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Novartis Research and Development

LNA043

A 5-year, randomized, double-blind, placebo-controlled, multi-center study assessing the efficacy, safety, and tolerability of intra-articular regimens of LNA043 versus placebo in patients with symptomatic knee osteoarthritis (ONWARDS)

Clinical Trial Protocol CLNA043A12202 / NCT04864392

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List of abbreviations

ACI	autologous chondrocyte implantation
ACR	American College of Rheumatology
ADA	anti-drug antibodies
AE	adverse event
AIR	Acute Inflammatory Reaction
AKI	Acute kidney injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANGPTL3	angiopoietin-like 3 protein
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BMI	Body Mass Index
BSP	Biomechanical Sensor Platform
BUN	blood urea nitrogen
CFR	Code of Federal Regulation
CK	creatinine kinase
cMTFC	central medial tibiofemoral compartment
COX-2	Cyclooxygenase 2
CR-MSCs	cartilage resident-mesenchymal stromal cells
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTIS	Clinical Trials Information System
CSR	Clinical Study Report
CV	coefficient of variation
DLTs	dose limiting toxicities
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EOS	End of Study
EOT	End of Treatment
eSAE	Electronic Serious Adverse Event
FDA	Food and Drug Administration
FIH	First-In-Human
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
i.a.	intra-articular
i.v.	intravenous
IB	Investigator's Brochure

ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IG	Immunogenicity
IMU	inertial measurement units
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
CCI	[redacted]
IUD	intrauterine device
IUS	intrauterine system
JSW	joint space width
K-L	Kellgren/Lawrence
KAM	knee adduction moment
KFM	knee flexion moment
kg	Kilogram
latJSN	lateral Joint Space Narrowing
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LLQ	lower limit of quantification
MAR	missing at random
MCID	minimal clinically important difference
MedDRA	Medical dictionary for regulatory activities
medJSN	medial Joint Space Narrowing
mg	milligram(s)
mL	milliliter(s)
MMRM	mixed-effect model repeated measures
CCI	[redacted]
MR	Magnetic Resonance
MRI	Magnetic resonance imaging
NOAEL	No Observed Adverse Effect Level
NRS	Numerical rating scale
NSAIDs	Nonsteroidal anti-inflammatory drugs
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OMERACT	Outcome Measures in Rheumatology
PCR	Protein-creatinine ratio
PD	pharmacodynamic(s)
PGA	Patient Global Assessment
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PoC	proof of concept
PoM	proof of mechanism
PRO	Patient Reported Outcomes
PRP	platelet-rich plasma

PT	prothrombin time
CCI	CCI [redacted]
QMS	Quality Management System
QoL	quality of life
SAE	serious adverse event
sCr	serum creatinine
SD	standard deviation
SDC	smallest detectable change
SF-12	Short Form 12 Health Survey
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
TFCs	tibiofemoral compartments
TKR	total knee replacement
ULN	upper limit of normal
VKR	Virtual Knee Replacement
CCI	CCI [redacted]
WHO	World Health Organization
WOMAC	Western Ontario and McMaster Universities Arthritis Index
WPI	Widespread Pain Index
µg	Microgram

Glossary of terms

Assessment	A procedure used to generate data required by the study.
Clinical Trial Team	A group of people responsible for the planning, execution and reporting of all clinical trial activities. Examples of team members include the Study Lead, Medical Monitor, Trial Statistician etc.
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial.
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day).
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant.
Enrollment	Point/time of 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).
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up), which applies across all arms of a study.
Estimand	As defined in the ICH E9(R1) addendum, estimand is a precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same participants under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug” or “test substance”.
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system.
Mis-randomized subjects	Mis-randomized subjects are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study.
Non-investigational medicinal Product (NIMP)	Products which are not the object of investigation (e.g. any background therapy administered to each of the clinical trial subjects, regardless of randomization group, rescue medication, active drug run-ins etc.).
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.
Participant	An individual participating into the trial.
Patient	An individual with the condition of interest.

Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient about the status of a participant's health condition without amendment or interpretation of the patient's report by a clinician or anyone else.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment.
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol.
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.
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s).
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date.
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either 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.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of consent (WoC) / Opposition to use of data /biological samples	Withdrawal of consent from the study is defined as when the participant explicitly requests to stop use of their biological samples and/or data (opposition to use data and biological samples) AND no longer wishes to receive study treatment, AND does not want any further visits or assessments (including further study-related contacts). This request should be in writing (depending on local regulations) and recorded in the source documentation.

Amendment 02 (03-JUN-2024)

Enrollment is completed; CCI patients have been screened and 576 patients have been enrolled in the study.

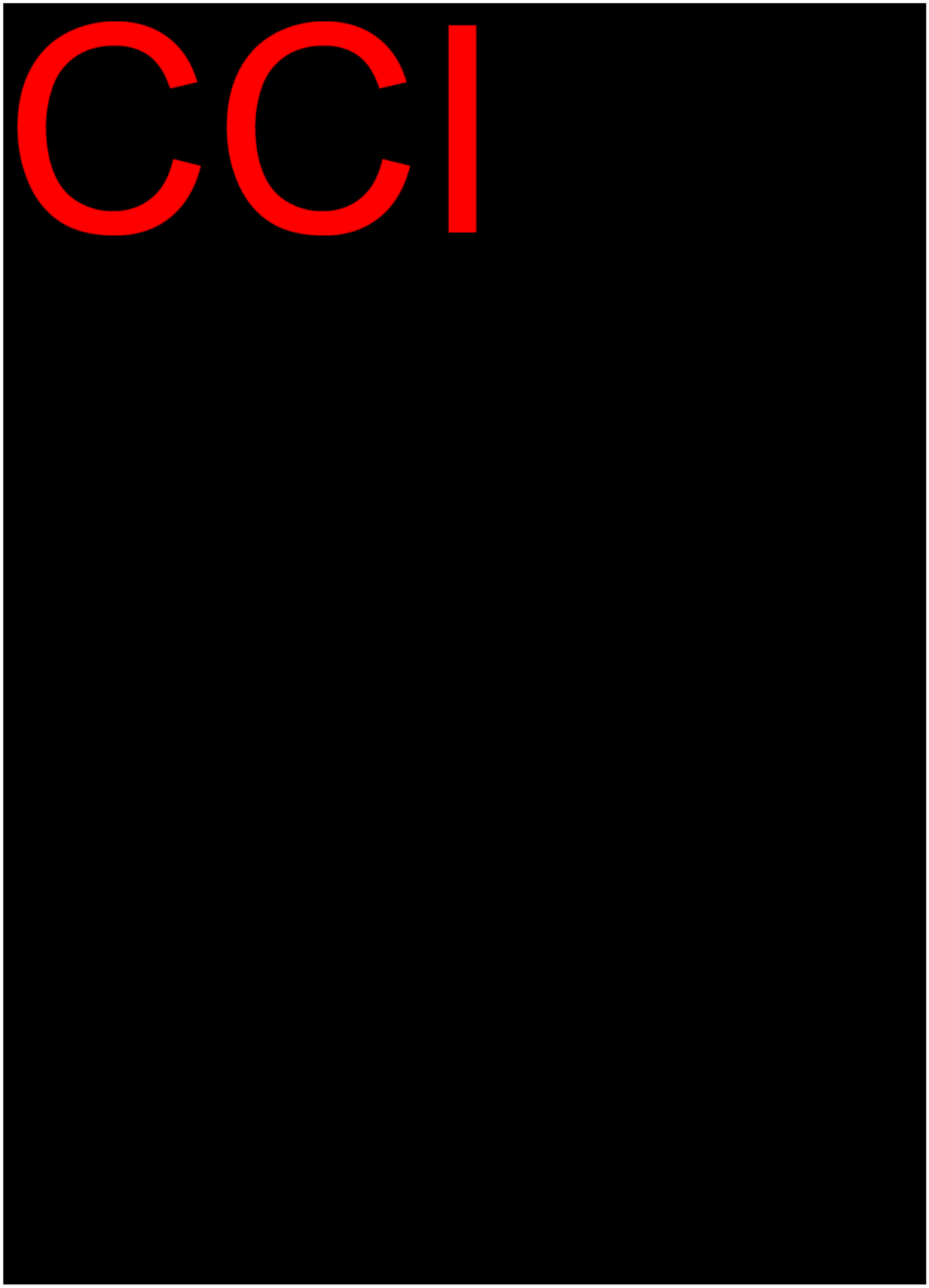
Amendment rationale:

The purpose of this protocol amendment is to implement the following changes:

- Addition of CCI . The rationale for adding CCI This information is not currently being collected in the trial.
- Addition of Hy's Law reporting language to follow safety language updates on Hy's Law reporting guidance of Novartis.
- Addition of relevant content from latest Novartis protocol template (OneCTP template V8.0).

List of changes to the protocol:

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 underline for insertions.


CCI

IRBs/IECs

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

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

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

Amendment 01 (29-NOV-2021)

Amendment rationale

Amendment 1 is to correct an inconsistency in the description of inclusion criterion #6 between the protocol summary and body; to introduce flexibility in the assessment schedule including pre-screening; to define optional pre-screening assessments; to clarify prohibited medications; to add PROs in the Extension Period; to better explain how to handle disruptions of the dosing scheme; to introduce flexibility in the exploratory Gait assessment; and to introduce additional minor clarifications and administrative changes.

A revision of inclusion criterion #6 was needed to correct the inconsistency between the protocol body and the protocol summary to clarify that eligible patients should have stable WOMAC Pain, between 20 and 45 (out of 50) in the target knee, at both assessments (double baseline) during screening.

Flexibility on the timing of assessments at Screening Visit 1 and 2 was introduced in the screening period in response to the COVID-19 pandemic, in order to facilitate execution of the protocol-mandated procedures required to determine study eligibility.

Possibility for conducting optional pre-screening assessments after signature on a pre-screening ICF was introduced to facilitate selection of eligible participants at an earlier stage while reducing unnecessary burden for ineligible patients.

Prohibited i.a. injections with corticosteroids have been clarified, by allowing treatment in non-knee joints before double baseline WOMAC pain assessment, because of the limited impact on pain assessment in the knees, and to align with the 1 injection/year allowance during the Core and Extension Periods.

WOMAC, SF-12 and PGA assessments were changed from every [redacted] in the Extension Period, in order to ensure proper assessment of pain, function and quality of life.

The language describing the gait assessment has been edited, in order to allow more flexibility in the devices set up and parameters to be collected and assessed in consideration of the technical complexity of this platform.

Several administrative changes have been introduced to ensure data quality and minimize risk of inconsistent interpretation.

The amendment is expected to have a negligible impact on the study population.

At the time of amendment, the study is actively recruiting patients with approximately 20 patients randomized. First patient screened was 31-May-2021 and first patient randomized was 08-Sep-2021. Participants already randomized in the study will need to be re-consented as a consequence of this amendment, mainly to reflect study assessments updates.

Screening can be continued under original protocol until amendment is approved.

Changes to the protocol

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 underline for insertions.

The following sections have been changed in the amended protocol:

IRBs/IECs

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

The changes described in this amended protocol are non-substantial and do not require IRB/IEC approval prior to implementation unless required by local regulations.

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

Protocol summary

Protocol number	CLNA043A12202
Full Title	A 5-year, randomized, double-blind, placebo-controlled, multi-center study assessing the efficacy, safety, and tolerability of intra-articular regimens of LNA043 versus placebo in patients with symptomatic knee osteoarthritis (ONWARDS)
Brief title	Study of efficacy, safety, and tolerability of LNA043 in patients with symptomatic knee osteoarthritis
Sponsor and Clinical Phase	Novartis Pharma AG Phase IIb
Investigation type	Biological
Study type	Interventional
Purpose and rationale	The purpose of this study is to assess the efficacy, safety and tolerability of different doses (CCI mg and CCI mg), number of injections in a dosing cycle (CCI) and dosing cycle frequency (CCI) of intra-articular LNA043.This study will determine the optimal dosing regimen of LNA043 leading to structural changes, symptomatic relief and improvement in function/quality of life of participants with knee osteoarthritis (OA). Results of this study will inform later phases of the LNA043 clinical development program.
Primary Objective(s)	To evaluate structural changes from baseline in the central medial tibiofemoral compartment (cMTFC) of LNA043 compared with placebo in the target knee at Week 104.
Secondary Objectives	• To evaluate changes from baseline in OA pain in the target knee of LNA043 compared with placebo at Week 104 • To evaluate changes from baseline in physical function of LNA043 compared with placebo at Week 104 • To evaluate structural changes from baseline in the total, medial and lateral tibiofemoral compartments (TFCs) in the target knee of LNA043 compared with placebo at Week 104 • To evaluate changes from baseline in performance-based physical function assessment of LNA043 compared with placebo at Week 104 • To evaluate structural progression in the target knee of LNA043 compared with placebo using imaging techniques • To evaluate safety and tolerability of the various LNA043 regimens
Study design	This is a multicenter, randomized, parallel-group, double-blind, placebo-controlled Phase IIb study consisting of a 2-year Core Period, followed by a 3-year Extension Period (of 2-year treatment and 1-year follow-up).
Study population	Male and female participants 40 to 75 years old, with predominantly unilateral medial radiographic Kellgren/Lawrence (K-L) grade 2-3 knee osteoarthritis, and moderate to severe pain in the target knee (WOMAC Pain of 20-45 out of 50).
Key Inclusion criteria	• Males and females between 40 and 75 years of age • Body mass index (BMI) < 40 kg/m^2 • Diagnosis of primary tibiofemoral knee OA by standard American College of Rheumatology clinical and radiographic criteria • Radiographic disease K-L grade 2 or 3 knee OA with a predominantly medial TFC involvement defined as medial Joint Space Narrowing (medJSN) 1-2 and medJSN > lateral Joint Space Narrowing (latJSN) in the target knee • Participants with WOMAC Pain of 20-45 (out of 50) for the target knee at both (double baseline) assessments during screening period after discontinuation of analgesics, anti-inflammatories and low potency opioids within 48 hours or an equivalent of 5×$T_{1/2}$ wash out period (whichever is longer) • Symptomatic OA with pain in the target knee for at least 6 months • Primary source of pain throughout body is due to OA in the target knee: Widespread Pain Index score of ≤6 and a Symptom Severity score of <7
Key Exclusion criteria	• Participants with radiographic knee OA K-L grade = 4 on the non-target knee • Participants with WOMAC Pain > 15 (out of 50) in the non-target knee

