered adequate to monitor safety and assess potential efficacy of the drug using MRI. Randomization will be 1:1:1 (2 treatment groups:placebo), in order to also maximize statistical power for showing differences in the primary efficacy endpoint between subjects exposed to either of the two doses of LRX712 vs. placebo.

The subject population (with medial OA of the medial compartment of the knee) has been selected in order to i) ensure homogeneity in a relatively small population; ii) focus on cartilage regeneration in relatively less advanced stages of OA anchored to fmJSW 1.5-3.5 (females) or 2—4 (males); iii) maximize relevance of the findings as the medial compartment is the most frequently affected region of the knee in patients with OA (Wise et al 2012); and iv) minimize bias caused by pain from the contralateral knee affecting the reporting of pain from the index knee as well as knee function.

CCI [redacted]

Cardiac safety monitoring is performed by triplicate 12-lead digitized ECG at T_{max} after the first dose and throughout the study as per assessment schedule. This is considered adequate for safety assessment during repeated dosing with LRX712 15 or 25 mg because of the absence of effects on QT, QRS, PR, heart rate and blood pressure CCI [redacted]

4.2 Rationale for dose/regimen and duration of treatment

The duration of treatment in this exploratory study will be 8-weeks with 3 consecutive doses every 4 weeks. This will be followed by a 44-week observation period to allow for the anticipated therapeutic effect of the drug to evolve resulting in a total study period of 52 weeks.

Human pharmacokinetics was predicted based on dog PK after i.v. and i.a. administration using a semi-physiological model (CCI). Human plasma clearance and distribution volume were predicted to be 17 L/h and 373 L, respectively, with an accompanying plasma half-life of 15 h after i.v. dosing. The plasma half-life after i.a. administration of the extended-release formulation is much longer.

For the calculation of animal exposure multiples, as summarized in Table 4-1, the plasma exposure at NOAEL in animals after i.v. administration was compared to the observed human plasma exposure at single intra-articular doses of 15, 25 and 75 mg, the relevant dose levels for this study. Based on the AUC at NOAEL in rats and dogs, exposure multiples of 18 and 188, respectively, at the highest dose of 75 mg are calculated.

Hence, utilizing the maximum dose of 25 mg is based on the following reasons: (i) the dose-exposure relationship in preclinical models, as explained above and the dose-efficacy relationship in rate and canine models of OA, as outlined in the following section; (ii) the reasonable systemic exposure multiples, as described in Table 4-1; (iii) the finding of only minimal-to-mild and reversible local foreign body histological reactions in rats (CCI and dogs treated i.a. with a high dose of LRX712 ER microcrystal formulation CCI (iv) the clinical data from the FIH study, which showed an acceptable systemic safety profile of LRX712 across the dose range from 0.5 mg/knee to 75 mg/knee. Transient, mild tolerability reactions were, however, observed at all dose levels.

4.3 Efficacious dose predictions and justification of top dose

Furthermore, in the rat meniscal tear model, medial femoral cartilage repair of 70% and 92% was observed after administration of 250 µg (25 µL of a 10 mg/mL extended release (ER) formulation) and 1250 µg (25 µL of a 50 mg/mL formulation) LRX712 ER micro-crystal suspension, respectively. CCI

The efficacious dose for rats was found to be 250 µg. This would convert to an estimated efficacious dose of 25 mg in man by using simple allometric principles. In other words, the synovial fluid volume is approximately 100-fold larger in man (5 mL) than in rat (50 µL).

CCI

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

Currently there is no approved cartilage-anabolic compound able to regenerate/restore articular cartilage in the knee on the market in Europe or the rest of the world. Therefore, the comparator will be placebo (i.e., intra-articular saline solution).

4.5 Purpose and timing of interim analyses/design adaptations

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 or tolerability concerns. Additional information is presented in the interim analysis Section 12.7.

4.6 Risks and benefits

Given that study subjects will have mild/moderate OA and LRX712 has shown promising chondrogenic effects in preclinical studies, it is possible that the three consecutive doses of the drug may elicit beneficial effects on structural lesions in the articular cartilage with potential implications for joint pain and function. Occasional and transient local tolerability findings upon intra-articular injection are expected.

Appropriate eligibility criteria and dose discontinuation and stopping rules are included in this protocol. Recommended guidance for supportive management of study-drug induced adverse events are provided in Section 6.6.2.

The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as by close clinical monitoring, and by focusing on mild/moderate OA (KLG 2 or 3), which seems to offer the best subset to explore early evidence of structural benefits in patients with knee OA, such as improved cartilage composition and morphometrics in the affected knee joint.CCI [redacted] This will enable an assessment of preliminary results on the risk-benefit profile of LRX712 in subjects with mild/moderate knee OA.

4.6.1 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected over a period of 7 months, from each subject as part of the study. Additional samples may be required for safety monitoring.

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

A summary blood log is provided in the Site Operations Manual (SOM). Instructions for all sample collection, processing, storage and shipment information are also available in the SOM and central laboratory manual.

See Section 8.5.2.2 on the potential use of residual samples.

4.6.2 LRX712 on-target risks

No undue risks are expected based on the preclinical safety data accompanying the use of LRX712. The molecular target has not been identified, but most likely involves a chondrocyte specific signaling pathway. LRX712 has not been observed to promote *in vitro* cell proliferation in any cell type examined to date. In fact, in a naive rodent joint, local delivery of LRX712 did not lead to proliferation or overgrowth of the healthy cartilage (synovial or fibrocartilage), but it did evoke the replacement of injured cartilage with normal cartilage tissue following acute damage to the joint. These data suggest that LRX712 does not have a gross histological effect on the tissues in a healthy joint and does not trigger the risk of cartilage overgrowth.

Assessment of cardiovascular safety pharmacology *in vitro* showed a significant inhibitory effect on the hERG current with an IC_{50} value of 8.5 µM. However, this effect did not translate into QT interval changes in dogs. Assessment of cardiovascular safety pharmacology *in vivo* showed no effects on the QT interval at the CCI [redacted] In addition, no effects on heart rate, blood pressure, PR or QRS intervals, or body temperature were observed. Along these lines, the FIH study testing single injections of various doses up to 75 mg did not raise specific cardiovascular safety findings when compared with the effects of placebo. The present study expands exposure to three consecutive injections of two dose levels tested in the FIH (15 and 25 mg) and will monitor QT duration by triplicates of 12-lead digitized ECG throughout the study, with a focus on one day pre- vs. post-injections. Vital signs will be monitored at every study visit.

4.6.3 Study related risks

4.6.3.1 Intra-articular injection and arthrocentesis risks

As with any intra-articular injection, a risk of iatrogenic infection exists. Recent reports found infection rates following i.a. injection of steroids between 1 in 3000 and 1 in 50,000 (Lavelle et al 2007). However, few orthopedists and rheumatologists have encountered a case of post-steroid septic arthritis (Charalambous et al 2003). In addition, when proper technique is applied in a healthy population, and when a non-steroidal drug is used, this rate of infection after a single i.a. injection is considerably lower. Sterile technique will be used in all phases of drug reconstitution and administration to prevent this potential complication of the procedure.

Other expected adverse effects may include local injection-site reactions marked by transient local pain, swelling or inflammation at the injection site. Potential adverse events will be monitored and documented.

4.6.3.2 Blood draw risks

During the collection of blood samples, subjects may experience pain and/or bruising at the insertion site of the needle/catheter. Although rare, localized clot formation, infections and nerve injury may occur. Lightheadedness and/or fainting may also occur during or shortly after the blood draw.

4.6.3.3 Pregnancy related risks

Women of childbearing potential will not be included in the study. The study drug may involve unknown risks to the fetus if pregnancy were to occur during the study. Reproductive and teratogenicity studies have not yet been conducted with LRX712. The risk-benefit profile is not justifiable for healthy women of childbearing potential.

Sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus, if pregnancy were to occur during the study, and must 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 subject will not reliably comply, they should not be entered or continue in the study.

4.6.3.4 Risk of MR imaging procedure

The 7T MRI scanner used in this study is considered an exploratory device. MRI is a non-invasive radiology technique that has no x-ray radiation exposure. No health risk has been associated with the employment of ultra-high field (7T) applications beyond the typical contraindications to the use of MRI. Since switching gradients are the same as those used for modern 3T or 1.5 T MR systems, no special safety management is needed for a 7T scanner. The presence of metal in the body creates a safety hazard (as with lower field MRI scanners) and adversely affects the image quality (for more information, see related exclusion criterion). However, the specific absorption rate (SAR), a measure of the rate at which the energy is absorbed by the human body when exposed to a radiofrequency (RF) electromagnetic field, increases with the field strength of the MR system. As such, there is potential at 7T for heating of the subject due to the application of the RF energy necessary to produce the MRI signal, especially in tissues where non-ferromagnetic implants are present. Ultimately, each subject will be evaluated for potential medical and physical contraindications prior to any imaging examination and the Site Radiologist will have final approval of the subject's eligibility to have the imaging modality performed.

4.6.3.5 Risk of X-ray imaging procedure

For screening purposes, a standing weight-bearing fixed flexion position and PA view of the patello-femoral joint are required. The total amount of radiation exposure per participant from these X-rays will be about 100 μSv. This amount of radiation is equivalent to approximately 13.8 days of background exposure (approximately 0.3 μSv per hour at sea level). For effective radiation doses under 3 mSv (300 mrem), the risk is considered to be minimal. Therefore, the radiation exposure in this study involves minimal risk and is necessary to ensure eligibility of patients.

4.7 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities (i.e., pandemic, epidemic, or natural disaster), mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public Health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

4.7.1 SARS-CoV-2 related risks

The current SARS-CoV-2 pandemic may pose a challenge to integrity of the trials, protection of subjects' rights, safety and wellbeing, as well as the safety of study staff. Therefore, risk mitigation strategies have been established and will be evaluated on an ongoing basis for the duration of the study, in line with health and governmental authority guidance. If the dynamics of the SARS-CoV-2 outbreak change in such a way that the safety of the subjects and study staff, or integrity of the data collected cannot be guaranteed, the study will be halted.