	• Severe malalignment (>7.5° varus or valgus) in the anatomical axis of the target knee • Clinical signs of moderate-severe inflammation (i.e., redness, warmth, effusion) of the target knee or requiring aspiration in the target knee within 12 weeks prior to Screening • Arthroscopy of the target knee within the 6 months prior to Screening • Previous surgical treatment of the target knee using mosaicplasty, microfracture, meniscectomy >50% or osteotomy, partial or complete joint replacement or planned knee surgery for either knee during the study • Unstable target knee joint (including, but not limited to, posttraumatic or congenital laxity) or insufficiently reconstructed ligaments based on medical history and/or physical examination by the Investigator • Other pathologies affecting the knee, including subchondral insufficiency fractures, bone fracture (acute or subacute in less than 6 months prior to screening) or bone bruise, osteonecrosis, malignant bone marrow infiltration, solid tumors, and/or patellofemoral dysplasia based on clinical assessment, X-ray or MRI • Symptomatic hip OA on either hip or hip prosthesis recently implanted (within 1 year) or foreseen within the study period (either hip) • Other pain conditions that could confound assessments of the pain associated with knee OA, as judged by the Investigator
Study treatment	Investigational drug: LNA043 CCI mg, CCI mg Control: Placebo (saline solution)
Treatment of interest	This study will assess the efficacy, safety and tolerability of LNA043 in different doses (CCI mg and CCI mg), number of injections in a cycle (CCI) and dosing cycle frequency (CCI).
Efficacy assessments	• Change from baseline in cartilage thickness in the cMTFC at Week 104 assessed by MRI of the target knee • Change from baseline at Week 104 in WOMAC pain • Change from baseline at Week 104 in WOMAC function • Change from baseline in cartilage thickness in the total, medial and lateral TFCs at Week 104 assessed by MRI of the target knee • Change from baseline in physical function at Week 104; 40-meter (4×10m) fast-paced walk test, 30-second chair stand test, and 6-minute walking test • Proportion of participants demonstrating structural progression at Week 104 in the target knee defined as change above the smallest detectable change of cartilage thickness by MRI and a loss of medial minimum joint space width ≥ 0.70 mm from baseline by X-ray
Key safety assessments	• Adverse Event monitoring • Physical examination, vital signs, height and weight • Incidence of Acute Inflammatory Reactions (AIRs) • Laboratory evaluations (hematology, chemistry, lipids panel (fasting), urinalysis) • ECG • Anti-drug antibody to LNA043
Data analysis	The primary efficacy variable is change from baseline in cartilage thickness in the cMTFC at Week 104 determined by qMRI of the target knee in participants with knee OA. The primary analysis will be conducted using mixed-effect model repeated measures (MMRM) which is valid under the missing at random (MAR) assumption, with treatment and analysis visit as factors and baseline score as a covariate in the model. Treatment by analysis visit and baseline score by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for this model. The significance of the treatment effects for LNA043 regimens at Week 104 will be determined from the pairwise comparisons using the Dunnett test performed between LNA043 regimens and placebo at α =0.05.
Key words	knee osteoarthritis, LNA043, DMOAD

1 Introduction

1.1 Background

Osteoarthritis (OA), a slowly progressive disease with a multifactorial pathophysiology, is one of the most common chronic health conditions in the world, and a leading cause of pain and disability among adults (Osteoarthritis Research Society International (OARSI) 2016). Approximately 10-12% of the adult population has symptomatic knee OA with a worldwide estimate of ~263 million people being affected by knee OA in 2017 (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators 2018). The prevalence of OA is progressively rising due to an increase in life expectancy and population ageing, along with rising prevalence of predisposing risk factors such as obesity and related metabolic comorbidities. Pain and loss of function due to OA are accompanied by an increased risk of additional comorbidities such as type 2 diabetes and cardiovascular disease (Fernandes and Valdes 2015). The hallmark of OA is joint pain and progressive degradation of articular cartilage, synovitis, and alterations in subchondral bone and periarticular tissues (Goldring and Otero 2011). In the United States alone, over 1,000,000 total knee replacements (TKR) were planned in 2020 (Singh et al 2019).

The mainstay of knee OA treatment includes non-pharmacological and pharmacological measures to reduce pain (analgesic medication) and improve knee and lower-extremity function (physiotherapy). Current pharmacological treatments are directed only at symptoms without structural improvement or modification of disease progression, posing an unmet medical need for patients. Despite major efforts in the past decades, there are no approved disease-modifying OA drugs. Therefore, the quest for novel compounds that can potentially halt or reverse the structural changes associated with OA continues.

LNA043 is a modified C-terminal fragment of a recombinant version of the human angiopoietin-like 3 protein (ANGPTL3). Similar to ANGPTL3, LNA043 acts directly on cartilage resident-mesenchymal stromal cells (CR-MSCs) and articular chondrocytes through binding to α5β1 and αVβ3 integrins to transmit its anabolic repair effects on cartilage cells, promoting the formation of articular cartilage extracellular matrix proteins in mature chondrocytes and in CR-MSCs while supporting re-growth of CR-MSCs. In contrast to ANGPTL3, LNA043 does not demonstrate triglyceride modulation nor angiogenesis, based on *in vitro* assays, because it does not contain the N-terminal portion of the full protein. To evaluate LNA043 *in vivo*, rat CCI meniscal injury models were utilized (Gerwin et al 2010). In brief, 8-week-old male Lewis rats were subjected to surgery to completely sever the medial collateral ligament and the medial meniscus to destabilize the joint so that future weight-bearing would lead to rapid degeneration of the cartilage. CCI , one week following the surgery, a single dose of LNA043 or saline was injected intra-articularly (i.a.). CCI , it was determined that a single i.a. injection up to 200 µg of LNA043 (rats) CCI significantly repaired the surgically damaged cartilage in a dose-related manner.

CCI

CCI

CCI

The completed first-in-human (FIH) study (CLNA043X2101) of LNA043 was performed in primary OA participants who were scheduled for total knee replacement (TKR). Up to CCI mg LNA043 was administered intra-articularly as a single dose 3 weeks, 1 week or 2 hours prior to surgery and safety, tolerability, pharmacokinetics (PK), and immunogenicity (IG) data were collected. In summary, (i) no significant drug-related Adverse Events (AE) or Serious Adverse Events (SAE) were reported; (ii) LNA043 was rapidly eliminated from the synovial fluid of the knee and the plasma (LNA043 levels were below limit of quantification after 7 days in both samples); and (iii) no anti-drug antibodies (ADA) were detected. A dose of CCI mg in 3 participants demonstrated a favorable safety profile, with only 1 participant (CCI mg single dose) reporting AEs of dry mouth and dysgeusia, both mild in severity. No participant experienced a hypersensitivity reaction.

The completed proof of mechanism (PoM) study (CLNA043X2201) was performed in participants undergoing autologous chondrocyte implantation (ACI) to treat a cartilage lesion, receiving a single injection of CCI mg LNA043. Both the extent of tissue growth and the quality of tissue composition were evaluated with 7 Tesla MRI. Results showed that tissue compatible with early hyaline cartilage was detected at the donor sites at 4 and 12 weeks post-LNA043 dose. No drug-related safety signal including hypersensitivity reaction was reported. There

were no deaths or SAEs during the study and all of the AEs reported were mild to moderate in severity. There were no clinically relevant laboratory or vital signs abnormalities during the conduct of the study, and single intra-articular administration of LNA043 did not lead to formation of ADAs.

The proof of concept (PoC) study (CLNA043X2202 - Part A) completed dosing and follow up in participants with knee cartilage injury, receiving 4 weekly injections of CCI mg LNA043 and followed up for 52 weeks (Part A). Results confirm the cartilage anabolic activity of LNA043 in humans at 28 weeks follow up measured with 3T MRI. Overall, at the interim analysis, the treatment was well-tolerated and no relevant systemic safety signal was reported. There were no deaths and no discontinuations due to study treatment. One (1) SAE was reported (low back pain) but was not considered to be related to study treatment. A higher incidence of joint swelling (9.3% vs 0%) and arthralgia (11.6% vs 6.7%) was reported for LNA043 vs placebo respectively. Most of these occurred after the i.a. injection, resolved spontaneously or with paracetamol/NSAIDs and are consistent with a mild/moderate local reaction of the knee to the drug. No AEs compatible with hypersensitivity reactions have been reported. No anti-LNA043 antibodies were detected in any of the tested samples. The PoC study CLNA043X2202 Part B, in participants with mild-moderate knee OA, receiving CCI injections of CCI mg or CCI mg LNA043, is currently ongoing. An ethnic sensitivity study (CLNA043A11101) in the Japanese population, receiving a single i.a. injection of CCI mg or CCI mg LNA043, completed treatment and follow up with no SAEs reported.

A more detailed review of the available pre-clinical and clinical information on LNA043 can be found in the Investigator's Brochure (IB).

1.2 Purpose

The purpose of this study is to assess the efficacy, safety and tolerability of different doses (CCI mg and CCI mg), number of injections in a dosing cycle (CCI) and dosing cycle frequency (CCI) of i.a. LNA043 to determine an optimal dosing regimen for the treatment of knee OA.

This study will determine the optimal dosing regimen of LNA043 leading to structural changes, symptomatic relief and improvement in function/quality of life (QoL) of participants with knee OA. Results of this study will inform later phases of the LNA043 clinical development program.

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 evaluate structural changes from baseline in the central medial tibiofemoral compartment (cMTFC) of LNA043 compared with placebo in the target knee at Week 104	• Change from baseline in cartilage thickness in the cMTFC at Week 104 assessed by qMRI
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**

Objective(s)	Endpoint(s)

• To evaluate changes from baseline in OA pain in the target knee of LNA043 compared with placebo at Week 104	• Change from baseline at Week 104 in:
	  • WOMAC pain
	  • WOMAC pain walking on flat surface item

• To evaluate changes from baseline in physical function of LNA043 compared with placebo at Week 104	• Change from baseline at Week 104 in: • WOMAC function
• To evaluate structural changes from baseline in the total, medial and lateral tibiofemoral compartments (TFCs) in the target knee of LNA043 compared with placebo at Week 104	• Change from baseline in cartilage thickness in the total, medial and lateral TFCs at Week 104 assessed by qMRI

• To evaluate changes from baseline in performance-based physical function assessment of LNA043 compared with placebo at Week 104	• Change from baseline in physical function at Week 104
	  • 40-meter (4×10m) fast-paced walk test
	  • 30-second chair stand test
	  • 6-minute walking test

• To evaluate proportion of patients with structural progression in the target knee of LNA043 compared with placebo using imaging techniques	• Proportion of participants demonstrating structural progression at Week 104 defined as:
	  • change above the smallest detectable change (SDC) of cartilage thickness by qMRI
	  • a loss of medial minimum joint space width (minJSW) ≥ 0.70 mm from baseline by X-ray

• To evaluate safety and tolerability of the various LNA043 regimens	• Safety and tolerability demonstrated by assessing:
	  • Adverse events (AEs) and serious adverse events (SAEs)
	  • Incidence of Acute Inflammatory Reactions (AIRs) on the target knee
	  • Clinically significant changes in laboratory measures and vital signs, as assessed by the Investigator
	  • Incidence of binding and neutralizing ADAs in serum

Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
• To evaluate structural changes in the cMTFC of the target knee over time	• Change from baseline in cartilage thickness in the cMTFC assessed by qMRI at Weeks CCI [redacted]

• To evaluate changes from baseline in OA pain in the target knee over time	• Change from baseline at Weeks CCI [redacted] in:
	  • WOMAC pain
	  • WOMAC pain walking on flat surface item

• To evaluate changes from baseline in physical function over time	• Change from baseline at Weeks CCI [redacted] in: • WOMAC function
• To evaluate structural changes in the total, medial and lateral TFCs in the target knee over time	• Change from baseline in cartilage thickness in the total, medial and lateral TFCs assessed by qMRI at Weeks CCI [redacted]

• To evaluate the proportion of patients with structural progression over time in the target knee using imaging techniques	• Proportion of participants demonstrating at Week CCI [redacted] structural progression defined as:
	  • change above the SDC of cartilage thickness by qMRI
	  • a loss of medial minJSW ≥ 0.70 mm from baseline by X-ray

Objective(s)	Endpoint(s)
• To evaluate changes in performance-based physical function assessment over time	• Change from baseline in physical function at Weeks CCI • 40-meter (4×10m) fast-paced walk test • 30-second chair stand test • 6-minute walking test
• To evaluate changes from baseline in total WOMAC score over time	• Change from baseline at Weeks CCI in: • WOMAC total score
• To explore change in disease activity over time	• Change from baseline at Weeks CCI in OA disease activity as assessed by Patient Global Assessment (PGA) • Change from baseline at Weeks CCI in OA disease activity as assessed by Patient Global Impression of Severity (PGIS) • OA disease activity at Weeks CCI as assessed by Patient Global Impression of Change (PGIC)
• To assess change in QoL using SF-12v2 over time	• Change from baseline at Weeks CCI in QoL using: • SF-12v2 physical component summary • SF-12v2 mental component summary • Total SF-12v2 score
• To explore change in CCI as measured by CCI	• CCI at Weeks CCI : • Change from baseline at Weeks CCI in the following assessments: • CCI • Change from baseline at Weeks CCI in the following assessments: • CCI
• To evaluate changes in structure over time using X-ray	• Change from baseline to Weeks CCI in: • fixed-location medial JSW measured on X-ray • medial minJSW measured on X-ray
• To explore the change from baseline CCI	• Change from baseline to CCI
• To explore responders using the WOMAC minimal clinically important difference (MCID) over time	• Proportion of participants who achieved WOMAC pain MCID CCI • Proportion of participants who achieved WOMAC function MCID CCI

Objective(s)	Endpoint(s)
• To explore responders using the OMERACT-OARSI responder criteria over time	• Proportion of OMERACT-OARSI responders at CCI [redacted]
• To evaluate CCI [redacted]	• Change from baseline CCI [redacted]

• To explore the pharmacodynamic effect on cartilage extracellular matrix metabolism over time	• Change over time in biomarker levels, including but not limited to:
	  • CCI [redacted]
	  • CCI [redacted]
	  • CCI [redacted]

• To evaluate LNA043 pharmacokinetics (PK)	• Serum concentrations of LNA043
• To evaluate endogenous ANGPTL3 levels	• Serum concentrations of ANGPTL3
• To explore CCI [redacted] physical activity and mobility by wrist actigraphy over time	• Change from baseline at Weeks CCI [redacted] in measures of physical activity and mobility parameters.
• To explore disease progression by means of TKR and Virtual Knee Replacement (VKR)	• Proportion of participants with total knee replacement (TKR) at Week CCI [redacted] and time to event • Proportion of participants at Weeks CCI [redacted] fulfilling the following criteria for VKR as defined by: WOMAC Pain ([0-100] scale) + WOMAC Function ([0-100] scale) ≥ 80 points for at least 2 consecutive visits with and without radiographic progression, defined as loss of medial minJSW ≥ 0.50 mm from baseline (Manno et al 2012)
• To perform exploratory DNA assessments relating to drug metabolism, cartilage repair, drug target pathway, or other genetic pathways on response (optional)	• Exploratory DNA assessments
• To explore biomechanical gait parameters by means of a Biomechanical Sensor Platform (BSP) in a subset of participants over time (optional, performed at selected sites only)	• Explore changes over time in gait parameters
• Explore CCI [redacted]	• CCI [redacted]

2.1 Primary estimands

The clinical question of interest is: What is the effect of each LNA043 regimen versus placebo on change from baseline in cartilage thickness in the central medial tibiofemoral compartment (cMTFC) of the target knee assessed by qMRI at Week 104 in participants with knee OA who are drug naive or receiving permitted concomitant therapy, had participants taken the assigned treatment for the entire core study duration and regardless of adherence to the allowed period of permitted concomitant therapy?

The justification for targeting this treatment effect is that we wish to estimate the effect of the study drug for the full duration when administered with or without the permitted concomitant therapy.

The primary estimand is described by the following attributes:

1. Population: defined through appropriate inclusion/exclusion criteria to reflect the targeted OA population. Further details about the population are provided in Section 5.
2. Primary variable: change from baseline to Week 104 in cartilage thickness of the cMTFC of the target knee.
3. Treatment of interest: the randomized treatment (LNA043 regimens or placebo) taken for the entire core study duration with or without the permitted concomitant therapy. Further details about the investigational treatment and control treatment are provided in Section 6.

Handling of remaining intercurrent events:

- Treatment discontinuations/disruptions for any reason: had participants taken the assigned treatment for the entire core study duration (hypothetical strategy)
- Unforeseen non-adherence in the allowed period of permitted concomitant therapies: ignore (treatment policy strategy)

The summary measure: difference in variable means between the treatments.

2.2 Secondary estimands

Pain and Function

The clinical questions of interest for secondary objectives pertaining to pain or function are:

- What is the effect of each LNA043 regimen versus placebo on change from baseline in OA pain at Week 104 in participants with knee OA who are drug naive or receiving permitted concomitant therapy, had participants taken the assigned treatment for the entire core study duration and adhered to the allowed period of permitted concomitant therapy?
- What is the effect of each LNA043 regimen versus placebo on change from baseline in function in the target knee at Week 104 in participants with knee OA who are drug naive or receiving permitted concomitant therapy, had participants taken the assigned treatment for the entire core study duration and adhered to the allowed period of permitted concomitant therapy?
- What is the effect of each LNA043 regimen versus placebo on change from baseline in performance-based physical function assessment in the target knee at Week 104 in participants with knee OA who are drug naive or receiving permitted concomitant therapy, had participants taken the assigned treatment for the entire core study duration and adhered to the allowed period of permitted concomitant therapy?

The justification for targeting this treatment effect is that we wish to estimate the effect of the study drug for the full duration when administered with the permitted concomitant therapy.

The estimand definition is described by the following attributes:

1. Population: defined through appropriate inclusion/exclusion criteria to reflect the targeted OA population. Further details about the population are provided in Section 5.

2. Variable: change from baseline to Week 104 in the variable of interest.
3. Treatment of interest: the randomized treatment (LNA043 regimens or placebo) taken for the entire core study duration with the permitted concomitant therapy. Further details about the investigational treatment and control treatment are provided in Section 6.

Handling of remaining intercurrent events:

- Treatment discontinuations/disruptions for any reason: had participants taken the assigned treatment for the entire core study duration (hypothetical strategy)
- Unforeseen non-adherence in the allowed period of permitted concomitant therapies: had participants adhered to the allowed period of permitted concomitant therapies (hypothetical strategy)

The summary measure: difference in variable means between the treatments.

Structure

The clinical questions of interest for secondary objectives pertaining to structure are:

- What is the effect of each LNA043 regimen versus placebo on change from baseline in the total, medial and lateral tibiofemoral compartments (TFCs) in the target knee at Week 104 in participants with knee OA who are drug naive or receiving permitted concomitant therapy, had participants taken the assigned treatment for the entire core study duration and regardless of adherence to the allowed period of permitted concomitant therapy?
- What is the effect of each LNA043 regimen versus placebo on the proportion of participants demonstrating structural progression in the target knee at Week 104 in participants with knee OA who are drug naive or receiving permitted concomitant therapy, had participants taken the assigned treatment for the entire core study duration and regardless of adherence to the allowed period of permitted concomitant therapy?

The justification for targeting this treatment effect is that we wish to estimate the effect of the study drug for the full duration when administered with or without adherence to the allowed period of permitted concomitant therapy.

The estimand definition for the secondary objective related to change from baseline is described by the following attributes:

1. Population: defined through appropriate inclusion/exclusion criteria to reflect the targeted OA population. Further details about the population are provided in Section 5.
2. Variable: change from baseline to Week 104 in the variable of interest.
3. Treatment of interest: the randomized treatment (LNA043 regimens or placebo) taken for the entire core study duration with or without adherence to the allowed period of permitted concomitant therapy. Further details about the investigational treatment and control treatment are provided in Section 6.

Handling of remaining intercurrent events:

- Treatment discontinuations/disruptions for any reason: had participants taken the assigned treatment for the entire core study duration (hypothetical strategy)
- Unforeseen non-adherence in the allowed period of permitted concomitant therapies: ignore (treatment policy strategy)

The summary measure: difference in variable means between the treatments.

The estimand definition for the secondary objective related to proportion is described by the following attributes:

1. Population: defined through appropriate inclusion/exclusion criteria to reflect the targeted OA population. Further details about the population are provided in Section 5.
2. Variable: proportion of participants demonstrating structural progression at Week 104 in the variable of interest.
3. Treatment of interest: the randomized treatment (LNA043 regimens or placebo) taken for the entire core study duration with or without adherence to the allowed period of permitted concomitant therapy. Further details about the investigational treatment and control treatment are provided in Section 6.

Handling of remaining intercurrent events:

- Treatment discontinuations/disruptions for any reason: had participants taken the assigned treatment for the entire core study duration (hypothetical strategy)
- Unforeseen non-adherence in the allowed period of permitted concomitant therapies: ignore (treatment policy strategy)

The summary measure: difference in proportions of participants demonstrating structural progression between the treatments.

3 Study design

CLNA043A12202 is a 2-period, multicenter, randomized, parallel-group, double-blind, placebo-controlled Phase IIb study consisting of a 2-year Core Period, followed by a 3-year Extension Period (with 2-year treatment and 1-year follow-up) aiming to assess the short and long term efficacy, safety and tolerability of multiple intra-articular regimens of LNA043 versus placebo. Optional pre-screening can be considered (see Section 8.1.1). Participants with radiographically determined K-L grades 2 or 3 and moderately to severely symptomatic knee OA in the target knee as indicated by a WOMAC pain score of 20-45 on a 0-50 scale prior to initiating study drug will be enrolled.

Following the signing of informed consent, participants will be assessed for eligibility during a screening period. The screening period should last up to 8 weeks.

On Week 0 (Randomization Visits) of the Core Period, eligible participants will be randomized to one of the five treatment groups at a 1:1:1:1:1 allocation. During the entire study, participants will receive [redacted] mL i.a. injections of either LNA043 [redacted] mg or [redacted] mg or placebo (Figure 3-1). Approximately 550 participants will be randomized.

During the Core Period, all participants will receive i.a. injections of LNA043 or placebo ([redacted]) every [redacted] for 2 years (Table 3-1). LNA043 treatment arms will receive active LNA043 [redacted] mg [redacted] every [redacted], [redacted] mg [redacted] every [redacted], [redacted] mg [redacted] every [redacted], or [redacted] mg [redacted] every [redacted] administered i.a. to the target knee. Participants randomized to placebo will receive i.a. injections of saline solution for injection [redacted] every [redacted] in the Core Period. At the end of the Core Period, participants will enter the Extension Period. During the Extension Period, all participants will receive one i.a. injection of LNA043

or placebo every CCI for 2 years (Table 3-1). Participants who received active LNA043 every CCI in the Core Period will receive one injection of the same dose of active LNA043 correspondingly in the Extension Period (every 6 CCI, respectively). Placebo injections will be used throughout the study in order to keep the same number of injections for all arms and ensure blinding, based on the assigned frequency of treatment. Participants in at least one of these four LNA043 arms may be discontinued from the Extension Period based on efficacy and safety results from the Week 104 primary endpoint database lock. Participants who received placebo during the Core Period will continue to receive placebo every CCI for the Extension Period. The last 1 year of the Extension Period will be a no-treatment follow-up for all arms.

Figure 3-1 Study Design

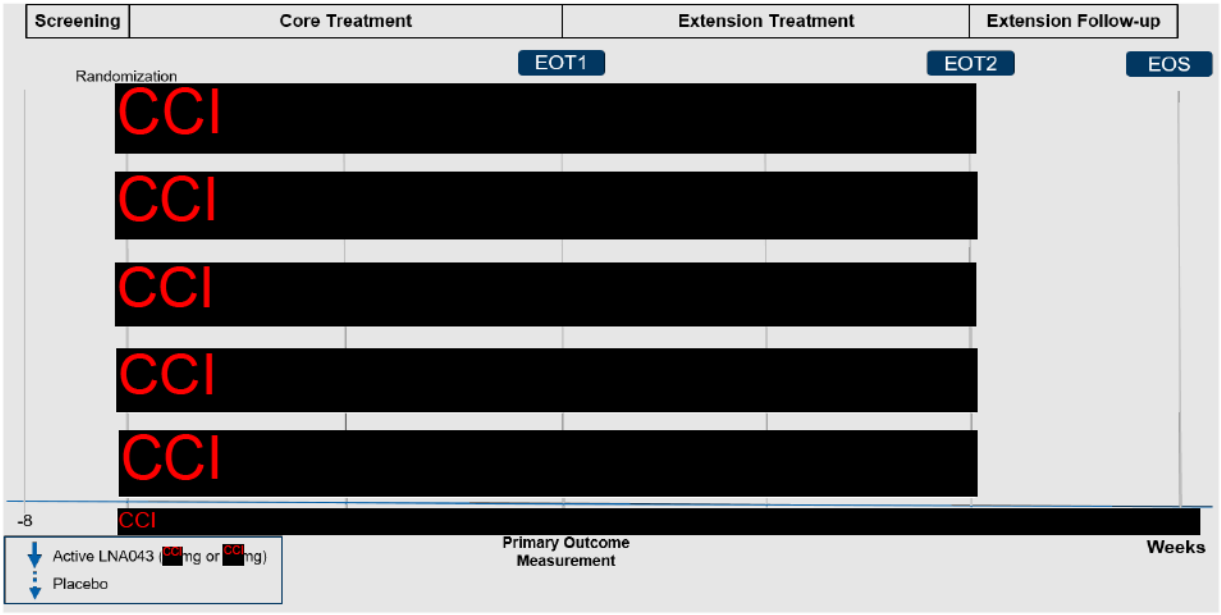


Table 3-1 Summary of study period and treatment

Screening	Core Period	Extension Period
8 weeks	104 weeks	104 weeks
	LNA043 CCI mg i.a. CCI every CCI	LNA043 CCI mg i.a. CCI every CCI
	LNA043 CCI mg i.a. CCI and CCI i.a. CCI every CCI	LNA043 CCI mg i.a. CCI every CCI
	LNA043 CCI mg i.a. CCI followed CCI (after first injection) by CCI i.a. CCI Cycle every CCI	LNA043 CCI mg i.a. CCI followed CCI by CCI i.a. CCI Cycle every CCI
	LNA043 CCI mg i.a. CCI every CCI	LNA043 CCI mg i.a. CCI every CCI
	Placebo i.a. CCI every CCI	Placebo i.a. CCI every CCI

The primary objective will be to assess the efficacy of each regimen of LNA043 compared to placebo at Week 104 as measured by the mean change from baseline in cartilage thickness of the cMTFC using qMRI of the target knee. An interim analysis will be conducted when CCI
Additional interim analyses may be conducted.