4.7.1.1 Risk for study subjects and site staff

To reduce the risk of SARS-CoV-2 infections among subjects and site staff, sites in participating countries will follow measures and procedures as per national guidelines or regulatory requirements.

See Section 8.4.6 COVID-19 Contingency plan, and Section 6.1.4 Impact of the investigational drug on COVID-19 disease, for further details.

5 Population

This study is designed for patients affected by mild/moderate knee OA in the medial tibio-femoral compartment with a fmJSW between 1.5 and 3.5 (females) 2 and 4 (males) mm (at X=0.225) and without significant malalignment (≥7.5°), history or presence of massive effusion, extensive meniscal damage (>50% of meniscal area), and widespread pain score higher than 4. Patients will be screened for eligibility with standing X-Ray using fixed flexion technique to confirm radiographic presence of OA, and the presence of mild to moderate cartilage erosion by fmJSW being in the targeted range of 1.5-3.5 (females) or 2-4 (males) mm in the medial tibio-femoral compartment at the x=0.225 location.

See Section 9.1 for details on discontinuation and replacement policies.

5.1 Inclusion criteria

To be eligible for inclusion in this study patients must meet all the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Patient must be between 35 and 75 years old at Screening
3. Patient must weigh at least 50 kg to participate in the study, and must have a body mass index (BMI) within the range of 18 - 35 kg/m2 at Screening. BMI = Body weight (kg) / [Height (m)]^2
4. Patient must have knee osteoarthritis (OA) at Screening. Structural signs of OA need to be confirmed by radiography taken in standing weight-bearing fixed flexion position and PA view, indicating Kellgren-Lawrence grade 2 or 3 in the index knee.
5. Patient must have symptomatic disease predominantly in one (the index) knee, with minimal or no symptoms in the contralateral knee. Symptomatic disease is defined as having pain in the knee ≥ 4 days of the week for at least 3 months at Screening.
6. Patient must have radiographic confirmation of a medial joint space width of 1.5 to 3.5 mm for females, or 2 to 4 mm for males, measured at the X=0.225 (Neumann et al 2009)

fixed point location within the medial tibio-femoral compartment of the index knee, at Screening.

7. Patient must be able to communicate well with the investigator, to understand and comply with the requirements of the study.
8. Patient must be ambulatory (able to walk without assistive devices).

5.2 Exclusion criteria

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

1. Patient has a known autoimmune disease, inflammatory or chronic arthropathy other than OA (including but not limited to rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, SLE (systemic lupus erythematosus), CPPD (calcium pyrophosphate dihydrate crystal deposition disease), gout and fibromyalgia), active acute or chronic infection of the joint, Lyme disease involving the knee, systemic cartilage disorder, or a known systemic connective tissue disease
2. Patient has had surgical treatment of the target knee using mosaicplasty or microfracture, resecting more than 50% of meniscal tissue (Note: prior diagnostic arthroscopy with debridement and lavage, <50% meniscectomy, lateral release, patellar realignment, medial patellofemoral ligament reconstruction are acceptable if performed at least 6 months prior to Screening; anterior cruciate ligament reconstruction is acceptable if the patient recovered completely from surgery based on Investigator's evaluation)
3. Patient had partial or complete joint replacement in either or both knees
4. Patient has symptomatic, isolated patello-femoral pain in the index knee as per the Investigator's examination at Screening
5. Patient has malalignment (valgus- or varus-deformity) ≥ 7.5° in the index knee as per anatomic PA axis measured by weight-bearing short knee radiography, at Screening.
6. Patient has an unstable target knee joint or insufficiently reconstructed ligaments based on medical history and physical examination by the Investigator at Screening
7. Effusion in the index knee that clinically required aspiration in the past 12 weeks prior to Screening, or that is clinically relevant in the index knee as per physical examination (bulge sign, patellar tap) at Screening or Day 1
8. Chronic infection with Hepatitis B (HBV) or Hepatitis C (HCV). Positive HBV surface antigens (HBsAg) test, or if standard local practice, a positive HBV core antigen test. Patients with a positive HCV antibody test should have HCV RNA levels measured. Patients with positive (detectable) HCV RNA should be excluded
9. Any active systemic infection requiring treatment with IV anti-infectives within 4 weeks prior to Day 1
10. History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result
11. History of drug abuse or unhealthy alcohol use within the 12 months prior to Day 1, 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." or "A typical pattern of alcohol consumption of greater than 2 drinks daily (1 drink is 12 oz of beer, 4 oz of wine or 1.5 oz of spirits)."

12. Smoker of 20 cigarettes or more per day or using of other tobacco products in amounts corresponding to 20 cigarettes or more per day (per subject reported information) at Screening.
13. Any local i.a. treatment into the knee, including but not restricted to viscosupplementation and corticosteroids within 12 weeks prior to Screening visit
14. Corticosteroid use in any dose and by any route except topical, intranasal and ophthalmic, 4 weeks prior to Screening visit (see specific timeline for i.a. corticosteroid use on criterion 13)
15. Treatment with oral glucosamine, chondroitin sulfate, or any nutraceutical with potential activity on the extracellular matrix of articular cartilage within 12 weeks prior to Screening visit
16. Previous use of LRX712 or use of other investigational drugs within 5 half-lives of enrollment or within 30 days, whichever is longer; or longer if required by local regulations
17. History of significant cardiac conduction/electrophysiological disorder, e.g. familial long QT syndrome or known family history of Torsades de Pointes or prolonged QT syndrome or QTcF $\geq$ 450 msec (Fridericia Correction) for males and $\geq$ 460 msec for females at Screening or Day 1 (by local 12-lead digitized ECG reading).
18. Confirmed clinically significant cardiac arrhythmia (e.g., 2nd/3rd degree heart block, SVT, VTach, arrhythmia requiring an internal automated cardioverter/defibrillator)
19. Concomitant use of agents known to prolong the QT interval unless they can be entirely discontinued for the duration of the study
20. History of hypersensitivity to any of the study treatments or excipients or to drugs of similar chemical classes
21. 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
22. Donation or loss of 500 mL or more of blood within eight weeks prior to Day 1, or longer, if required by local regulation
23. Significant coagulopathy (e.g., platelet count less than 75,000/mm^3) or significant anemia (i.e., hemoglobin less than 9.0 g/dL)
24. Type I or poorly controlled Type II diabetes mellitus (fasting blood glucose level $\geq$ 9.0 mmol/L)
25. Abnormal liver function tests such as SGOT (AST), SGPT (ALT), or serum bilirubin (except if accompanying Gilbert's Disease) as defined by:
    - Any single transaminase > 3 x the upper limit of normal (ULN). A single parameter elevated up to and including 3 x ULN should be re-checked as soon as possible, and in all cases, prior to randomization, to rule out any lab error
    - Serum bilirubin > 1.6 mg/dL (27 µmol/L)
26. CCI [redacted]

CCI [redacted]

27. Patients requiring the use of the following medications:
    a. Opioids, either oral (i.e., tramadol) or transdermal (i.e., fentanyl patches) formulations
    b. Centrally acting analgesics (i.e., duloxetine)
28. Patients requiring the use of indomethacin within 2 weeks prior to Screening visit
29. Patient is unable to undergo magnetic resonance imaging (MRI) or presents absolute contraindications to MRI (e.g., metallic implants, metallic foreign bodies, pacemaker, defibrillator)
30. Presence of severe acute or chronic liver disease (e.g., cirrhosis) or conditions with hepatotoxic potential (e.g., known gallbladder or bile duct disease causing biliary stasis, acute or chronic pancreatitis).
31. Sexually active males unwilling to use a condom during intercourse while taking investigational drug and for 8 weeks after treatment completion/withdrawal. A condom is required for all sexually active male subjects to prevent them from fathering a child AND to prevent delivery of the investigational drug via seminal fluid to their partner.
    In addition, male subjects should not donate sperm for the time period specified above
32. Pregnant or nursing (lactating) women
33. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant.
    - Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks prior to Screening visit. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of childbearing potential
34. Any other condition or laboratory finding, or any post-operative condition or complication, which in the investigator's opinion may interfere with participation in the study (poor compliance to protocol requirements), and might confound the results of the study, or pose additional risk in injecting LRX712 i.a., at Screening
35. Signs or symptoms, in the judgment of the investigator, of a clinically significant systemic viral, bacterial or fungal infection within 30 days prior to screening.
    - COVID-19 specific: It is highly recommended that PCR or antigen testing for COVID-19 be completed within 1 week prior to first dosing. If testing is performed, negative test results are required prior to enrolment into the study. Additional testing may occur at the discretion of the investigating physician. COVID-19 testing should be completed via nasal or throat swabs. If testing is not performed, the investigator must document their discussion with the subject regarding testing, and the rationale for not testing, in the source documentation. This requirement may be ignored if the pandemic is declared ended by the country where the site is located, and resumed if the pandemic recurs.

6 Treatment

6.1 Study treatment

Details on the storage and management of study medication, randomization, and instructions for prescribing and taking study treatment are outlined in Section 2 (Treatment) of the SOM.

6.1.1 Investigational and control drugs

The investigational drug, LRX712 (25 mg/1mL suspension for injection) will be prepared by Novartis and supplied to the Investigator sites as open-label bulk medication.

An unblinded pharmacist or authorized designee is required to prepare the study drug.

Commercial saline will be used as placebo and be procured by the clinical site. Clinical supplies are to be dispensed only in accordance with the specified study procedures (please refer to SOM).

Table 6-1 Overview of study medication

Study drug name	Formulation	Appearance	Unit dose	Packaging	Provided by
LRX712	Suspension for injection	White	25 mg/1mL	CCI	Novartis
Placebo (commercial saline)	Solution for injection	Transparent	0 mg		Site

6.1.2 Additional study treatments

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

6.1.3 Treatment arms/group

Subjects will be assigned to one of the three (3) parallel arms, each consisting of approximately 13 subjects, and three consecutive i.a. doses of either LRX712 15 mg, LRX712 25 mg, or placebo will be evaluated. Injections will be given at monthly intervals (i.e., at Day 1, Day 29 and Day 57) under optional ultrasound guidance.

The volume of the i.a. injection will be fixed at 3 mL for all doses and prepared by the unblinded pharmacist to reach the final dose of LRX712 or placebo to be delivered.

6.1.4 Impact of the investigational drug on COVID-19 disease

Based on the mechanism of action of LRX712 and the available information in the Investigator's Brochure (IB), there is currently no reason to believe that LRX712 could increase the susceptibility of study subjects to the SARS-CoV-2 virus, or worsen or mask any COVID-19 signs, symptoms or complications.

6.2 Other treatment(s)

Subjects experiencing symptoms such as pain or swelling following i.a. injections may use ice and/or take analgesic medication (e.g., paracetamol), as needed.

See Section 6.2.3 for further information.

6.2.1 Concomitant therapy

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study (Screening) and during the study (all from Day 1 to Week 28 (included), and then only the ones related to SAEs or AEs of special interest from Week 28 to Week 52), must be recorded on the Concomitant medications/ Significant non-drug therapies section of the eCRF. Medication entries should be specific to generic name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

In the event of an available COVID-19 vaccine, vaccination of study subjects will be permitted during the study duration. However, a 30-day interval from vaccination to study treatment is recommended to avoid interfering AEs. The investigator must document their discussion with the subject regarding COVID-19 vaccination in the source documentation, and follow the instructions described above related to the eCRF.

6.2.2 Prohibited medication

Except for medication that may be required to treat adverse events and standard of care medication in line with inclusion and exclusion criteria, no medication other than study drug will be allowed from Screening visit or dosing on Day 1 until all the Study Completion evaluations have been conducted, as per timelines displayed in Table 6-2.

Any i.a. treatment into the knee, including but not restricted to viscosupplementation and corticosteroids, and any nutraceutical with potential activity on the articular cartilage (e.g., chondroitin sulphate, glucosamine) are prohibited from 12 weeks prior to Screening visit until the end of the study. CCI

Use of the treatments displayed in the below table are not allowed in the reported timeframe.

Table 6-2 Prohibited medication

Medication	Prohibition period	Action taken
Local i.a. treatment into the knee, including but not restricted to viscosupplementation and corticosteroids (impact on tissue repair/confounding of efficacy)	12 weeks prior to Screening visit to EoS	Discontinue study treatment
Corticosteroid use by any route except topical, intranasal and ophthalmic (impact on tissue repair)	4 weeks prior to Screening visit to EoS	Discontinue study treatment
Oral glucosamine, chondroitin sulfate, or any nutraceutical with potential activity on cartilage repair (confounding of efficacy)	12 weeks prior to Screening visit to EoS	Must be recorded on the Concomitant medications/ Significant non-drug therapies section of the eCRF.
Indomethacin, (inhibitory effect on GAG synthesis and thereby on the regenerative capacity in arthritic cartilage)	2 weeks prior to Screening visit to EoS	Discontinue study treatment
Paracetamol greater than 3000 mg per day (confounding of liver function) See Section 6.2.3 (Rescue medication) for exceptions	From Day 1 to EoS	Must be recorded on the Concomitant medications / Significant non-drug therapies section of the eCRF
Opioids, either oral (i.e., tramadol) or transdermal (i.e., fentanyl patches) formulations Centrally acting analgesics (i.e., duloxetine)	From Screening visit to EoS	Must be recorded on the Concomitant medications / Significant non-drug therapies section of the eCRF

6.2.3 Rescue medication

When local pain to the index knee requires analgesic medication, the use of paracetamol/ acetaminophen up to 3000 mg/day is the recommended/preferred treatment of choice during the study. In case paracetamol/acetaminophen is not effective, NSAIDs will be allowed, if the treatment follows the recommended dose and treatment duration defined by local guidelines. However, the use of indomethacin will remain prohibited due to its known inhibitory effect on GAG synthesis limiting the regenerative capacity of articular cartilage (Dingle 1993, Dingle1999, and Hauser 2010).

Use of rescue medication must be recorded on the Concomitant medications/Significant non-drug therapies eCRF after start of study drug.

6.2.4 Restriction for study subjects

For the duration of the study, subjects should be informed and reminded of the restrictions outlined in Section 6.2.4.1.

Non-drug treatments (e.g., physiotherapy) must be reported in the Concomitant medications/ Significant non-drug therapies eCRF. Further recommendations are given in the SOM.

6.2.4.1 Dietary restrictions and smoking

- No cigarettes/use of nicotine products are allowed from Screening visit to EOS, it is not allowed to smoke 20 cigarettes or more per day **or** using of other tobacco products in amounts corresponding to 20 cigarettes or more per day.
- No alcohol for 48 hours before each dosing day.
- In order to avoid wide variations in urine volumes on PK collection days, subjects should be encouraged to have a fluid intake of approximately 240 mL every 4 hours during their waking hours, in addition to the fluid taken with meals (only on PK collection days).

6.2.4.2 Other restrictions

- After dosing, physical activity (e.g., climbing stairs, running, bicycling) should be minimized for 48-72 hours. Normal pace walking is allowed.
- No strenuous physical exercise is allowed from 48 hours prior to first dosing until study completion evaluation (e.g., weightlifting, long-distance running (>3000 m), intensive ball games (football, handball, volleyball and basketball), or tennis on a regular basis >1 time weekly). In general, activities causing heavy loading or rapid movements/rotations of the knee are not advised.
- Subjects will be required to adhere to the measures and procedures outlined by the study site, to prevent SARS-CoV-2 infections among them and clinical site staff.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

The subject number assigned at Screening remains the unique identifier for the subject throughout the study. For information on subject numbering, please see ‘Subject numbering’ section in the SOM.

6.3.2 Treatment assignment, randomization

This is a non-IRT study with a unique randomization list.

A treatment code will be assigned to each individual subject by way of a randomization number.

The randomization number is only used to identify the treatment to which the subject has been assigned.

If a subject requires a replacement, the replacement subject will be assigned a replacement randomization number corresponding to the original subject. Any additional subjects enrolled will use sequential subject numbering.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A randomization list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio.

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

Follow the details outlined in the Site Operations Manual regarding the process and timing of treatment assignment and randomization of subjects.

6.4 Treatment blinding

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

The identity of the treatments will be concealed using unblinded site staff independent of the study team, since study treatment and placebo are not identical in appearance and odor. See details below.

Site staff

Except for any unblinded site staff identified below, all site staff (including study investigator and study nurse) will be blinded to study treatment during treatment allocation and subject dosing.

Unblinding a single subject on site for safety reasons (necessary for subject management) will occur via an emergency system in place at the site (see Section 6.7).

Site staff may also be unblinded to the treatment assignment of one or more subjects at Interim Analyses if deemed appropriate to aid decision-making.

Drug product will be supplied in bulk, so an **unblinded pharmacist** who is independent of the study team will be required in order to maintain the blind. This unblinded pharmacist will receive a randomization list or treatment allocation cards from Global Clinical Supply with the appropriate treatment allocation numbers. Appropriate measures must be taken by the unblinded pharmacist to ensure that the treatment assignments are concealed from the rest of the site staff.

Administration of study drug will be performed by an **unblinded practitioner** trained in i.a. injection procedures, who is independent of the study team. Appropriate measures must be taken by the unblinded practitioner to ensure that the treatment assignments are concealed from the rest of the site staff. Please refer to SOM for more details on administration process.

Imaging site staff

To prevent bias in the imaging analyses, all staff at the imaging site will be blinded to investigational drug throughout the study, while there is no need for blinding related to the 7T MRI measurements.

Sponsor staff or delegate

The following unblinded sponsor roles are required for this study:

The **unblinded field monitors** are required to review drug accountability and allocation at site. The unblinded monitors are not provided with a randomization list directly but will be unblinded through review of source documentation, compiled by the unblinded pharmacist, which details treatment allocation to individual subjects. The unblinded monitors will also be able to review the treatment allocation cards/randomization list provided to the unblinded pharmacist. The names of the unblinded monitor(s) are detailed in the Monitoring Plan.

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.

The **study statistician** will be able to access the full randomization list from the start of the study and can share unblinded information with the rest of the clinical trial team as appropriate for internal decision purposes, as outlined in the SOM (see Blinding levels). For example, unblinded summaries and unblinded individual data can be shared with the team whenever necessary.

The study statistician is also allowed to share treatment assignments with the investigator following Interim Analyses when knowledge of the treatment assignments could aid decision-making.

Study programmers and other personnel involved in study data analysis (e.g., biomarker expert) can access treatment assignment information from the start of the study for the purpose of data analysis.

The **clinical trial team** can share unblinded results with other sponsor staff (e.g., decision boards) as required for internal decision making on the study or the project while the study is ongoing. In order to monitor the scenarios described in the study and treatment arm stopping rules, the study will have a dedicated unblinded sponsor staff outside the clinical trial team.

All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure except as described above. Please refer to Blinding plan table in the SOM.

Following final database lock all roles may be considered unblinded.

Table 6-3 Blinding levels

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

B Remains blinded

NA Not applicable

UI Allowed to be unblinded on individual patient level

6.5 Dose escalation and dose modification

There is no planned dose escalation in this trial.

Investigational treatment dose adjustments and/or interruptions are permitted only under the circumstances described in Section 9.1.1, Section 9.1.5 and Section 9.1.6.

6.6 Additional treatment guidance

LRX712 will be administered into the knee via i.a. injection which will occur at the study site. Ultrasound-guided injection for the repeated drug administration is optional. See the SOM for further details.

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

6.6.1 Treatment compliance

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects treated with LRX712, as detailed in Section 8.5.1.

6.6.2 Recommended treatment of adverse events

Treatment of adverse events should be in line with the Institution's procedures.

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

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

For the management of allergic reaction and anaphylaxis, it is recommended to follow the guidelines by the National Cancer Institute Common Toxicity Criteria (CTC-AE).