In the event a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that limits or prevents the conduct of on-site study visits, study treatment at home may be considered. Special effort should be made for the EOT/EOS visit. If it is not feasible to conduct the EOT/EOS visit on-site, virtual visits or visits to the participant´s home might be considered.

4 Rationale

4.1 Rationale for study design

The design of this study addresses the primary objective of cartilage regeneration and subsequent clinical benefit in participants with moderately to severely symptomatic (WOMAC Pain 20-45) knee OA (K-L 2-3) and takes into account (i) the clinical need for drugs in halting OA disease progression and controlling symptoms; (ii) clinical and preclinical data on LNA043; (iii) current practice with intra-articular injectable drugs; and (iv) the burden on participants with knee OA.

According to the latest FDA draft guidance "Osteoarthritis: Structural Endpoints for the Development of Drugs, Devices, and Biological products for treatment" (CDER 2018), the ability of structural changes to predict clinical benefit in terms of improvement in pain and function has not been established. For this reason, both structural progression and clinical benefit must be assessed when developing a drug for the treatment of OA. The current study design, which CCI
(Hochberg et al 2019, CCI), well-established PROs in knee OA (Collins et al 2011), and performance-based functional assessments (Dobson et al 2013) will ensure appropriate evaluation of LNA043 effect, from both a structural and a clinical standpoint. Knee joint survival will also be assessed by means of virtual knee replacement endpoint, a surrogate outcome for OA progression (Manno et al 2012), as well as TKR.

The parallel design for the entire study duration ensures (i) comparison of potential adverse events by dose/frequency of administration, as well as the ability to distinguish AEs from procedure-related AEs (intra-articular injections); and (ii) differentiation from a confounding placebo effect of i.a injections on pain. The trial will consist of a screening period of up to 8 weeks, a core treatment period of 104 weeks, an extension period composed of a 2-year maintenance treatment and a 1 year treatment-free period to allow for: (i) evaluation of both articular cartilage healing and consequential clinical improvement; (ii) better understanding of the kinetics of LNA043 induced cartilage growth and durability of the regenerated tissue following reduction and discontinuation of treatment; and (iii) assessment of the safety and tolerability of i.a. LNA043 (CCI mg and CCI mg) over a period of 4 years with an additional year of treatment-free follow-up.

The study has been designed as participant- and Investigator- blinded in order to reduce bias from both Investigators and participants, so that a difference between the treated and control groups can be interpreted as an effect of study treatment. In addition, in order to maintain the blind i.a. LNA043 or placebo injections will be administered to keep the same number of total injections (CCI every CCI in the Core Period and CCI every CCI for 2 years in the Extension Period) in all treatment groups (Figure 3-1).

4.2 Rationale for dose/regimen and duration of treatment

This study is aimed at defining the optimal dose regimen of i.a. LNA043 in moderately to severely symptomatic (WOMAC Pain 20-45) knee OA (K-L 2-3) participants. To this purpose, we will testCCI

. The rationale for these options is explained below.

CCI

CCI

CCI

This 4-year treatment duration (Core + Extension Period) is considered necessary, based on previous studies (Hochberg et al 2019), to provide enough time to demonstrate both persistent structure modification and clinical benefit as justified by the slow progression of knee OA.

In summary, CCI [redacted]

Based on these efforts, the optimal regimen(s) for the LNA043 Phase III clinical program will be established.

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

Since there are no approved disease-modifying drugs for knee OA, placebo (saline solution) intra-articular injections will be used as a control. Standard of care treatments and medications for knee OA pain are allowed throughout the study, as described in Section 6.2. To maintain the blinding, both the intra-articular injections of active LNA043 and placebo will be provided so that each arm of the study will include injections once CCI [redacted] for CCI [redacted] every [redacted] for 2 years during the Core Period (Figure 3-1), then once every CCI [redacted] for 2 years during the Extension Period. The placebo solution will be composed of saline for injection prepared by an unblinded pharmacist (who will not be involved in participant evaluation). A volume of [redacted] mL of LNA043 or placebo will be used for each intra-articular injection. The placebo will not contain a preservative as it is to be used for single-dose administration only and it is indistinguishable from LNA043, ensuring blinding of the Investigator performing the i.a. injection.

4.4 Purpose and timing of interim analyses/design adaptations

The primary efficacy analysis will be performed at Week 104 to assess efficacy and safety variables. The final analysis at Week 260 will be performed as a safety and efficacy follow-up assessment. CCI [redacted]

4.5 Risks and benefits

Based on preclinical data and available clinical data from the completed and ongoing studies, a cartilage anabolic effect resulting in regeneration of the articular cartilage is expected in knee OA participants. Based on the positive results from early phase studies, a disease modifying effect is anticipated, although to be confirmed in the knee OA K-L 2-3 population. The overall risk to knee OA participants in this study is expected to be low due to the safety profile observed in completed clinical trials. This risk will be minimized by adherence to the inclusion/exclusion criteria, close clinical monitoring, selection of Investigators with experience in i.a. injections,

and safety reviews performed at least once every 6 months by an independent Data Monitoring Committee (DMC).

The overall risk/benefit assessment of LNA043 is supportive of the conduct of this Phase IIb study in knee OA participants.

A more detailed description of potential risks related to the i.a. administration of LNA043, and related mitigation strategies are reported below.

Invasive, study-specific procedures include synovial fluid aspiration and i.a. injection. As with any invasive procedure (i.a. injection), a risk of inflammation/swelling, pain, infection, and/or bleeding exists; for i.a. injections these complications can occur both at the injection site and within the joint space. Recent reports found infection rates following i.a. injection of steroids between 1 in 3,000 and 1 in 50,000 (Lavelle et al 2007). However, few orthopedists and rheumatologists have seen 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 is considerably lower. Aseptic technique will be used in all phases of CCI [redacted] administration to further prevent the above-mentioned risks. Local reactions will be monitored clinically. Synovial fluid aspiration will be performed at the same time as the i.a. injection of LNA043, only if enough synovial fluid is present in the joint as judged by the Investigator, with no additional harm or discomfort for the participant.

CCI [redacted] Based on a comprehensive analysis of all safety data from both completed and ongoing clinical studies, there is no evidence to suggest that treatment with LNA043 increases the risk of hypersensitivity in humans. No drug-related serious adverse events (SAE) have been reported to date.

To mitigate the possible risk of hypersensitivity reactions in humans, participants with a history of hypersensitivity reactions to any of the study treatments or excipients will be excluded from participation in this study (Section 5.2), participants who experience any grade hypersensitivity reaction to study treatment will not be re-dosed, and the study will be paused and no further dosing will occur pending a full safety review if two (2) or more participants develop an acute allergic reaction of Grade 3 severity or greater, or one or more participants with life-threatening (Grade 4) or fatal acute allergic reaction according to the NCI-CTCAE/v5.0 Criteria within 24 hours following LNA043 administration (i.e., active drug), unless clearly caused by exposure to a known allergen (i.e., peanut allergy). Events of hypersensitivity reactions will also be reviewed by an independent DMC.

No participant developed ADA after a single i.a. injection of up to CCI [redacted] mg LNA043 nor upon four weekly i.a. injections of CCI [redacted] mg LNA043. The impact of neutralizing antibodies that may cross react with endogenous ANGPTL3 is not known, but the likely impact is considered relatively low. Humans with loss-of-function variants in both copies of the ANGPTL3 gene have low plasma LDL-C, low HDL-C, and low triglycerides, but no obvious adverse consequences, suggesting that absence of ANGPTL3 does not result in any serious effects. Development of anti-LNA043 antibodies as well as any potential reactions related to such antibodies will be monitored closely with the corresponding safety plan in place.

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

ANGPTL3 is expressed in human glomerular endothelial cells and could increase the permeability, resulting in proteinuria. The C-terminal of endogenous ANGPTL3 affects glomerular permeability by inducing F-actin rearrangement which is involved in podocyte detachment and apoptosis. Podocytes are an integral member of the filtration barrier in renal glomeruli. As LNA043 is a modified, recombinant version of the human angiopoietin-like protein 3 (ANGPTL3), comprising the major part of its C-terminal domain, there is a theoretical risk of proteinuria. For this reason, participants with nephrotic syndrome and or significant proteinuria ($\geq$ 3+ on dipstick or protein-creatinine ratio $\geq$ 1 g/g Cr) are excluded from this study.

While there is no indication of hepatotoxicity or renal toxicity from pre-clinical or clinical studies conducted to date, participants with clinically significant liver disease or liver injury, or participants with moderate to severe renal impairment (estimated glomerular filtration rate (GFR) < 50 mL/min/1.73 m^2 by the CKD-EPI formula) are excluded from this 5-year study due to the poor prognosis and life expectancy associated with these conditions.

More detailed information is available in the current IB.

There may be unknown risks of LNA043 which may be serious.

Risks of imaging procedures

A posteroanterior view X-ray of the target and contralateral knees are often performed during the routine evaluation of patients with knee pain, but not always. Consequently, in some participants they will be obtained only for research purposes. The total amount of radiation exposure per participant from these X-rays will be about 150 µSv in 5 years. For effective radiation doses under 3 mSv (300 mrem), the risk is "minimal". Yearly background radiation is around 3mSv (2.7 mSv based on UK guidance) which is more than 65 times higher than the 1st study year exposure (45 µSv) or 20 times higher than total study exposure (150 µSv in 5 years). Therefore, the radiation exposure in this study involves minimal risk and is necessary to ensure eligibility of participants and to monitor disease progression.

MRI is a non-invasive radiology technique that has no X-ray radiation exposure. No MRI contrast agent will be administered in this study. Thus, in principle, MRI scans can be repeated in the same participant as often as necessary. The MRI scanning equipment may cause a feeling of claustrophobia in susceptible persons. The presence of metal in the body may also be a safety hazard or affect MRI image quality.

4.6 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 as declared by local or regional authorities should be discussed among investigators and Novartis. All procedures

adapted to the situation must be submitted, if required as per local regulations, through a protocol amendment for approval by local or regional Health Authorities and Ethics Committees prior to implementation of mitigation procedures.

5 Study Population

The study population will be comprised of male and female participants 40 to 75 years old with predominantly unilateral medial radiographic K-L grade 2-3 knee osteoarthritis and moderate to severe pain in the target knee (WOMAC Pain of 20-45 out of 50 on no medication or after pain medication washout) in the target knee during the screening period. A total of approximately 550 participants will be randomized. Participant selection is to be established by applying all eligibility criteria at Screening Visits 1 and 2. A relevant record (e.g., checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from any entry criterion excludes a participant from randomization into the study.

Participants failing during the screening period may be eligible for rescreening as per instructions in Section 8.1.

Participants who are randomized and fail to start treatment, e.g., participants randomized in error, will be considered as mis-randomized.

Participants who have been randomized once cannot be screened or randomized again.

5.1 Inclusion criteria

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

1. Participant must be able to understand and communicate with the Investigator, comply with the requirements of the study, and must give a written, signed and dated informed consent before any study assessment is performed.
2. Males and females between 40 and 75 years of age.
3. Body mass index (BMI) < 40 kg/m^2 at Screening Visit 1.
4. Diagnosis of primary tibiofemoral knee OA in the target knee by standard American College of Rheumatology (ACR) clinical and radiographic criteria (Section 16.3) at Screening Visits.
5. Radiographic disease K-L grade 2 or 3 knee OA with a predominantly medial TFC involvement defined as medial Joint Space Narrowing (medJSN) 1-2 and medJSN > lateral Joint Space Narrowing (latJSN) in the target knee at Screening Visit 1.
6. Participants with WOMAC Pain of 20-45 (out of 50) for the target knee at both (double baseline) assessments during screening period after discontinuation of analgesics, anti-inflammatories and low potency opioids within 48 hours or an equivalent of $5 \times T_{1/2}$ wash out period (whichever is longer).
7. Symptomatic OA with pain in the target knee for at least 6 months prior to Screening Visit 1.
8. Primary source of pain throughout body is due to OA in the target knee: Widespread Pain Index (WPI) score of ≤6 and a Symptom Severity score (SS score) of <7 at Screening Visit 2.