6.6.3 Emergency breaking of assigned treatment code

Emergency unblinding should only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. A complete set of emergency code break cards will be provided to the investigator site(s) and a complete set will be available at Novartis. All code break cards must be retained until the end of the study and returned to Novartis. They must be stored in a secure place but be accessible in case of emergency. The investigator will receive a blinded code break card for each subject, with the details of drug treatment covered by a removable, scratch-off cover. In an emergency, the scratch-off cover can be removed to determine the treatment. The scratch-off covers are not to be removed for any reason other than an emergency. When the investigator removes the scratch-off cover he/she must note the date, time, and reason for removing it and retain this information with the case report form documentation. **The unblinded treatment code should not be recorded on the eCRF.** The investigator must also immediately inform the Novartis local monitor that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the code break cards in case of emergency. If appropriate, the investigator will inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable.

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

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under the investigational and control drugs section.

LRX712 will be administered to the subject via the following route of administration: Intra-articular into the knee. Administration will be performed at the study site.

See the Site Operations Manual and Pharmacy Manual for further details.

7 Informed consent procedures

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

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject can do so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Written informed consent must be obtained before conducting any study-specific procedures (e.g., all the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents and performed by site staff appropriately trained in study informed consent and Screening procedures.

Novartis will review the investigators' proposed written informed consent form to ensure it complies with the ICH E6 GCP guidelines and regulatory requirements and is considered appropriate for this study. Any further changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the subject informed consent and should be discussed with the subject 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 subject.

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

CCI [redacted]

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

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

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

Refer to the SOM for a complete list of ICFs included in this study.

8 Visit schedule and assessments

Subjects should be seen for all visits on the designated day, with the assessments performed as per schedule, within the allowed "visit/assessment window" specified. For visits where no time point is specified, assessments should be carried out at approximately the same time each day, and in the same order as listed in the SOM. All assessments at -1.5h should be conducted within 1.5 hours prior to dosing.

As per Section 4.7, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that 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 and depending on operational capabilities, phone calls, virtual contacts (e.g. tele consult) or visits by site staff/ home nursing staff to the subject´s home, can replace on-site study visits, for the duration of the disruption until it is safe for the subject to visit the site again.

Table 8-1 Assessment Schedule

Period	Screening	Treatment											Post-Treatment Follow-Up						
Visit Name	**Screening**	**Day 1**						**Day 2**	**Day 8**	**Day 29**	**Day 30**	**Day 36**	**Day 57**	**Day 58**	**Day 64**	**Day 113**	**Day 197**	**Day 224**	**Day 294**	**EOS**
Days	**-45 to -6**	**1**						**2**	**8**	**29**	**30**	**36 ± 1**	**57**	**58**	**64 ± 1**	**113 ± 7**	**197 ± 7**	**224**	**294**	**364 + 30**
Weeks	**-7 to -1**	**0**						**0**	**1**	**4**	**4**	**5**	**8**	**8**	**9**	**16**	**28**	**32**	**42**	**52**
Time (post-dose)	-	**-1.5h pre-dose**	**0h**	**0.5h**	**4h**	**8h**	**12h**	-	-	-	-	-	-	-	-	-	-	-	-	-
CCI																				
Medical history/current	X																			

Period	Screening	Treatment												Post-Treatment Follow-Up						
Visit Name	Screening	Day 1						Day 2	Day 8	Day 29	Day 30	Day 36	Day 57	Day 58	Day 64	Day 113	Day 197	Day 224	Day 294	EOS
Days	-45 to -6	1						2	8	29	30	36 ± 1	57	58	64 ± 1	113 ± 7	197 ± 7	224	294	364 + 30
Weeks	-7 to -1	0						0	1	4	4	5	8	8	9	16	28	32	42	52
Time (post-dose)	-	-1.5h pre-dose	0h	0.5h	4h	8h	12h	-	-	-	-	-	-	-	-	-	-	-	-	-
medical conditions																				
Inclusion / Exclusion criteria	X	X																		
Demography	X																			
Body Height	X																			
Body Weight	X																			
Knee X-ray	X																			
Knee 7T MRI	X[11]															X	X			X
Randomization		X[12]																		
Dose administration			X							X			X							
Hepatitis and HIV Screen	S																			
ECG evaluation[1]	X	X						X		X	X		X	X			X			
Pregnancy and assessments of fertility[2]	S	S															S			S
Alcohol Test and Drug Screen	S	S																		

Period	Screening	Treatment											Post-Treatment Follow-Up						
Visit Name	**Screening**	**Day 1**						**Day 2**	**Day 8**	**Day 29**	**Day 30**	**Day 36**	**Day 57**	**Day 58**	**Day 64**	**Day 113**	**Day 197**	**Day 224**	**Day 294**	**EOS**
Days	**-45 to -6**	**1**						**2**	**8**	**29**	**30**	**36 ± 1**	**57**	**58**	**64 ± 1**	**113 ± 7**	**197 ± 7**	**224**	**294**	**364 + 30**
Weeks	**-7 to -1**	**0**						**0**	**1**	**4**	**4**	**5**	**8**	**8**	**9**	**16**	**28**	**32**	**42**	**52**
Time (post-dose)	**-**	**-1.5h pre-dose**	**0h**	**0.5h**	**4h**	**8h**	**12h**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Physical Examination[3]	S[4]	S					S	S	S	S	S	S	S	S	S	S	S			S[4]
Blood Pressure	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Pulse rate	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Body Temperature	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Hematology	X	X						X			X			X			X			
Clinical Chemistry	X	X						X			X			X			X			
Urinalysis	X	X						X			X			X			X			
Coagulation Panel	X	X						X			X			X			X			
hs-CRP[5]	X	X					X	X	X	X	X	X	X	X	X	X	X			
PK blood collection[6]	See table below																			

CCI

Period	Screening	Treatment											Post-Treatment Follow-Up						
Visit Name	Screening	Day 1						Day 2	Day 8	Day 29	Day 30	Day 36	Day 57	Day 58	Day 64	Day 113	Day 197	Day 224	Day 294	EOS
Days	-45 to -6	1						2	8	29	30	36 ± 1	57	58	64 ± 1	113 ± 7	197 ± 7	224	294	364 + 30
Weeks	-7 to -1	0						0	1	4	4	5	8	8	9	16	28	32	42	52
Time (post-dose)	-	-1.5h pre-dose	0h	0.5h	4h	8h	12h	-	-	-	-	-	-	-	-	-	-	-	-	-
CCI																				
Concomitant therapies[13]	As required																			
Adverse Events[13]	As required																			
Comments	As required																			
Safety follow-up call																		X	X	
Study completion information																				X

Period	Screening	Treatment											Post-Treatment Follow-Up						
Visit Name	Screening	Day 1						Day 2	Day 8	Day 29	Day 30	Day 36	Day 57	Day 58	Day 64	Day 113	Day 197	Day 224	Day 294	EOS
Days	-45 to -6	1						2	8	29	30	36 ± 1	57	58	64 ± 1	113 ± 7	197 ± 7	224	294	364 + 30
Weeks	-7 to -1	0						0	1	4	4	5	8	8	9	16	28	32	42	52
Time (post-dose)	-	-1.5h pre-dose	0h	0.5h	4h	8h	12h	-	-	-	-	-	-	-	-	-	-	-	-	-

[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] Triplicate 12-lead digitized ECGs to be performed
[2] For all women: Pregnancy test from safety blood sample at Screening and Week 28, and in urine at Day -1 and EOS
[3] Complete PE as per Assessment Schedule, and symptom-directed PE at any visit at PI discretion.
[4] Full-body examination is required
[5] The sample must be taken pre-dose on dosing days
[6] PK blood collection is pre-dose on dosing days 29 and 57.
CCI [redacted]
[9] Sample volume: 10 mL.
[redacted] CCI [redacted]
[11] MRI at Screening visit should only be completed after all eligibility criteria have been confirmed.
[12] Randomization can be performed the days before study drug administration on Day 1 (Day -5 to Day -1), only after eligibility confirmation.
[13] Please see Section 6.2.1 and Section 10.1.1.1 for details on reporting periods

Table 8-2 PK blood collection

Period	Visit Name	Days	Weeks	Time (post-dose)	PK blood collection[1]
Screening	Screening	-45 to -6	-7 to -1	-	-
Treatment	Day 1	1	0	-1.5h pre-dose	X
				0.5h	X
				12h	X
	Day 2	2	0	24h	X
	Day 8	8	1	168h	X
	Day 29	29	4	pre-dose	X
	Day 30	30	4	24h	X
	Day 36	36 ± 1	5	168h	X
	Day 57	57	8	pre-dose	X
Post-Treatment Follow-Up	Day 58	58	8	24h	X
	Day 64	64 ± 1	9	168h	X
	Day 113	113 ± 7	16	1344h	X
	Day 197	197 ± 7	28	3360h	X
	EOS	364 +30	52	-	-

X Assessment to be recorded in the clinical database or received electronically from a vendor
[1] PK blood collection is pre-dose on dosing days 29 and 57.

8.1 Screening

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

In the case that a safety laboratory assessment at Screening and/or baseline is outside of the range specified in the exclusion criteria, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the subject must be excluded from the study.

Re-screening is permitted if the reason(s) for failing the initial screening were unrelated to the knee X-ray. The subject will not need to undergo another knee X-ray and the initial one may be used for re-screening purposes, if re-screening occurs within 6 months of the X-ray date. Likewise, the subject will not need to undergo another knee 7T MRI and the initial imaging may be used for rescreening purposes, if rescreening occurs within three months of the original 7T MRI date. The objective of this measure is to avoid unnecessary radiation exposure, given that meaningful radiologic changes are not likely to occur during the period of re-screening.

8.1.1 Eligibility screening

All subjects will be screened for HIV, Hepatitis B and C, and for substances of abuse.

See the SOM for details.

8.1.2 Information to be collected on screening failures

Information on what data should be collected for screening failures is outlined in the SOM.

8.2 Subject demographics/other baseline characteristics

Demographic and baseline characteristic data will be collected on all subjects. Relevant medical history/current medical conditions data will also be collected until signature of informed consent. Presence of symptomatic OA (KLG score and pain) and fmJSW will be collected in the eCRF as baseline characteristics. Details are outlined in the SOM.

Investigators have the discretion to record abnormal test findings on the medical history eCRF, if in their judgment, the test abnormality occurred prior to the informed consent signature.

Hepatitis screen, HIV screen

All subjects will be screened for Hepatitis B surface antigen (HBsAg). Screening for Hepatitis C will be based on HCV antibodies. Evaluation for HIV seropositivity will be performed, and if positive, confirmation by a second technique available at the laboratory site, e.g., Western blot. Appropriate subject counseling will be made available by the Investigator in the event of a positive finding. Notification of authorities, as required by law, will be the responsibility of the Investigator. Results will be available as source data and will not be recorded within the eCRF.

Alcohol test and Drug screen

Subjects will be tested for substances of abuse (e.g., alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates) at Screening and Day 1. Results will be available as source data and will not be recorded within the eCRF.

8.3 Efficacy

Efficacy will be assessed mainly by 7T MRI of the index knee as described in Section 8.3.1:

1. Regeneration of articular hyaline cartilage composition in the medial femoral condyle
2. Restoration of the morphometrics of the articular cartilage in the medial femoral condyle
3. Ultrastructure of hyaline cartilage in the medial femoral condyle
4. Regeneration of hyaline cartilage in other parts of the knee join
5. Integrity and thickness of the osteochondral junction
6. OA-related features in the knee joint

CCI [redacted]

8.3.1 Knee MRI

MRI will be obtained from the index knee with manifest OA to visualize the cartilage tissue in the femoral, tibial and the patellar regions. Hyaline cartilage is characterized by two main distinct layers between the articular surface and bone interface, marked by orientation of collagen fibrils (superficial and deep layer). Besides the collagen matrix, glycosaminoglycans (GAG) are also abundant in hyaline cartilage. The imaging protocol was developed to evaluate collagen fibril organization (T2 relaxation) and morphometric changes (i.e. cartilage thickness and volume); quantify changes in GAG content (assessed by sodium content); and, when visible, bone marrow lesions (sub-chondral bone edema), effusion and synovitis. Details pertinent to image acquisition and analysis can be found in the imaging charter.

8.3.1.1 Image collection

All Magnetic Resonance (MR) image acquisitions will be performed by a trained MRI professional at a specific imaging site using a clinical 7T MRI scanner. The MRI radiologist will be blinded to the treatment received by the subject.

During the 7T MRI, subjects will be positioned in a supine position with feet first in the 7T magnet as it is usually done with knee MR examinations. For sodium examination, a -double tuned coil will be used to collect proton (^{1}H) and sodium [^{23}Na] signals at 7T.

Every effort will be made to get a similar position of the knee at the different time-points during the study, for example, by using a custom-made positioning device to fix the leg from the knee downwards and a vacuum mattress enabling an even better fixation of the lower leg. Should a mattress be used, it will have to stay in place during the coil change to ensure an exact repositioning of the knee. This positioning is typically very comfortable for the subject and increases subject compliance. While remaining in the supine position, the subject will need to raise his/her leg for a few seconds to change the coil. The total measurement time should not exceed 90 min. More details on the 7T MRI procedures can be found in the imaging charter.

MR images will be sent for independent central review by imaging specialists. The reviewers will be blinded to the treatment received by the subject.

8.3.1.2 Image processing

The image analysis will be performed by the same expert, as defined in the imaging charter, in order to assess changes in cartilage quality in the defective region as well as in weight-bearing and non- weight-bearing regions of articular cartilage. Other endpoints will include the extent of restoration at the site of cartilage degeneration in the medial TF-compartment as measured by cartilage thickness or volume of articular cartilage, together with other features such as presence of bone marrow edema, synovitis/effusions and changes in the osteochondral junction. The coded medical images will be used primarily for analysis as described in this protocol; however, the images may also be used for the development and evaluation of new analysis methods directly related to the area of research that this study covers.

8.3.2 Clinical Outcome Assessments (COAs)

8.3.2.1 CCI

CCI

[redacted]

8.3.3 Appropriateness of efficacy assessments

The primary and secondary efficacy variables, morphometric measurements and the sodium-based proteoglycan assessment measured by 7T MRI, will detect changes in cartilage thickness/volume in the main region of interest, specifically, the weight-bearing area of the femur in the medial tibio-femoral compartment of the affected knee, as well as its composition, a high content of proteoglycans in the newly generated matrix pointing to the formation of hyaline rather than fibrous cartilage. The medial T-F compartment is the most affected sub-region of the knee and the location of the most pronounced cartilage lesions, except for subjects with valgus malalignment promoting lateral disease.

Changes in cartilage composition is the earliest sign of OA and the structural variable that first responds when exposed to chondroanabolic agents. Sodium MRI has been shown to strongly correlate with the GAG concentration in the cartilage (Borthakur et al 2006) and is therefore considered as an adequate CCI for monitoring loss of GAG and cartilage degradation over time in patients with knee OA, as well as for monitoring the pharmacodynamic effects of chondroanabolic drugs stimulating synthetic activities (Qvist 2008; Trattnig et al 2019).

Quantitative and semi-quantitative morphometric measurements of tibio-femoral cartilage and the whole joint as an organ have been well-established and validated (reviewed by Roemer 2014), and are currently used extensively in Phase 2 and 3 interventional clinical trials (e.g. Yazici et al 2018). Pathophysiological implications of the morphometric measures of articular cartilage in the T-F compartment for prediction of joint replacement surgery have been reported by Eckstein et al 2013.

Image analyses will be performed by the same Central reader.

8.4 Safety

Safety assessments are specified below, with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to Section 10.1.1.

The methods, assessment, specification, and recording for each assessment will be detailed in the SOM.

As per Section 4.7, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, the following mitigation actions are accepted:

- Regular phone or virtual calls can occur for safety monitoring and discussion of the subject´s health status, until it is safe for the subject to visit the site again.
- If subjects cannot visit the site for safety lab assessments conducted through central labs, local lab collection may be used
- If subjects cannot visit the site to have serum pregnancy tests, urine pregnancy test kits may be used. Relevant subjects can perform the urine pregnancy test at home and report the result to the site. It is important that subjects 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 subject so that the Site is informed and can verify the pregnancy test results (e.g., following country specific measures).

Table 8-3 Assessments and Specifications

Assessment	Specification
Physical examination	A complete physical examination - to be performed at Screening and baseline and at the end of the study - will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A knee joint examination will also be performed, including examination for bulge sign and patellar tap sign as well as for patellofemoral pain. Targeted physical examinations to elaborate self-reported symptoms, complaints, injection site reactions or post-injection flares as applicable, can be done at any visits. Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs include systolic and diastolic pressure, body temperature and heart rate measurements. After the subject has been resting in supine position for five minutes, blood pressure will be measured at least 2 times (with 1-2 min pause between measurements) using a validated automated device, e.g., OMRON, with an appropriately sized cuff. If the difference between the two measurements is larger than 10 mmHg, a third measurement is also performed. Mean of the consecutive measurements (2 or 3) will be used for the record. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured. Body mass index (BMI) will be calculated as body weight (in kg) divided by body height (in m) squared.

The methods for each assessment and data recording details are specified in the SOM.

8.4.1 Laboratory evaluations

Clinically significant abnormalities of laboratory test results occurring during or at completion of the study, must be recorded as either medical history/current medical conditions or adverse events, as appropriate, and discussed with Novartis personnel.

All abnormal lab results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met. For those lab adverse events, repeated evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant.

Subjects will be fasting for at least 8 hours prior to laboratory evaluations. Please see the central laboratory manual for details.

Clinically notable laboratory findings are defined in Appendix 1.

Table 8-4 Laboratory evaluations

Test Category	Test Name
Hematology	Hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differentials and platelet count will be measured.
Chemistry	Sodium, potassium, creatinine, urea, uric acid, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, LDH, GGT, AST, ALT, glucose, total cholesterol, triglycerides. If the total bilirubin concentration is increased above >18.0 µmol/L, conjugated bilirubin should be measured. hs-CRP will be measured in the circulation as per Assessment Schedule with the aim to capture acute inflammatory responses, if any local tolerability issues arise and to see if the potential effect is reversible.
Urinalysis	Dipstick measurements for protein, blood, and WBC/leukocytes will be performed. If dipstick measurement results are positive (abnormal), results will be captured in the eCRF. Microscopy must be assessed following a clinically meaningful abnormality of the dipstick test (as per investigator's judgement) test with results captured in the eCRF.
Coagulation	Prothrombin time (PT) also reported as INR and activated partial thromboplastin time (aPTT) will be measured.
Hepatitis markers	HBV-DNA, HbsAg, HbsAb, HbcAb, HCV RNA-PCR (baseline)
Pregnancy Test	Serum / Urine pregnancy test (see Section 8.4.3)

8.4.2 Electrocardiogram (ECG)

A standard 12-lead digitized electrocardiogram will be performed in triplicate (3 tracings of at least 10 sec duration to be obtained within a 2-5 min window) at visits indicated in the Assessment schedule in Table 8-1. Triplicates are required to properly assess the presence of QT prolongation, which requires observations of at least 2 out of 3 readings showing QTcF above the predefined risk threshold.

All ECGs must be performed on the ECG machines provided to the study site by an assigned vendor.

The original ECGs, appropriately signed and dated, should be collected and archived at the study site. Each ECG tracing should be labelled with study number, subject number, date and time, be appropriately signed and dated to confirm review, and filed in the study site source documents. For any ECGs with subject safety concerns, two additional ECGs should be performed to confirm the safety finding. Clinically significant ECG findings prior to dosing with investigational treatment must be discussed with the Sponsor. Any relevant findings will be followed by the site as medically indicated.

Clinically significant abnormalities should be recorded on the relevant section of the Medical history/Current medical conditions/AE eCRF page as appropriate.

The eCRF will contain:

- Date and time of ECG
- Heart rate
- RR and PR interval
- QRS duration
- QT duration
- QTcF

The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

8.4.3 Pregnancy and assessments of fertility

A condom is required for all sexually active male subjects to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male subjects should not donate sperm for the time period specified above.

All women enrolled in the study will have pregnancy testing regardless of fertility status. See the Assessment schedule (Table 8-1), for timing of the protocol-required pregnancy testing; additional pregnancy testing may be performed to meet local requirements. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative.