9. Participants with depression or anxiety must be clinically stable for 12 weeks prior to screening, and, if on treatment for depression or anxiety, be on 12 weeks of stable therapy.

5.2 Exclusion criteria

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

1. Radiographic knee OA K-L = 4 on the non-target knee at Screening Visit 1.
2. WOMAC Pain > 15 (out of 50) in the non-target knee at Screening Visit 2.
3. Severe malalignment (>7.5° varus or valgus) in the anatomical axis of the target knee, measured using X-ray at Screening Visit 1.
4. Clinical signs of moderate-severe inflammation (i.e., redness, warmth, effusion) of the target knee or clinically requiring aspiration in the target knee within 12 weeks prior to Screening Visit 1 or during the screening period.
5. Arthroscopy of the target knee within the 6 months prior to Screening Visit 1 or planned during the study.
6. Previous surgical treatment of the target knee using mosaicplasty, microfracture, meniscectomy >50% or osteotomy; partial or complete joint replacement for either knee; planned knee surgery for either knee during the study.
7. Unstable target knee joint (including, but not limited to, posttraumatic or congenital laxity) or insufficiently reconstructed ligaments based on medical history and/or physical examination by the Investigator.
8. Other pathologies affecting the knee, including subchondral insufficiency fractures, bone fracture (acute or subacute in less than 6 months prior to screening) or bone bruise, osteonecrosis, malignant bone marrow infiltration, solid tumors, and/or patellofemoral dysplasia based on clinical assessment, or imaging.
9. Symptomatic (moderate-severe pain on most days) hip OA on either hip at Screening Visit 1 or hip prosthesis recently implanted (within 1 year prior to Screening Visit 1) or foreseen within the study period (either hip).
10. Other pain conditions that could confound assessments of the pain associated with knee OA, as judged by the Investigator:
    - Diagnosis of a systemic disease that may affect joints
    - Neuropathic disorders
    - Paget's disease affecting the knees
    - Regional pain caused by lumbar compression with radiculopathy
    - Any other pain condition that could confound the efficacy assessments
11. Inability to undergo MRI (e.g., claustrophobia, body size, leg not fitting in the coil) or contraindications to MRI (e.g., non MRI-compatible metallic implants, metallic foreign bodies, pacemaker, defibrillator).
12. History of coagulopathy (hemophilia, von Willebrand disease, Factor X deficiency, etc.) or medical condition requiring anticoagulation which would preclude knee injection. Note: Anticoagulant management is allowed as per local practice, however, patients taking coumarins (e.g., warfarin) must have INR <3 before the study drug injection. Low-dose aspirin is allowed. Suspension of novel oral anticoagulants (NOACs; e.g., apixaban,

dabigatran, rivaroxaban, and edoxaban) before i.a. injection should be assessed by the treating physician, based on local prescribing information.

13. Known autoimmune disease with inflammatory arthritides (including but not limited to rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus), crystal-induced arthritides (gout, pseudogout associated arthritis), active acute or chronic infection or past infection of the knee joint, reactive arthritis, systemic cartilage disorders, or a known systemic connective tissue disease.
14. Metabolic or genetic abnormalities associated with arthropathy.
15. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed), regardless of whether there is evidence of local recurrence or metastases.
16. History of hypersensitivity to any of the study treatments or excipients or to drugs of similar classes.
17. Drug or alcohol abuse use within the 12 months prior to the study drug administration, or any diagnosed psychiatric condition that includes, but is not limited to, a history of mania, bipolar disorder, psychotic disorder, schizophrenia, or schizoaffective disorder.
18. Any known active infections, including infection of skin at the injection site, or knee infections or infections that may compromise the immune system such as HIV or chronic hepatitis B or C infection.
19. Participants with wounds at the investigational product administration site.
20. History or current diagnosis of electrocardiogram (ECG) abnormalities: concomitant clinically significant cardiac arrhythmias, e.g. sustained ventricular tachycardia, and clinically significant second or third degree atrioventricular block without a pacemaker, history of familial long QT syndrome or known family history of Torsade de Pointes.
21. History or current clinically significant liver disease or liver injury as indicated by abnormal liver function tests such as SGOT (AST), SGPT (ALT), alkaline phosphatase, or serum bilirubin. The Investigator should be guided by the following criteria:
    - Any single parameter may not exceed 2× upper limit of normal (ULN). A single parameter elevated up to and including 2× ULN should be re-checked once more as soon as possible, and in all cases, at least prior to enrollment/randomization, to rule out lab error
22. Nephrotic syndrome and/or significant proteinuria (≥ 3+ at urinalysis test or protein-creatinine ratio ≥ 1 g/g Cr).
23. Moderate to severe renal impairment (estimated GFR < 50 mL/min/1.73 m^2 by the CKD-EPI formula).
24. Hemoglobin < 8.5 g/dL (85 g/L) or platelet count < 100,000/μL.
25. Use of electrotherapy, traditional Chinese medicine (including but not limited to acupuncture, massage, herbs) and/or chiropractic treatments for knee OA pain within 4 weeks prior to Screening Visit 1 and during Screening period.
26. Use of the following medications is prohibited:

- Within 26 weeks prior to double baseline assessment of WOMAC Pain, local i.a. treatment into the target knee, including but not restricted to long-acting corticosteroids (e.g., *Zilretta*®), platelet-rich plasma (PRP) and stem cell therapies
- Within 12 weeks prior to double baseline assessment of WOMAC Pain, high potency opioids (e.g., methadone, hydromorphone, morphine, oxycodone), corticosteroid use by any route (except topical, inhaled and i.a. injection in other non-knee joints), i.a viscosupplementation (e.g., hyaluronans) in the target knee, centrally acting analgesics (e.g., duloxetine) unless on a stable dose for at least 12 weeks, anticonvulsants unless used for seizure and on a stable dose for at least 12 weeks
- Within 48 hours or $5\times T_{1/2}$ (whichever is longer) prior to each of the WOMAC Pain assessments during screening period, NSAIDs by any route, aspirin (greater than 100 mg/day), paracetamol/acetaminophen, low potency opioids (e.g., tramadol), COX-2 inhibitors
- Within 4 weeks prior to each of the WOMAC Pain assessments during screening period, oral glucosamine, chondroitin sulfate, or any nutraceutical with potential activity on the articular cartilage, unless stable for at least 4 weeks

27. Women who have a positive pregnancy result prior to initiation of study drug, or are pregnant or lactating.
28. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of investigational drug and for 15 days after stopping medication. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant
    - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS)

    In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

    Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms). Women are considered not of child bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed

by follow up hormone level assessment is she considered not of child-bearing potential. If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

29. Any surgical, medical, psychiatric or additional physical condition that the Investigator feels may potentially jeopardize the participant during the study or could interfere with the study objectives, conduct or evaluation.
30. Any significant chronic condition that has not been well-controlled for a minimum of 3 months e.g. - Uncontrolled hypertension, diabetes or chronic heart failure (patients with New York Heart Association status of class III or IV), or poor functional status unable to perform self-care.
31. Vulnerable participants, e.g., participants kept in detention, soldiers, and employees of the sponsor or a clinical research organization involved in this study.
32. Use of other investigational drugs within 5 half-lives of enrollment, or until the expected pharmacodynamic effect has returned to baseline, whichever is longer.
33. Previous participation in the treatment arm of another LNA043 trial.

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Novartis will supply open-label LNA043 CCI mg CCI , which will be used as the investigational drug. CCI . Saline solution, provided locally by the site, will be used as placebo and for dilution of LNA043 solution. CCI saline used for study treatment preparation should be for the study use only and dispensation of CCI saline should be recorded in Pharmacy Drug Accountability Log.

The volume of the i.a. injection will be fixed at CCI mL for both LNA043 and placebo (saline) and prepared by the unblinded pharmacist (or delegated unblinded and qualified site staff) to reach the final dose of LNA043 or placebo to be delivered.

Prepared syringes with the IRT assigned study treatment (LNA043 CCI mg, CCI mg or placebo) will be provided to blinded staff by the unblinded pharmacist/delegate for i.a. injection at each visit. A document with the participant number and details on the preparation (without disclosing any unblinding information) e.g., date/time/condition of the medication will document the transfer.

Details on the requirements for storage and management of study treatment, and instructions to be followed for prescribing/dispensing by unblinded pharmacists are outlined in the Pharmacy Manual. Details on the requirements for i.a. injection of study treatment by blinded Investigator are outlined in the Directions for Use of Study Treatment.

Table 6-1 Investigational and control drug

Investigational/Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
LNA043 CCI mg	CCI	Intra-articular use	Open label supply; CCI	Novartis Pharma AG
Placebo	Saline solution	Intra-articular use	Not supplied by Sponsor	

6.1.2 Additional study treatments

No other treatment beyond investigational drug is included in this trial.

6.1.3 Treatment arms/group

In the Core Period, participants will be assigned to one of the following 5 treatment arms/groups in a ratio of 1:1:1:1:1:

- LNA043 CCI mg CCI , Cycle every CCI
- LNA043 CCI mg CCI and CCI , Cycle every CCI
- LNA043 CCI mg CCI followed CCI later (after first injection) by CCI , Cycle every CCI
- LNA043 CCI mg CCI , Cycle every CCI
- Placebo CCI , Cycle every 6 CCI

During the first two years of the Extension Period, participants assigned to either of LNA043 CCI mg or CCI mg every CCI cycle arms in Core Period will transition to a single injection every CCI of the same dose of LNA043 as in Core Period). Participants assigned to LNA043 CCI mg CCI every CCI cycle arm in Core Period will receive LNA043 CCI mg every CCI and CCI every other CCI . Participants who received placebo during the Core Period will continue to receive placebo every CCI for the Extension Period. One or more LNA043 arms may be discontinued from the Extension Period based on efficacy and safety results from the Week 104 primary endpoint database lock, and participants in the discontinued arm(s) will be followed-up for at least 6 months. The last 1 year of the Extension Period will be a treatment-free follow-up.

In each cycle in the Core Period, intervals of consecutive study treatment injections should be CCI . After completion of the first cycle (Week CCI to Week CCI), the date of first study treatment in each cycle should be calculated based on the Week 0 (randomization visit) date, and it can be CCI weeks from the calculated date; e.g. Week 26 date should be determined as 26 weeks after the Week 0 visit date, and study treatment at Week 26 should be between 26 and 30 weeks after the Week 0 date. In the Extension Period (CCI cycles) the date of the study treatment should also be calculated based on the Week 0 (randomization visit) date, and it can be CCI weeks from the calculated date.

6.1.4 Treatment duration

The planned duration of the Core Period is 2 years followed by the Extension Period of 3 years (2-year treatment and 1-year follow-up), for a total of 5 years. Participants may be discontinued

from treatment earlier due to unacceptable toxicity, disease progression and/or at the discretion of the Investigator or the participant.

6.2 Other treatment(s)

No additional treatment beyond investigational drug is provided in this trial.

6.2.1 Concomitant therapy

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

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

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Participants undergoing physical or occupational therapy (e.g., diet for weight loss, insole wedges) and/or taking NSAIDs, COX-2 inhibitors, low potency opioids or paracetamol/acetaminophen can continue to do so in the study as long as they are on a stable regimen in the opinion of the Investigator for at least 4 weeks prior to screening. Participants can continue taking these medications during the trial but will need to temporarily withdraw prior to WOMAC assessments, as described in Section 6.2.2. Investigators are encouraged to minimize changes to concomitant therapies including physical and occupational therapies during the Core Period.

CCI [redacted] (see Section 6.2.2 for Prohibited medication).

- Caution should be exercised when using oral NSAIDs including COX-2 inhibitors with regards to their potential gastrointestinal, liver and cardio-renal toxicity; therefore, when choosing an agent and dose, individual participant risk factors (diabetes, hypertension, cardiovascular disease, gastrointestinal bleeding, renal impairment, etc.) including age should be considered. It is recommended to prescribe oral NSAIDs/COX-2 inhibitors at the lowest effective dose for the shortest possible period with additional protective medication, such as proton pump inhibitors as per physician's judgement
- Regular monitoring for hepatotoxicity is required for participants who receive acetaminophen on a regular basis, particularly at the recommended maximum dosage of 4 g daily in divided doses
- Pain at other joints should be treated carefully, with regard to the potential impact of the assessment of pain in the target knee. If needed, 1 injection per year of corticosteroid is allowed in other knee and a non-knee joint at least 12 weeks prior to the 52-week and 104-week assessments

It is advised that Investigators consider other analgesics/analgesic formulations (e.g., topical NSAIDs) than oral NSAIDs in a person with osteoarthritis on low-dose aspirin or anticoagulants like coumarins or heparin. Bleeding diathesis monitoring should be conducted before each LNA043 or placebo injection, with INR <3 qualifying for the study drug administration to participants on coumarins (e.g., warfarin). Suspension of NOACs before i.a. injection should be assessed by the treating physician, based on local prescribing information.