Refer to Section 10.1.4 for details on Reporting Pregnancy.

Assessments of Fertility

Refer to Section 5.2 for criteria to identify women who are not of childbearing potential.

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

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

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

8.4.4 Safety follow-up call

All randomized and/or treated subjects will have a safety follow-up call conducted at weeks 32 and 42, with the following objectives:

1. To follow-up on subjects' safety between week 28 and 52, when no site visits are scheduled
2. To collect information on AEs of special interest, SAEs and concomitant medication (NSAID use must be reported as accurately as possible), and COVID-19-related symptoms

Documentation of attempts to contact the subject should be recorded in the source documentation.

8.4.5 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/subject population.

8.4.6 COVID-19 contingency plan

The sponsor recommends that subjects in the study are screened for asymptomatic carriage of SARS-CoV-2 within 1 week prior to first dosing. Adequate viral testing availability and turnaround is required for site participation. SARS-CoV-2 testing should always be performed as per national regulatory requirements or guidelines in participating countries.

Any subject that presents COVID-19-related symptoms, in the opinion of the investigator, and/or has a positive SARS-CoV-2 PCR or antigen test within 1 week prior to first dosing will not be enrolled in the study until the infection has resolved and will receive follow-up medical attention as per local site-specific procedures. The subject may be rescreened. Refer to Section 8.1 for details on screening and rescreening procedures.

Any subject that presents COVID-19-related symptoms, in the opinion of the investigator, and/or has a positive SARS-CoV-2 PCR or antigen test from Day 1 to EoS will receive follow-up medical attention as per local site-specific procedures and follow COVID-19 national guidelines. Where possible, subjects should return for the upcoming assessments indicated in the Assessment Schedule after the subject has a negative SARS-CoV-2 PCR or antigen test. However, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

8.5 Additional assessments

8.5.1 Pharmacokinetics

8.5.1.1 PK blood and synovial fluid samples collection

PK blood collections will be done in all subjects. For details on PK blood collection and processing, labeling and shipment instructions, see SOM.

PK samples will be collected at the time points or collection intervals defined in the Assessment schedule/Sample Log. All samples will be given a unique sample number and a collection number. For plasma, the exact data and time of sampling will be entered on the PK blood collection page of the eCRF by the medical personnel or sent as electronic files. These actual sampling times will be used for determination of PK parameters. Sampling problems will be noted in the comments section of the eCRF.

LRX712 and metabolite MAE344 concentrations will be determined in plasma and synovial fluid using validated LC-MS/MS methods. The anticipated lower limit of quantification (LLQ) for LRX712 and MAE344 will be approximately 25 and 100 pg/mL ng/mL, respectively, for plasma.

A non-validated method will be used for additional metabolite investigations / exploratory work, if required, in line with defined exploratory objectives. Untreated samples (placebo) will not be analyzed. Concentrations will be expressed in mass per volume units and will refer to the free base. Concentrations below the LLQ will be reported as “zero” and missing data will be labeled as such in the Bioanalytical Data Report.

CCI [redacted]

8.5.1.2 PK parameters in plasma

For standard PK abbreviations and definitions see the list provided at the beginning of this protocol.

The following plasma PK parameters of LRX712 will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.2 or higher): Cmax, Tmax, Cmin from the plasma concentration-time data after multiple intra-articular dose administration of LRX712.

8.5.2 Biomarkers

CCI

Sample(s) will be collected at the time point(s) defined in the Assessment Schedule (Table 8-1).

Follow instructions for sample collection, numbering, processing, and shipment provided in the laboratory manual.

CCI

8.5.2.1 Additional biomarker assessments

CCI

8.5.2.2 Use of residual biological samples

Residual blood, urine, and synovial fluid samples may be used for another protocol-specified endpoint.

CCI [redacted]

8.5.2.3 Hypothesis free/Protein profiling

CCI [redacted]

Serum and synovial fluid samples will be collected at the time points defined in the Assessment schedule (Table 8-1). Instructions are outlined in the SOM regarding sample collection, numbering, processing and shipment.

Markers to be assessed include but are not limited to profiling proteins.

Detailed descriptions of the assays will be included in the Bioanalytical Data Reports.

8.5.2.4 Soluble biomarkers in circulation

Serum and urine samples will be collected according to the detailed instructions outlined in the SOM.

CCI [redacted]

The list may be changed or expanded further, as it is recognized that more relevant or novel biomarkers may be discovered during the conduct of the study.

Sample(s) will be collected at the time point(s) defined in the Assessment Schedule (Table 8-1).

Instructions for sample collection, numbering, processing, and shipment are provided in the laboratory manual and/or SOM.

8.5.2.5 Soluble biomarkers in synovial fluid

Synovial fluid samples will be collected by appropriately equipped and trained staff.

CCI [redacted]

The list may be changed or expanded further, as it is recognized that more relevant or novel biomarkers may be discovered during the conduct of the study.

Sample(s) will be collected at the time point(s) defined in the Assessment Schedule (Table 8-1).

Follow instructions for sample collection, numbering, processing, and shipment provided in the laboratory manual and/or SOM.

8.5.3 Synovial fluid volume

CCI [redacted] In case of dry taps, synovial fluid volume will not be calculated in order to avoid joint lavage.

CCI [redacted]

8.5.5 Knee X-ray

Radiography will serve an important role in assessing and verifying 3 eligibility criteria for adequate subject selection:

1. Kellgren-Lawrence grade to confirm the presence of knee OA of mild or moderate severity (KLG 2 or 3) .
2. Joint space width measured at a fixed location (x=0.225) in the medial tibio-femoral compartment of the index knee, in the range of 1.5-3.5 (females) or 2 to 4 (males) mm.
3. The anatomic PA axis as assessed by AP weight-bearing short knee radiography, to verify that there is no radiographically meaningful varus or valgus malalignment in the index knee (i.e., ≥ 7.5 degree).

All measurements will be performed locally by qualified staff at the investigational sites or delegated third party staff e.g., at specialized X-ray imaging facilities. For details, please refer to the Imaging Charter.

The following characteristics must be used for Kellgren & Lawrence grading (Schiphof et al 2008):

Grade 0: no changes
Grade I: possible osteophytes only
Grade II: definite osteophytes and possible joint space narrowing
Grade III: moderate osteophytes and/or definite joint space narrowing

Grade IV: large osteophytes, severe joint space narrowing and/or bony sclerosis

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the subject or the investigator.

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

Study treatment must be discontinued under the following circumstances:

- Subject/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in Section 6.2.2
- Subject presenting with a SAE that is suspected to be related to LRX712
- At least Moderate or Severe (Grade 2 or 3) local tolerability reaction according to the CTC-AE criteria (causes disability, limits self-care ADL, requires elective operative intervention and thereby hospitalization)
- At least Moderate or Severe (Grade 2 or 3) allergic reaction according to the CTC-AE criteria (results in bronchospasm with or without urticaria, edema/angioedema, hypotension, and it requires parenteral infusion therapy)
- Any protocol deviation that results in a significant risk to the subject's safety
- If a liver or renal event occurs, follow the guidelines outlined in Appendix 1 and Appendix 2 regarding discontinuation of study treatment
- Any laboratory abnormalities that in the judgment of the investigator prevents the subject from continuing participation in the study
- Any situation in which continuing study participation might result in a safety risk to the subject
- Following emergency unblinding

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

Subjects who discontinue 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 their consent (see Section 9.1.3). **Where possible, subjects who discontinued study treatment should return for the upcoming assessments indicated** in the Assessment Schedule. Alternatively, they should return for an EOS visit (CCI [redacted]) for the last safety assessments. If they fail to return for these assessments for unknown reasons, every effort (e.g., telephone, e-mail, letter) should be made to contact the

subject/pre-designated contact as specified in Section 9.1.4. This contact should preferably be done according to the study visit schedule.

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

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

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

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section.

9.1.2 Replacement policy

Given that the adequate statistical assessment of the primary and secondary (7T MRI-related) endpoints requires 13 subjects in each treatment arm to complete the Week 16 and 28 visits of the study, discontinued subjects who did not complete the three injections and/or did not provide the MRI results for Week 16 and 28, will be replaced by another subject, unless these discontinuations are due to any of the study stopping rules,

If any subject is discontinued due to a positive SARS-CoV-2 PCR test or any other reason than those outlined above, replacement will be decided upon Sponsor and investigator's agreement.

9.1.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

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 subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table (Table 8-1).

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until the time of withdrawal) according to applicable law.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.4 Lost to follow-up

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

9.1.5 Study stopping rules

The study will be stopped with no further dosing pending a full safety review, if any of the following criteria are met:

- Two (2) or more subjects presenting with the same SAE (as determined by CTC-AE criteria) that are all deemed as possibly/probably related to LRX712 by the Investigator or the Sponsor's Drug Safety Expert.
- Two (2) or more subjects presenting with a severe local tolerability issue of at least Grade 3 confirmed by the Investigator or the Sponsor's Drug Safety Expert.
- Two (2) or more subjects with acute allergic reaction of at least Grade 3 (as per CTC-AE criteria) following i.a. LRX712 administration.
- Two (2) or more subjects experience acute exacerbation of the knee OA with related intense pain symptoms confirmed by the Investigator or the Sponsor's Drug Safety Expert.
- The Sponsor considers that the number and/or severity of AEs, abnormal safety monitoring tests or abnormal laboratory findings justify putting the study on hold.
- One (1) or more patients presenting with a SADE related to the 7T MRI.

The study may resume following the safety review, if the Investigator and Sponsor agree it is safe to proceed.

9.1.6 Treatment arm stopping rules

Any of the treatment arms will be paused with no further dosing of that dose level pending a full safety review, if any of the following criteria are met:

- Two (2) or more subjects in the same treatment arm present with moderate or severe injection site AE of warmth and swelling that is deemed as possibly or probably related to LRX712 injection.
- The Sponsor considers that the number and/or severity of AEs, abnormal safety monitoring tests or abnormal laboratory findings justify putting the treatment arm on hold.

In the event that one treatment arm is paused for full safety review, the other treatment arm and the placebo arm will continue as per assessment schedule.

If after the full safety review of the paused treatment arm the Sponsor considers that it needs to be stopped, the study will continue with the placebo arm and the other treatment arm e.g., placebo and 15 mg LRX712.

The study subjects randomized to the stopped treatment arm may continue the study or resume dosing following the safety review, if the Investigator and Sponsor agree it is safe to proceed for them e.g. they did not experienced any of the injection site AEs that led to the discontinuation of study treatment and pausing that treatment arm:

1. In the event any subject has not completed the full dosing regimen (3 doses), he/she will continue the study on the other dose level until completing the full dosing regimen e.g.,15 mg LRX712
2. In the event any subject has completed the full dosing regimen, he/she will continue the study per the assessment schedule

The pending number of subjects that would have been randomized to the stopped treatment arm will be randomized to the other treatment arm e.g., if the 25 mg LRX712 treatment arm was stopped after 5 subjects were randomized to it, then the remaining 10 will be randomized to the 15 mg LRX712 by means of a new randomization list.

9.1.7 Early study termination by the sponsor

The study can be terminated by Novartis for various reasons. These may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. 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 subject's interests.

The investigator or sponsor, depending on the local regulation, will be responsible for informing IRBs/IECs and Health authorities of the early termination of the trial.

Novartis will clearly explain the reasons and describe follow-up measures taken for safety reasons, if any.

9.2 Study completion and post-study treatment

Study completion is defined as the time point when the last subject completes his/her End of Study visit, and any repeated assessment associated with this visit have been documented and followed up appropriately by the Investigator. Study completion may also be defined by an early study termination decision, i.e., the date of that decision.

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them.

10 Safety monitoring and reporting

In this trial, safety monitoring will be done for:

1. The investigational drug LRX712 and its placebo

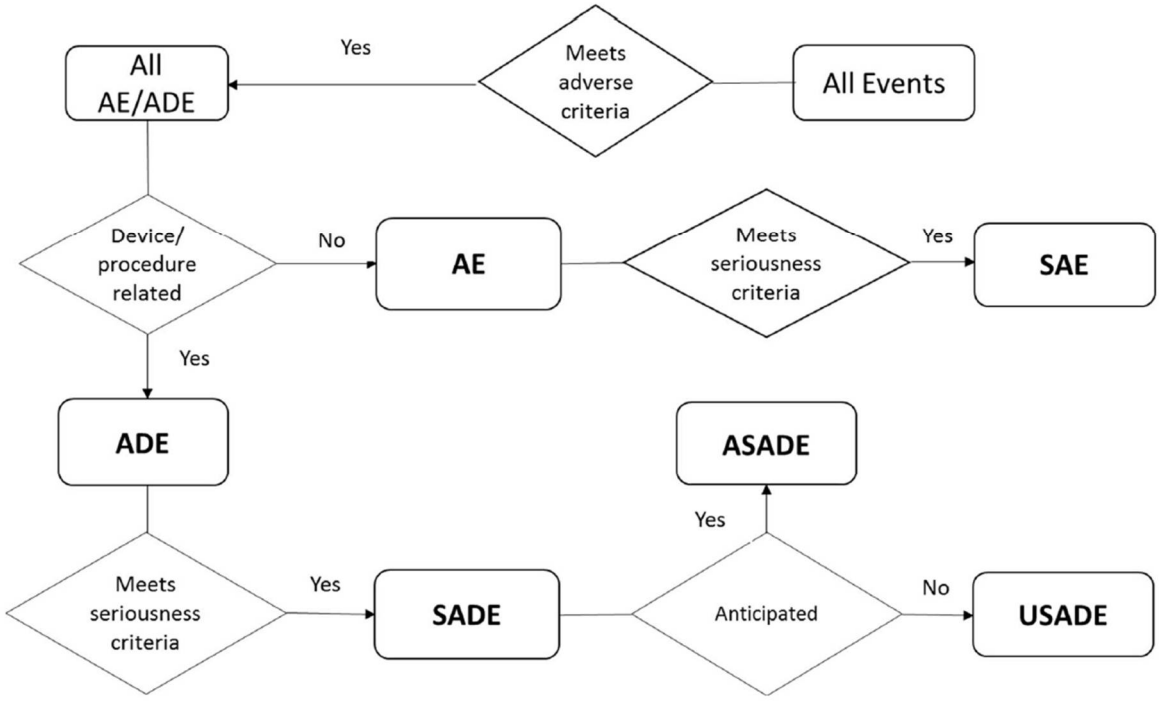
2. The 7T MRI exploratory device

By reporting:

- **Device related events:** Adverse device effects (ADE) and serious adverse device effects (SADE), device deficiency that might lead to a SADE and new findings/updates to already reported events for the device.
- **Not device related events:** Adverse events and serious adverse events (which may or may not be related to the investigational drug).

Device related cases (such as device malfunction, device deficiency, procedural errors, device deterioration, inaccurate instructions, degradation or destruction of the device) not meeting the definition of an adverse event are not considered ADE and will not be collected.

Figure 10-1 Safety monitoring



10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events and adverse device effects

10.1.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject 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 subjects and identifying adverse events.

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

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

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

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

1. The severity grade as per Common Terminology Criteria (CTC) AE grade.

If CTC-AE grading does not exist for an adverse event, use:

- 1=mild,
- 2=moderate,
- 3=severe
- 4=life threatening.

CTC-AE grade 5 (death) is not used, but is collected in other eCRFs (e.g., Study Completion, Death/Survival).

2. Its relationship to the investigational treatment (no/yes)
3. Its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported
4. Whether it constitutes a serious adverse event (SAE) See Section 10.1.2 for definition of SAE
5. Action taken regarding LRX712 treatment

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

- Dose not changed
- Dose reduced/increased
- Drug interrupted/withdrawn

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 subject.

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

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

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

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

Adverse event monitoring should be continued for at least 30 days (or 5 half-lives or end of study visit, whichever is longer) following the last dose of study treatment. In order to ensure adequate and efficient safety monitoring, the following activities will be considered for documentation:

1. From enrollment until Week 28 (included), any AE will be reported as per instructions described above
2. From Week 28 until Week 52, only the AEs of special interest listed below and any local procedure performed in the index knee (i.e., arthroscopy or surgery), will be reported, alongside any associated prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions).

   These are defined as follows:

   a. Any adverse event in the index knee linked to symptoms and/or signs of pain, dysfunction, local inflammation (warmth or swelling, e.g.) or stiffness
   b. Any adverse event that may be related or is the result of events mentioned in the previous bullet point i.e., a fall caused by sudden pain and related dysfunction in the index knee
   c. Any adverse event, which in the investigator's opinion is related to the medical condition of the index knee

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

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Follow the instructions found in the Site Operations Manual for data capture methodology regarding AE collection for subjects that fail Screening.

10.1.1.2 Adverse device effects (ADE)

An ADE is an adverse event related to the use of a device. In this study, an ADE refers to the 7T MRI. This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the device(s). This includes also any event that is a result of an error in use or intentional misuse.

The occurrence of adverse device effects should be sought by non-directive questioning of the subject at each visit during the study. Adverse device effects also may be detected when they are volunteered by the subject during or between visits.

Adverse device effects must be recorded on the Adverse Event eCRF page under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

1. The severity grade:
   - Mild: usually transient in nature and generally not interfering with normal activities
   - Moderate: sufficiently discomforting to interfere with normal activities
   - Severe: prevents normal activities
2. Its relationship to the device(s) in the comment section
3. Its duration (start and end dates or if the event is ongoing an outcome of not recovered/not resolved must be reported)
4. If it constitutes a serious adverse device effect (SADE) the SADE Report Form in paper has to be completed

Once an adverse device effect is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the medicinal product or device(s), the interventions required to treat it, and the outcome.

Information about known side effects of the device(s) can be found in the Informed Consent form. This information will be included in the subject's informed consent and should be discussed with the subject during the study as needed.

The Investigator should also instruct each subject to report any new adverse event/adverse device effect (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to the device used. This information should be recorded in the Investigator's source documents; however, if the ADE meets the SADE, it must be reported to Novartis.

10.1.2 Serious adverse events and serious adverse device effects

10.1.2.1 Serious adverse events

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

- fatal
- life-threatening

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

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect

- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, 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 subject'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 subject 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 subject 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 malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

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

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

10.1.3 SAE reporting

Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

Screen Failures

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

Randomized Subjects

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until the last study visit, must be reported to Novartis within 24 hours of learning of its occurrence, as described below. Any SAEs experienced after this period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

SAEs will be collected between the time the subject signs the ICF until 30 days after the subject has discontinued or until the last study visit.

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 within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported event must be reported separately as a new event.

Follow- up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable) and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

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

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

10.1.3.1 Serious adverse device effects (SADE)

A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event:

- Led to a death, injury or permanent impairment to a body structure or a body function
- Led to a serious deterioration in health of the subject, that either resulted in:
  1. A life-threatening illness or injury, or
  2. A permanent impairment of a body structure or a body function, or
  3. In-patient hospitalization or prolongation of existing hospitalization, or
  4. In medical or surgical intervention to prevent life threatening illness
- Led to foetal distress, foetal death or a congenital abnormality or birth defect

10.1.3.2 SADE reporting

The Investigator of the specific imaging site must assess the relationship to the 7T MRI, complete and submit the SADE Report Form in English within 24 hours of learning of its occurrence.

The Investigator will distinguish between the SADE related to the device and those related to the procedures (any procedure specific to the clinical investigation).

Each SADE will be classified according to five different levels of causality. The Investigator will use the following definitions to assess the relationship of the serious adverse event to the investigational device or procedures:

1. **Not related:** relationship to the device or procedures can be excluded when:
   - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
   - the event has no temporal relationship with the use of the investigational device or the procedures;
   - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
   - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;
   - the event involves a body-site, or an organ not expected to be affected by the device or procedure;
   - the serious event can be attributed to another cause (e.g., an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment or other risk factors);
   - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;
   - harms to the subject are not clearly due to use error.

In order to establish the non-relatedness, the criteria listed above might not be met at the same time, depending on the type of device/procedures and the serious event.