6.2.2 Prohibited medication

Use of the treatments displayed in the table below are not allowed after screening, as indicated.

Table 6-2 Prohibited medications during Core Period

Medication	Prohibited period	Action to be taken
Local i.a. treatment into the target knee, including but not restricted to long-acting corticosteroids (e.g., *Zilretta*®), PRP and stem cell therapies	26 weeks prior to the first WOMAC Pain assessment during screening period until Week 104	Discontinue study treatment Record in CRF
Any therapy that may be authorized during the conduct of this study as a disease modifying treatment in OA	26 weeks prior to the first WOMAC Pain assessment during screening period until Week 104	Discontinue study treatment Record in CRF
Local i.a. treatment with hyaluronans in the target knee	12 weeks prior to the first WOMAC Pain assessment during screening period until Week 104	Record in CRF
Use of high potency opioids (e.g., methadone, hydromorphone, morphine, oxycodone)	12 weeks prior to the first WOMAC Pain assessment during screening period until Week 104	Record in CRF
Corticosteroid use by any route (except topical, inhaled and i.a. injection in other non-knee joints)[1]	12 weeks prior to the first WOMAC Pain assessment during screening period until Week 104	Record in CRF
Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin (greater than 100 mg/day); low potency opioids (e.g., tramadol); and COX-2 inhibitors by any route	48 hours or 5×$T_{1/2}$ (whichever is longer) prior to each WOMAC Pain assessment	Record in CRF
Paracetamol / Acetaminophen	48 hours prior to each WOMAC Pain assessment	Record in CRF
Oral glucosamine, chondroitin sulfate, or any nutraceutical with potential activity on cartilage repair unless stable for at least 4 weeks before Screening Visit 1	4 weeks prior to the first WOMAC Pain assessment during screening period until Week 104	Record in CRF
Centrally acting analgesics (e.g., duloxetine) unless on a stable dose for at least 12 weeks before Screening Visit 1	12 weeks prior to the first WOMAC Pain assessment during screening period until Week 104	Record in CRF
Anticonvulsants (e.g., gabapentin, pregabalin) unless used for seizure and on a stable dose for at least 12 weeks before Screening Visit 1	12 weeks prior to the first WOMAC Pain assessment during screening period until Week 104	Record in CRF
Electrotherapy, Traditional Chinese Medicine (including but	4 weeks prior to each of the two WOMAC Pain assessments	Record in CRF

not limited to acupuncture, massage, herbs) and/or chiropractic treatments for knee OA pain	during screening period, Weeks CCI [redacted]	
Any other therapy/intervention that could have an impact on knee OA	26 weeks prior to the first WOMAC Pain assessment during screening period until Week 104	Record in CRF
1 One injection per year in a non-knee joint is allowed for the treatment of non-knee joint pain; and one injection per year in the other knee is allowed for the treatment of joint pain until 12 weeks before Weeks CCI [redacted]		

Table 6-3 Prohibited medications during Extension Period

Medication	Prohibited period	Action to be taken
Local i.a. treatment into the target knee, including but not restricted to long acting steroids (e.g., *Zilretta*®), PRP and stem cell therapies	Until Week 260 visit	Discontinue study treatment Record in CRF
Any therapy that may be authorized during the conduct of this study as a disease modifying treatment in OA	Until Week 260 visit	Discontinue study treatment Record in CRF
Local i.a. treatment with hyaluronans in the target knee	12 weeks prior to each WOMAC Pain assessment	Record in CRF
Use of high potency opioids (e.g., methadone, hydromorphone, morphine, oxycodone)	Until Week 260 visit	Record in CRF
Corticosteroid use by any route (except topical, inhaled and i.a. injection in other non-knee joints)[1]	Until Week 260 visit	Record in CRF
Local i.a. treatment with corticosteroids in either knee[2]	12 weeks prior to each WOMAC Pain assessment	Record in CRF
Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin (greater than 100 mg/day); low potency opioids (e.g., tramadol); and COX-2 inhibitors by any route	48 hours or 5×$T_{1/2}$ (whichever is longer) prior to each WOMAC Pain assessment	Record in CRF
Paracetamol / Acetaminophen	48 hours prior to each WOMAC Pain assessment	Record in CRF
Oral glucosamine, chondroitin sulfate, or any nutraceutical with potential activity on cartilage repair unless on a stable dose during Core Period	Until Week 260 visit	Record in CRF
Centrally acting analgesics (e.g., duloxetine) unless on a stable dose during Core Period	Until Week 260 visit	Record in CRF
Anticonvulsants (e.g., gabapentin, pregabalin) unless used for seizure and on a stable dose during Core Period	Until Week 260 visit	Record in CRF
Electrotherapy, Traditional Chinese Medicine (including but not limited to acupuncture, massage, herbs) and/or	4 weeks prior to each WOMAC Pain assessment	Record in CRF

chiropractic treatments for knee OA pain		
Any other therapy/intervention that could have an impact on knee OA	Until Week 260 visit	Record in CRF
1 One injection per year in a non-knee joint is allowed for the treatment of non-knee joint pain. 2 One injection per year in either knee is allowed as rescue medication for otherwise intractable pain until 12 weeks before Weeks CCI [redacted]		

6.2.3 Rescue medication

For all participants experiencing pain or effusion to the target knee during the trial and requiring analgesic and/or anti-inflammatory medication, the use of topical NSAIDs (e.g. diclofenac topical)/capsaicin and/or paracetamol/acetaminophen is the recommended/preferred treatment of choice. In case these are not effective or offer insufficient pain relief, then substitution or addition respectively of NSAIDs/COX-2 inhibitors is allowed, as per the recommended dose and treatment duration defined by local guidelines. It is recommended to prescribe oral NSAIDs/COX-2 inhibitors at the lowest effective dose for the shortest possible period (Refer to Section 6.2.1.1).

During the Core Period, use of i.a. corticosteroids injections is not permitted as rescue medication for the treatment of target knee effusion and/or pain, while one i.a. injection of corticosteroids per year is allowed in the non-target knee, up until 12 weeks prior to the collection of WOMAC Pain at Weeks CCI [redacted]. During the Extension Period, one i.a. injection per year is allowed as a rescue medication when either knee effusion and/or pain cannot be treated appropriately with paracetamol/acetaminophen and NSAIDs/COX-2 inhibitors up until 12 weeks prior to the collection of WOMAC Pain at Weeks CCI [redacted]

During the whole study, one i.a. injection of corticosteroids per year is allowed in non-knee joints for otherwise intractable pain.

In the event of a hypersensitivity reaction, the treatment will be determined by the treating physician on a case-by-case basis, according to local protocols, and depending on the severity, using symptomatic treatment, antihistamines, NSAIDs, acetaminophen, intravenous fluids, corticosteroids, or adrenaline.

If the participant requires regular narcotic analgesia to control his/her arthritis pain, he/she should not be considered for the trial.

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

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a participant number (Participant No.) that is assigned when the participant is first enrolled for screening and is retained as the primary identifier for the participant throughout his/her entire participation in the trial. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative

site) with a sequential participant number suffixed to it, so that each participant is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available. A new Participant No. will be assigned at the subsequent enrolment if the Participant is re-screened.

6.3.2 Treatment assignment, randomization

At Week 0, all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. At Week 0, the site personnel (blinded or unblinded) will contact the IRT for randomization after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify (a) unique medication kit number(s) of study treatment to be dispensed to the participant for LNA043 treatment arms. For the participant randomized to placebo arm, a medication number would not be specified and no study medication will be dispensed in IRT.

Only the unblinded pharmacist will receive the treatment arm of randomized participant and the assigned kit number(s) by IRT. The unblinded pharmacist will prepare a syringe with study treatment (LNA043 CCI mg, CCI mg, or placebo) and deliver it to the blinded investigational site staff for administration to the participant. The unblinded pharmacist must not disclose treatment arm or assigned kit number(s) to any blinded staff.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and Investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis using a validated system that automates the random assignment of kit number(s) of the study treatment.

There will be no stratification at randomization.

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

6.4 Treatment blinding

Participants, blinded investigational site staff, persons performing the assessments, and select blinded sponsor team will remain blinded to the identity of the treatment from the time of randomization until final database lock, using the following methods: (1) randomization data are kept strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study with the following exceptions: randomization office (2) only unblinded site pharmacists and unblinded CRAs can access to the study medications, and the masking of the treatments prepared by unblinded site pharmacists will be ensured.

Unblinding of designated sponsor staff will also occur at the time of the interim analyses (see Section 12.7). Blinded core sponsor study team will remain blinded until at least primary efficacy (Week 104) database lock. Blinded investigational site staff, participants and blinded CRAs will remain blinded even after the interim analysis, until final database lock.

Once pharmacists and CRAs are assigned as unblinded site pharmacist and unblinded CRAs in this study, they should not be assigned as blinded site staff or blinded CRA.

Open label supply (LNA043 [redacted] mg [redacted]) will be provided to sites.

The randomization codes associated with participants from whom PK samples are taken will be disclosed to PK analysts who will keep PK results confidential until data base lock.

Unblinding may occur in the case of participant emergencies and at the conclusion of the study.

Unblinding of a participant for safety reason will result in the participant discontinuation from the study. See Section 6.6.3 for details.

6.5 Dose escalation and dose modification

Investigational study treatment dose adjustments (including partial dosing) are not permitted.

6.5.1 Definitions of dose limiting toxicities (DLTs)

Not applicable.

6.5.2 Dose modifications

No modifications to the dose are permitted during this study.

Injections to the target knee should not be considered when overlying skin infections, wounds or inflammatory diseases such as psoriasis are present, if the knee is acutely inflamed (flare), the participant has an INR >3 or significant thrombocytopenia (platelet count <75,000/mm^3), or in any other medical-related issue when the safety of the participants can be jeopardized by the injection, according to the Investigator's judgement.

In such cases, and in any other case when the participant can not receive the first i.a. injection of each cycle as planned, the start of the cycle can be delayed by a maximum of 4 weeks. Intervals between injections of the same cycle should be maintained at [redacted] week. Even if any of the i.a. injections are rescheduled in the previous cycle, the date of first visit in each cycle should be calculated based on Week 0 (for example, i.a. injection at Week [redacted] was delayed by 1 week, the scheduled date of Week [redacted] should be unaffected and [redacted] weeks after Week 0.

In any case, for interruptions of the dosing scheme due to AEs or for any other reasons, consultation and agreement with Novartis will be necessary to decide whether the participant can continue or needs to discontinue the study treatment.

See Section 9.1.1 for criteria for discontinuation of study medication.

6.5.3 Follow-up for toxicities

Participants whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical experts such as an ophthalmologist, endocrinologist, dermatologist, nephrologist, etc., should be consulted as deemed necessary.

All participants must be followed up for adverse events and serious adverse events until EOS (Week 260), or until the participant discontinues study participation.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

LNA043 serum concentrations (measures of treatment exposure) will be determined in all participants treated with LNA043.

Compliance to the treatment regimen is ensured by administration of LNA043 i.a. injections by the Investigator. Information on the study treatment administration or any deviation from the dose regimen must be recorded in the Case Report Form (CRF).

The unblinded pharmacist will prepare the syringe for i.a. injection of LNA043 (at the assigned dose) or placebo (saline solution), dispense an undistinguishable study medication to the blinded investigational site staff and record all details (including the kit number/s if applicable) in Pharmacy Drug Accountability Log. The blinded investigational site staff will document the dispensation (i.a. injection) to the participants in the participant Drug Accountability Log.

6.6.2 Recommended treatment of adverse events

Treatment of AEs should be in line with the investigational site procedures. To prevent post-injection flares, where possible, participants should refrain from physical activity for 48 hours post-dose, elevate the leg, and apply ice on the knee after the injection.

No case of systemic hypersensitivity reactions have been observed with LNA043 to date from past clinical studies, CCI [redacted] In case of any sign of acute reaction in this study, the participant will be managed with treatment as determined by the treating physician on a case-by-case basis, according to local protocols, and depending on the severity, using symptomatic treatment, antihistamines, NSAIDs, acetaminophen, intravenous fluids, corticosteroids, or adrenaline. Participants who experience hypersensitivity reaction of any grade considered to be caused by study drug must not be re-dosed.

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

6.6.3 Emergency breaking of assigned treatment code

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

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

- Protocol number
- Participant number

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

Any participant whose emergency code was broken due to safety reasons must discontinue the study treatment; however, where possible, the participant should return for the assessments indicated in the Assessment Schedule.

6.7 Preparation and dispensation

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

Please refer to the Pharmacy Manual for information on drug preparation prior to administration.

LNA043 CCI mg CCI will be supplied in a kit labeled with a unique kit number. Each kit will contain CCI labeled with the same kit number. The placebo will be saline, provided by the site.

Only participants on any of the LNA043 treatment arms will obtain study medications kit and no kits will be assigned for participants on placebo arm. The unblinded pharmacist will obtain the kit CCI from the IRT for each participant at each visit for study treatment: CCI for LNA043 CCI mg.CCI for LNA043 CCI mg, or CCI for placebo. The kit box containing the study medication CCI has a 2-part label (base plus tear-off label). Immediately before starting to prepare the syringe with the LNA043, the unblinded pharmacist will detach the outer part of the label from the packaging and affix it to the source document.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

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

The Investigator must ensure the maintenance of an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by unblinded monitors.

As per Section 4.6, 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, study treatment at home may be considered.

In the event the Investigator has decided that an on-site visit by the participant is not appropriate or possible, the study treatment may be stopped. In this case, regular phone calls or virtual contacts (possibly every 4 weeks) will occur between the site and the participant for instructional purposes, safety monitoring, investigation of any adverse events, ensuring participants continue study self-assessments as appropriate, and discussing of the participant's health status until the participants can resume visits at the study site.

At the conclusion of the study, and as appropriate during the study, the Investigator will return all unused study treatment, packaging, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the Investigator folder at each site.

7 Informed consent procedures

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

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

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

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

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

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

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

The study includes an optional study specific pre-screening consent for pre-screening assessments.

Eligible trial participants approaching their Week CCI visit, CCI Week CCI visit, will be eligible to participate in the CCI Participants must indicate their consent to participate by signature in the main ICF.

Declining to participate in these optional assessments (Pre-screening, DNA, CCI) will in no way affect the participant's ability to participate or remain in the main research study.

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

Participants might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience.

8 Visit schedule and assessments

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

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. X-rays of both knees, MRIs of target knee and/or any other assessments at the site visit may be conducted on a different day. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who prematurely discontinue the study for any reason during Core Treatment period or Extension Treatment period should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the End of Treatment visit (EOT1 or EOT2) will be performed. Participants who prematurely discontinue study treatment for any reason during the Core Treatment period or the Extension Treatment period, and wish to continue in the study, are not required to be scheduled for a visit as soon as possible and can continue per assessment schedule. The End of Study (EOS) visit will be performed at least 6 months after the last study treatment administration unless the participant wishes to continue in the study after discontinuation of study treatment. If the participant decides to discontinue the study at a later stage, the safety follow-up (EOS) visit should be conducted at least 6 months after the last injection of study treatment, unless assessments at the discontinuation visit were performed at least 6 months after the last injection of study treatment. At this final visit, all dispensed and administered study medications should be reconciled and the adverse event and concomitant medications should be recorded on the CRF.

Table 8-1 Assessment Schedule

Period	Screening		Core Period																										
Visit Name	Screening Visit 1 (SV1)	Screening Visit 2 (SV2)	0	CCI																									104/EOT1
Weeks	-8 to -1*		0																										104
In-office visit	X	X	X	CCI																									X
Telephone visit[1]																													
Informed consent[2]	X																												
Pharmacogenetic Informed Consent (Optional)	X																												
Gait analysis informed consent (optional, at selected sites only)	X																												
Demography / Medical history	X																												
Inclusion / Exclusion criteria	X	X	X																										
Vital Signs[3]	X	X	X	CCI																									X
Body Height	X																												
Body Weight	X		X	CCI																									X
Physical Examination	S																												S

Period	Screening		Core Period		
Visit Name	**Screening Visit 1 (SV1)**	**Screening Visit 2 (SV2)**	**0**	CCI	**104/EOT1**
Weeks	**-8 to -1***		**0**		**104**
Physical examination (symptom oriented)		S	S		
Physical examination (target knee)	X		X		X
Temporary discontinuation of pain medications[4]	Before WOMAC Pain assessment performed at home	X			X
WOMAC[5]	Performed at home after temporary discontinuation of pain medication	X			X
Widespread Pain Index (WPI) score		X			

Period	Screening		Core Period																								
Visit Name	Screening Visit 1 (SV1)	Screening Visit 2 (SV2)	0	CCI																							104/EOT1
Weeks	-8 to -1*		0																								104
Symptom Severity (SS) score		X																									
SF-12 Standard v2		X		CCI																							
Trial Feedback Questionnaire			X																								X
Patient Global Assessment (PGA)		X		CCI																							
Patient Global Impression of Severity (PGIS)[6]			X																								
Patient Global Impression of Change (PGIC)[6]																											
Performance based tests (30 second chair stand test, 4×10m fast-paced walk test, 6 minutes walking distance test)			X																								

Period	**Screening**		**Core Period**		
Visit Name	**Screening Visit 1 (SV1)**	**Screening Visit 2 (SV2)**	**0**	[redacted]	**104/EOT1**
Weeks	**-8 to -1***		**0**	[redacted]	**104**
Electrocardiogram (ECG)[7]	X			[redacted]	X
Hematology	X		X	[redacted]	X
Clinical Chemistry	X		X	[redacted]	X
hsCRP	X		X	[redacted]	X
Urinalysis (Macroscopic panel. Microscopic panel only if macroscopic is abnormal)	X		X	[redacted]	X
Coagulation test[8]	X		[redacted]		
Hepatitis and HIV Screen[9]	X				
Fasting lipid panel	X		X	[redacted]	X
Pregnancy Test (serum)[10]	S				S
Pregnancy test (urine)[11]			[redacted]		
Knee X-ray[12]	X			[redacted]	X
MRI of target knee[13]		X		[redacted]	X
PK blood collection[14]			[redacted]		

Period	Screening		Core Period																										
Visit Name	**Screening Visit 1 (SV1)**	**Screening Visit 2 (SV2)**	**0**	CCI																									**104/EOT1**
Weeks	**-8 to -1***		**0**																										**104**
ANGPTL3 blood collection[15]			CCI																										
Serum, urine and synovial fluid biomarkers[16]																													
Anti-drug antibody to LNA043[17]			X	CCI																									
Exploratory DNA Sampling (optional)			X																										
Actigraphy[18]	CCI																												
Gait assessment (optional, at selected sites only)[19]			X	CCI																									
Randomization			X																										
Study drug administration [20]			CCI																										
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Period	Screening		Core Period																								
Visit Name	Screening Visit 1 (SV1)	Screening Visit 2 (SV2)	0	CCI																							104/EOT1
Weeks	-8 to -1*		0																								104
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Non-drug therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI	CCI																										
CCI																											
eDiary for assessment of AIR (self reported local swelling and NRS pain)[23]																											
CCI [4]																											

Period	Extension Period	Extension Period - Follow-up
Visit Name	CCI	**260/EOS**
Weeks		**260**
In-office visit	CCI	X
Telephone visit[1]		
Vital Signs[3]		X
Body Weight		X
Physical Examination		S
Physical examination (symptom oriented)		
Physical examination (target knee)		X
Temporary discontinuation of pain medications[4]	CCI	
WOMAC[5]		
SF-12 Standard v2		
Trial Feedback Questionnaire		X
Patient Global Assessment (PGA)	CCI	
Patient Global Impression of Severity (PGIS)[6]		
Patient Global Impression of Change (PGIC)[6]		
Performance based tests (30 second chair stand test, 4×10m fast-paced walk test, 6 minutes walking distance test)		
Electrocardiogram (ECG)[7]	CCI	X
Hematology		X
Clinical Chemistry		X

Period	Extension Period										Extension Period - Follow-up				
Visit Name	CCI														**260/EOS**
Weeks															**260**
hsCRP															X
Urinalysis (Macroscopic panel. Microscopic panel only if macroscopic is abnormal)															X
Coagulation test[8]	CCI														
Fasting lipid panel	CCI														X
Pregnancy Test (serum)[10]										S					S
Pregnancy test (urine)[11]	CCI														
Knee X-ray[12]															
MRI of target knee[13]															
Serum and urine biomarkers															
Synovial fluid biomarkers[16]															
Anti-drug antibody to LNA043[17]															
Actigraphy[18]															
Gait assessment (optional, at selected sites only)[19]															
Study drug administration[20]															
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Non-drug therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI	CCI														
CCI															

Period	Extension Period	Extension Period - Follow-up
Visit Name	CCI	260/EOS
Weeks		260
eDiary for assessment of AIR (self reported local swelling and NRS pain)[23]	CCI	

[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.

* The screening period should last up to 8 weeks and include completion of two Screening Visits. SV1 can be -8 to -4 weeks before Week 0 and SV2 can be scheduled any time after SV1 up to -1 week before Week 0 provided X-ray eligibility report is available and first WOMAC pain assessment has been completed.
[1] Telephone visits should be conducted to assess AEs and concomitant medication use.
[2] Informed consent must be signed prior to any study-related procedures. Screening procedures may be conducted throughout the Screening period including the Screening 1 and Screening 2 visits.
[3] Vital signs include heart rate, blood pressure and body temperature.
[4] For subjects on pain medication, including NSAIDs/COX-2 inhibitors, opioids, paracetamol and any over-the-counter (OTC) and topical analgesics, it is required to discontinue these analgesics for at least 48 hours or 5 half-lives (whichever is longer) prior to any WOMAC pain and function assessment visits, including Screening, Weeks CCI 104, CCI .
[5] The first WOMAC pain assessment on the target knee will be performed at home on the handheld device after SV1 and temporary pain medications wash-out (if needed) and at least 4 days before SV2. During SV2, the second WOMAC pain for the target knee will be recorded on the tablet (complete WOMAC assessment), while the WOMAC pain for the non-target knee will be collected on the handheld device."
[6] Patient Global Impression of Severity and Patient Global Impression of Change will be assessed only when a local language version for the site/country is available. They should be completed after performance based tests.
[7] ECG can be performed locally at other timepoints if clinically indicated.
[8] PTT at central lab will be conducted for all the patients at SV1. Participants under known anticoagulation treatment with coumarins (e.g., warfarin) will perform PT-INR at local lab before the study drug injection.
[9] Hepatitis screen done with HBsAg and HCV-RNA.
[10] Pregnancy test: only for women of childbearing potential, serum pregnancy test will be performed locally at SV1, Week 104, Week 208 and Week 260/EOS. For all other visits, a urine pregnancy test (using locally sourced kits or provided by the central lab if available and compliant with local requirements) will be performed before study drug injection.
[11] Urine pregnancy test will be performed on a CCI basis on site or at home from Week 0 until Week CCI.
[12] All knee X-rays will be centrally read. Posteroanterior X-rays of both knees will be taken at SV1, Week CCI . An additional posteroanterior view of the target knee will be performed at Week CCI and Week CCI. Pre-screened or re-screened participants may utilize previous knee X-rays if taken within the past 3 months according to the protocol imaging criteria and using a Synaflexer™ leg holder.
[13] All MRIs will be centrally read. MRI at SV2 should be performed after confirmation of clinical, laboratory and X-ray eligibility criteria. MRIs after Week 0 may be performed up to 2 weeks before study drug injection.
[14] Blood samples for PK to be drawn prior to the study drug injection at Weeks CCI . Blood samples for PK 2 hours (± 15 minutes) after the study drug injection will be collected at Weeks CCI . Blood samples for PK 15 minutes (± 5 minutes) after the study drug injection will be collected at Weeks CCI at

Period	Extension Period	Extension Period - Follow-up
Visit Name	CCI	260/EOS
Weeks		260

selected sites.
[15] Blood samples for ANGPTL3 to be drawn prior to the study drug injection at Weeks CCI . Blood samples for 2 hours (± 15 minutes) after the study drug injection will be collected at Weeks CCI
[16] Synovial fluid to be aspirated just before the study drug injection at each dosing visit. If synovial fluid is unable to be aspirated on Week , then further collection of synovial fluid during the study is not required.
[17] When collected on the study drug administration days, immunogenicity samples should be collected before the injection. In case of suspected allergic hypersensitivity, the participant should return to the site and a sample to assess immunogenicity collected as near as possible to the event.
[18] Actigraphy will not be performed at sites where Health Authority and/or IRB/IEC did not approve Actigraphy assessments, if the device is not available on site or in case the investigator confirms that the patients should be exempted. Actigraphy during CCI
[19] Only for patients undergoing gait assessment. More details can be found in the separate Gait Assessment Manual.
[20] Women of child-bearing potential will receive study drug only after a negative pregnancy test at each visit.
[21] CCI
[23] Self reported local swelling and NRS pain will be collected via eDiary before every i.a. injection and daily for 3 days thereafter.
[24] CCI to be conducted CCI

8.1 Screening

8.1.1 Pre-screening

Prior to Screening Visit 1, optional study specific pre-screening assessments may be carried out, including but not limited to X-ray using a Synaflexer™ leg holder and knee physical examination (e.g. assessment of knee OA laterality), to assess participant eligibility for inclusion. Prior to any study specific assessments being carried out, the pre-screening informed consent form must be signed by the participant.

Only data related to SAE causally related to pre-screening study procedures (X-ray, knee examination) will be collected (see Section 10.1.3). All other data related to pre-screening will only be recorded in source documentation.

If an X-ray is taken during pre-screening according to the protocol imaging criteria it will not need to be repeated during screening. If the subject is then screened within 3 months, the X-ray taken during the pre-screening according to the protocol imaging criteria can be submitted for central reading review.

8.1.2 Screening

The screening period should last up to 8 weeks.

It is permissible to re-screen a participant once, including, but not limited for the reasons below. Other reasons should be discussed and agreed with the Sponsor on a case-by-case basis.

1) Participants with synovitis-related effusion within 12 weeks from Screening Visit 1. It is advisable to rescreen those participants once they have a 12-week period free of knee effusions.

2) In the case where a safety laboratory assessment at screening is outside of the range specified in the exclusion criteria, this assessment may be repeated once prior to randomization per the Investigator's discretion. If the repeat value remains outside of the specified ranges, the participant must be excluded from the study.

The screening window should be utilized to accommodate the repeated tests.