2. **Unlikely:** the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
3. **Possible:** the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
4. **Probable:** the relationship with the use of the investigational device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.

5. **Causal relationship:** the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:
   - the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
   - the event has a temporal relationship with investigational device use/application or procedures;
   - the event involves a body-site or organ that
     - the investigational device or procedures are applied to;
     - the investigational device or procedures have an effect on;
   - the serious event follows a known response pattern to the medical device (if the response pattern is previously known);
   - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact the serious event (when clinically feasible);
   - other possible causes (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
   - harm to the subject is due to error in use;
   - the event depends on a false result given by the investigational device used for diagnosis, when applicable.

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Once completed and signed the form is sent by the Investigator by fax within 24 hours of learning of its occurrence to the local Novartis Patient Safety Department. The telephone and fax number of the contact persons in the local department of Patient Safety, specific to the site, are listed in the SOM. The original copy of the form about SADE and the fax confirmation sheet must be kept at the study site. Follow-up information about the SADE should be provided using a new paper form stating that this is a follow-up to a previously reported SADE.

Follow-up information provided must describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

Events to be reported include:

- any SADE;
- SADEs which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other subjects, users or other persons or a new finding to it have to be reported immediately;
- new finding/updates in relation to reported events;
- any investigational device deficiencies that might lead to a SAE if:
  - suitable action had not been taken or
  - intervention had not been made or
  - if circumstances had been less fortunate

If the SADE is not previously documented and it is thought to be related to the study intervention a Patient Safety associate urgently may require further information from the Investigator of the specific imaging site 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 intervention that this SADE has been reported. A serious adverse device effect which, by its nature, incidence, severity or outcome has not been identified previously, is defined as an unanticipated serious adverse device effect (USADE). Unanticipated serious adverse device effects will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

10.1.4 Pregnancy reporting

Reproductive toxicity and teratogenicity data are not available for the investigational drug at this time; therefore, no guidelines on therapeutic recommendations in case of pregnancy are available. This study enrolls women who are of non-child-bearing potential, thus pregnancy is not an expected outcome for any female study participant. However, in the case that a pregnancy in a female study participant should occur, please follow the below reporting guidelines.

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning about its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

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

The study drug must be discontinued, though the subject may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Pregnancy outcomes will be followed-up at the following times:

- 12 months after the estimate date of delivery (for a live birth only)

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate eCRF irrespective of whether they are associated with an AE/SAE. Errors will be reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

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

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

For more information on AE and SAE definition and reporting requirements, please see Section 10.1.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

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

The following two categories of abnormalities / adverse events have to be considered during the study (irrespective of whether classified/reported as AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation; follow-up monitoring and contributing factors are recorded on the appropriate eCRFs

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

Every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-2. Repeat liver chemistry tests (i.e., ALT, AST, TBL, PT/INR, ALP and γ-GT) to confirm elevation.

- These liver chemistry repeats should be performed by the site's local laboratory. Repeated laboratory test results must be reported as appropriate.
- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 9.1.1), if appropriate
- Hospitalization of the subject, if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include, based on the investigator's discretion:
    - Serology tests, imaging and pathology assessments, hepatology consultation, 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 eCRF.

Refer to the SOM for additional details.

10.2.2 Renal safety monitoring

Every renal laboratory trigger or renal event must be followed up by the investigator or designated personnel at the trial site.

All follow-up information, and the procedures performed must be recorded as appropriate in the eCRF. Refer to the SOM for additional details.

11 Data Collection and Database management

11.1 Data collection

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

The investigator/designee is responsible for assuring that the data recorded on eCRFs 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 subject data for archiving at the investigational site.

Automatic validation programs check for data discrepancies, and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer to the vendor working on behalf of Novartis.

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

11.2 Database management and quality control

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

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

At the conclusion of a non-IRT study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused supplies to 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 a restricted area to be accessed by an independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

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

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

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

12 Data analysis and statistical methods

The statistical analysis will be carried out after end of study and data base lock. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

The safety analysis set will include all subjects that received any study drug.

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

The PD analysis set will include all subjects with available PD data and no protocol deviations with relevant impact on PD data.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including OA severity by KLG will be listed for all subjects and summarized descriptively by LRX712 and placebo treated groups using the Safety set.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For highly skewed continuous data, mean and standard deviation will not be presented. For selected parameters, 25th and 75th percentiles may also be presented.

Relevant medical histories and current medical conditions at baseline will be listed by treatment group and subject.

12.3 Treatments

Data for study drug administration and concomitant therapies will be listed by subject and treatment group.

12.4 Analysis of the primary endpoint(s)

12.4.1 Definition of primary endpoint(s)

Change in cartilage volume in the index region measured by 7T MRI from baseline to week 28 in LRX712- vs. placebo-treated subjects.

12.4.2 Statistical model, hypothesis, and method of analysis

It is hypothesized that LRX712 treatment will increase the cartilage volume of the impacted compartment from its baseline level, and that this change will be detectable using 7T MRI. For the primary analysis, the signal intensity (measured as an absolute change from baseline) will be analyzed using a Mixed effect Model with Repeated Measures (MMRM). The model will include treatment, time, treatment*time as fixed effects. An unstructured matrix will be used to model within-subject correlation. The signal intensity in pre-defined cartilage sub-regions of the different knee compartments may be, if needed, logarithmically transformed prior to analysis.

Least squares means of the treatment difference will be reported together with two-sided 90% confidence intervals. Analysis of the primary endpoint will be done at week 28 separately for LRX712 15mg vs. Placebo and LRX712 25mg vs. Placebo.

12.4.3 Handling of missing values/censoring/discontinuations

Missing values of the primary endpoint (cartilage volume at week 28) will be treated as missing at random and imputed by the MMRM.

12.4.4 Sensitivity and Supportive analyses

Supportive analyses which explore the treatment effect of pooling data from all subjects dosed with LRX712 together may be done following the same method described in Section 12.4.2. No adjustment for multiplicity is planned for this supportive analysis.

12.5 Analysis of secondary endpoints

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

The secondary PD endpoints (i.e., cartilage [^{23}Na] content, volume and thickness at weeks 16 and 52) will be analyzed in the same manner as the primary endpoint, by MMRM with an unstructured covariance matrix. The cartilage volume and thickness will both be analyzed on their original scales.

12.5.2 Safety endpoints

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

Adverse events

The number (and percentage) of subjects with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

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

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

To assess local tolerability of LRX712 with multiple injections, the probability of an injection site adverse event will be calculated for each treatment group. A Bayesian Poisson regression model will be fitted with treatment group as fixed categorical variable. Further details on the definition of injection site adverse events is given in the SAP.

Vital signs

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

12-lead digitized ECG

A standard 12-lead electrocardiogram will be performed in triplicate:3 tracings of at least 10 sec duration to be obtained within a 2-5 min window). A standard 12-lead electrocardiogram will be performed in triplicate (3 tracings of at least 10 sec duration to be obtained within a 2-5 min window.

1. PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each subject during the study. ECG data will be read and interpreted locally.
2. Categorical Analysis of QT/QTc interval data based on the number of subjects meeting or exceeding predefined limits in terms of absolute QT/QTc intervals or changes from baseline will be presented. In addition, a listing of these subjects will be produced by treatment group.

All ECG data will be listed by treatment group, subject and visit/time; abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, subject, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time. Shift tables using the low/normal/high/ classification will be used to compare baseline to the worst on-treatment value. A longitudinal representation of the data will be presented if deemed necessary.

12.5.3 Pharmacokinetics

LRX712 and MAE344 plasma as well as synovial concentration data will be listed by treatment, subject, and visit/sampling time point.

Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ (reported as zero).

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum, and maximum. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations.

Pharmacokinetic parameters will be listed by treatment and subject. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is Tmax where median, minimum, and maximum will be presented.

Table 12-1 Non-compartmental pharmacokinetic parameters

Cmax	The maximum (peak) observed plasma, blood, serum, synovial fluid, or other body fluid drug concentration (mass x volume-1)
Cmin	The minimum observed plasma concentration during the dosing interval
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)

12.5.4 PK/PD relationships

Not applicable.

12.6 Analysis of exploratory endpoints

12.7 Interim analyses

Interim analyses for exploratory and program-wide purposes may be performed at the sponsor's discretion.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

In the Proof of Concept (PoC) study CLNA043X2202 (EudraCT- number 2016-004052-30) a treatment different of 123 mm^3 change in medial femoral condyle cartilage morphometrics volume was observed at week 28. Assuming a similar treatment effect and a standard deviation of 130 mm^3, 13 subjects per arm will provide approximately 75% power to detect a statistically significant difference between LRX712 25 mg and placebo, or LRX712 15 mg and placebo at the two-sided 10% significance level. If necessary, sample size may be re-assessed at an interim analysis.

12.8.2 Secondary endpoint(s)

Not applicable.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

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

13.3 Publication of study protocol and results

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

13.4 Quality Control and Quality Assurance

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

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

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

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study subjects. Additional assessments required to ensure safety of subjects 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 subjects.

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

14.1 Protocol amendments

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

Only amendments that are required for subject 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 subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

Laboratory variable	Notable criterion
Hemoglobin	<8.0 g/dL
Glucose	≥9.0 mmol/L
Platelet count	<75000 mm^3
Estimated GFR	<30 mL/min
Total bilirubin concentration	>1.5 x ULN
Total serum bilirubin	>1.6 mg/dL or 27 µmol/L
AST	>3 ULN
ALT	>3 ULN
Vital signs	
Systolic blood pressure	>160 mmHg or <90 mmHg
Diastolic blood pressure	>100 mmHg or <50 mmHg
Heart rate	>100 bpm or <60 bpm
ECG	
QTcF	Men: >450 ms
	Women: >460 ms

The study will use a central laboratory for analysis.

16.2 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 16-1 Liver event and laboratory trigger definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤ 5 x ULN • 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × 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 TBL > 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*

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

Table 16-2 Follow up requirements for liver events and laboratory triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (subject is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate eCRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (subject is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit

Criteria	Actions required	Follow-up monitoring
Jaundice	• Discontinue the study treatment immediately • Hospitalize the subject • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate eCRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

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.