8.1.3 Information to be collected on screening failures

Subjects who sign an informed consent form and subsequently found to be ineligible prior to randomization will be considered a screen failure, except for those cases when rescreening is allowed once (see Section 8.1). The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, informed consent and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see SAE section for reporting details). Third-party data such as central laboratory results for participants who are screen failures may be transferred to Novartis database. If the participant fails to be randomized, the IRT must be notified immediately after the screen fail that the participant was not randomized.

8.2 Participant demographics/other baseline characteristics

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

Participant demographics (age, sex, height and weight) and baseline characteristic data will be collected upon sign off of the informed consent. Participant race and ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities. Relevant medical history/current medical conditions data will be collected at Screening Visit 1 with particular attention to conditions like other inflammatory arthropathies or generalised pain syndromes and concomitant treatments like i.a therapies affecting participant's eligibility.

Pain assessment (including pain for the last 6 months), double baseline pain (two independent pain measurements at least 4 days apart on a 0-50 WOMAC pain scale) on the target knee, WPI, PGA (NRS) and SF-12 v2 questionnaires must be completed for eligibility at or by Screening Visit 2 as baseline. Each WOMAC Pain assessment will be collected after at least 48 hours or 5 half-lives of analgesics (e.g., NSAIDs/COX2 inhibitors, low potency opioids, paracetamol / acetaminophen and any other OTC/topical analgesic medication) wash-out. Participants will be informed of the analgesics wash-out requirements. CCI [redacted]

WOMAC pain on the target knee will be collected twice during screening period: at least 4 days prior to Screening Visit 2 at home, and at Screening Visit 2. Double baseline pain assessment on the target knee has been selected to ensure the most accurate evaluation against the pain eligibility criterion. WOMAC Pain on non-target knee will be assessed at Screening Visit 2.

Bilateral posteroanterior knee X-ray will be performed to confirm K-L grade on both knees, JSW and JSN grade on the target knee at Screening Visit 1. Alternatively, K-L grade, JSW and JSN grade could be assessed by a pre-screening X-ray, if it was taken according to the protocol imaging criteria and within 3 months before Screening Visit 1.

Laboratory assessments will be performed at Screening Visit 1 and as close to visit Week 0 for eligibility and baseline. Coagulation tests will be carried out at the central lab for all patients at Screening Visit 1 for eligibility. Anticoagulant management is allowed per local practice however participants under known coumarins (e.g., warfarin) are still eligible for enrollment and can receive study drug as long as INR<3 is certified at local laboratory before study drug administration at any dosing visit. Suspension of NOACs before i.a. injection should be assessed by the treating physician, based on local prescribing information.

Participants will also be provided a wrist actigraphy sensor, trained and instructed to wear the sensor CCI [redacted] to collect baseline data.

Baseline data for the gait assessment will be collected during the visit at Week 0 prior to i.a. injection.

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.

8.3 Efficacy

The primary assessment of efficacy in this trial will focus on quantitative MRI evaluation of the treatment effect on knee cartilage thickness in the cMTFC. Secondary assessments of efficacy include quantitative MRI evaluation of knee sub compartments (medial and lateral) and of knee function and pain.

The effect on cartilage will be evaluated by means of a quantitative MRI as described in Section 8.3.1 and by means of X-ray (JSW measurement), while any treatment effect on the osteoarthritic CCI of the target knee. Changes i CCI The SDC threshold for cartilage thickness on qMRI will be computed from study-specific test-retest data (Eckstein et al 2012). The SDC will be calculated as 1.96 × the SD of the differences between changes observed at test-retest. Structural progression will also be assessed on X-ray, according to the definition of the Foundation for the National Institutes of Health (FNIH) OA biomarkers consortium: a decrease in minimum medJSW of ≥ 0.7 mm, which has a less than 10% chance of being due to measurement error (Hunter et al 2014).

The secondary treatment effect due to regenerating cartilage on clinical outcomes will be assessed by a set of performance-based functional tests and Patient Reported Outcome (PRO) questionnaires on function, pain, symptoms, and quality of life such as WOMAC, PGA, PGIS, PGIC, CCI and SF-12 v2. The WOMAC is a widely used, proprietary outcome measurement tool used to evaluate the condition of participants with OA of the knee, including pain (5 questions) and physical functioning (17 questions) of the joints. Each question is measured on an 11-point NRS scale (range 0-10). CCI PGIS and PGIC will be used to capture the participant's global impression of their target knee pain during functional assessments and measure global improvement with treatment. PROs and performance-based functional tests are further described in Section 8.5.1.

The Outcome Measures in Rheumatology – Osteoarthritis Research Society International (OMERACT-OARSI) responder rate (Pham et al 2004) will be determined as an exploratory analysis. The OMERACT-OARSI responder criteria involve changes that are deemed to be clinically relevant in three domains: pain, function, and Patient's Global Assessment.

Continuous physical activity over CCI will be explored by means of a wrist actigraphy sensor. The actigraphy sensor will be worn CCI At selected sites, gait temporospatial parameters will be explored by means of the Biomechanical Sensor Platform (BSP). Further details on the use of these digital devices are provided in Section 8.5.5.1 and Section 8.5.5.2.

All efficacy assessments should be performed prior to administration of study treatment. Details related to the administration of all PROs are provided in Section 16.4.

8.3.1 Knee MRI

MRI will be obtained from the target knee to visualize the cartilage tissue in the medial and lateral femoral and tibial regions, as well as in the total TF compartment. In addition, CCI [redacted]
Details of the MRI acquisition protocol and corresponding image analysis will be provided in the image acquisition manual and imaging charter.

Image collection

Magnetic Resonance (MR) images acquisition will be performed by a trained MRI professional at the imaging facility. Imaging facility for the study should be trained and qualified by central imaging lab prior to the first image is taken for the study assessment. The MRI radiologist will be blinded to the treatment received by the participant. All participants will be imaged using a clinical high-field MRI scanner. For each MRI session, images will be acquired as described in the Imaging Acquisition Guideline to assess over the course of the study the extent of cartilage loss or regeneration in the index region as well as potentially relevant knee OA structures such as bone marrow lesions.

MR images will be acquired at the imaging site(s) and sent for independent central review by the imaging core labs. The reviewers will be blinded to the treatment received by the participant. MRI analysis results will not be shared with the Investigators to maintain the blind. However, joint-related findings identified in MR scans will be reported in cases of safety concerns or any incidental finding of relevance for participant's health.

Image processing

The image analysis will be performed centrally, as defined in the imaging charter, in order to assess changes in cartilage structure (i.e., thickness and volume) in pre-defined areas of the knee, including in the target region. Other endpoints will include scoring of features assumed to be most relevant to the natural history of the disease including (but not restricted to) bone shape of the femur and the tibia, bone marrow lesions, cysts, cartilage, osteophytes, synovitis, effusion, meniscus, ligaments and tendon.

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.

Post-baseline analyzed data of MR and X-ray images will not be provided to the blinded study personnel before Database Lock.

8.3.2 Appropriateness of efficacy assessments

LNA043, a modified protein from the human ANGPLT family is characterized by its capacity to regenerate cartilage as evidenced by means of compositional and quantitative MRI methods used in the FIH, PoM and PoC studies, in participants with cartilage defects. In terms of sensitivity and responsiveness, quantitative MRI (Conaghan et al 2011, Pelletier et al 2013) has been shown better suited for the detection of changes in cartilage morphology than

semiquantitative MRI scoring systems and traditional X-rays. Therefore, it is considered as the technology of choice to demonstrate the treatment effect of LNA043 on cartilage.

8.4 Safety

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

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

As per Section 4.6, 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 visit, regular phone calls or virtual contacts can occur (possibly every 4 weeks) for safety monitoring and discussion of the participant's health status until it is safe for the participant to visit the site again.

Table 8-2 Assessments & Specifications

Assessment	Specification
Physical examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. Careful examination of the target knee will be performed at all visits by assessing redness, warmth, swelling, pain, range of motion, stability, and bulge sign, crepitus, flexion contracture, varus/valgus laxity, antero-post laxity, max extension and max flexion should be recorded. Full physical examination is not required at all visits, but target knee examination and symptom oriented examinations will be performed at all site visits. Information for all physical examinations must be included in the source documentation at the study site. Physical examinations on the target knee should be recorded on the CRF. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event. Vital signs Vital signs include BP and pulse measurements. After the participant has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.
Height and weight	Height and body weight (to the nearest 0.1 unit in indoor clothing, but without shoes) will be measured.

8.4.1 Laboratory evaluations

Unless otherwise specified, lab assessments will be sent to a central lab for analysis.

Clinically notable laboratory findings are defined in Section 16.1 and Section 16.2.

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

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, Red blood cells, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils) (absolute value preferred, %s are acceptable)
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphorus, Sodium, Potassium, Creatinine, Creatine kinase (CK), Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose, HbA1c
Lipids panel (fasting)	Total Cholesterol, LDL, HDL, Total Protein, Triglycerides
Urinalysis	Macroscopic Panel (Dipstick in all countries except China, lab tests in China) (Color, Bilirubin, Blood (Hemolyzed and non-hemolyzed), Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells) Note: Only in case of abnormal macroscopic panel.
Coagulation	PTT at central lab will be conducted at screening for all patients. PT-INR to be completed locally prior to study drug injection for patients taking coumarins (e.g., warfarin).
Hepatitis markers	HbsAg, HCV RNA-PCR
Additional tests	High-sensitivity C-Reactive protein (hsCRP), HIV-1 and HIV-2 antibodies
Pregnancy Test	Serum / Urine pregnancy test (local, where possible), FSH (local)

8.4.2 Electrocardiogram (ECG)

Single 12-lead ECGs are collected and read locally. The original ECGs, appropriately signed, must be collected and archived at the study site.

For any ECGs with participant safety concerns, two additional ECGs must be performed to confirm the safety finding. A monitoring or review process should be in place for clinically significant ECG findings throughout the study and especially at baseline before administration of study treatment.

In the event that a clinically significant ECG abnormality is identified at the site (e.g. severe arrhythmia, conduction abnormality of QTcF > 500 ms), the ECG is repeated to confirm the diagnosis. If the participant is hemodynamically compromised, the Investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example cardioversion).

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

8.4.3 Pregnancy and assessments of fertility

Contraception for male study participants is not required.

All women of childbearing potential will have pregnancy testing as outlined in Table 8-1. A woman is considered of childbearing potential from menarche until becoming post-menopausal unless permanently sterile. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause and an appropriate clinical profile.

Permanent sterilization methods include hysterectomy, bilateral tubal ligation, bilateral salpingectomy and bilateral oophorectomy. In the case of oophorectomy alone, only when the

reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered to be not of child-bearing potential.

Medical documentation of the permanent method of sterilization must be retained as source documents.

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

8.4.4 Appropriateness of safety measurements

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

8.4.5 Immunogenicity

Immunogenicity (IG) samples will be obtained at the time points defined in the Assessment Schedule (Table 8-1) and evaluated in all participants.

In case of suspected allergic hypersensitivity, an unscheduled sample to assess immunogenicity will be collected. Unscheduled samples should also be collected, in addition to planned samples, during scheduled visits in case of suspected allergic hypersensitivity after injection of study treatment.

In case of positive immunogenicity, backup of previous PK samples could be used to better characterize the onset of immunogenicity response.

Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing, and shipment.

Immunogenicity analytical method(s)

A validated ligand binding assay will be used for the detection of potential anti-LNA043 antibodies, and cross-reactivity to ANGPTL3. In case of the detection of antibodies cross reacting with ANGPTL3, a validated ligand binding assay will be used for the detection of potential cross-reactive anti-ANGPTL4 antibodies.

Confirmed immunogenicity positive samples will be further analyzed for presence of neutralizing antibodies using a validated method performed using ligand binding assay.

The detailed methods for immunogenicity assessment will be described in the Bioanalytical Data Reports.

IG samples remaining after immunogenicity analysis may be used for exploratory assessment or other bioanalytical purposes (e.g. cross check between different sites). Given the exploratory nature of the work, the analytical method used for those assessments will not be validated.

8.5 Additional assessments

8.5.1 Clinical Outcome Assessments (COAs)

Patient reported outcomes (PRO)

PROs completed at study visits should be completed before any assessments (e.g., physical examination) are conducted, except Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) to be performed after performance based tests. The PI should follow the instructions for PRO questionnaires and should instruct the participant appropriately. The participant's refusal to complete all or any part of a PRO measure should be documented in the study data capture system and should not be considered as a protocol deviation. Handling of protocol deviations can be modified if needed per study protocol.

Participant questionnaires should be completed in the language most familiar to the participant.

The participant should be given sufficient space and time to complete the PRO measure(s).

The site personnel should check PRO measure(s) for completeness and ask the participant to complete any missing responses. Completed measure(s) must be reviewed and assessed by the Investigator for responses which may indicate potential AEs or SAEs before any clinical study examinations. This assessment should be documented in study source records. If Aes or SAEs are confirmed, study Investigators should not encourage the participant to change responses reported in the completed questionnaires. Study Investigators must follow reporting instructions outlined in Section 10. The responses stored electronically in the database will be considered the source file.

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

The WOMAC has been developed to assess the course of disease or response to treatment in patients with knee or hip osteoarthritis (Collins et al 2011). It includes 24 items and three subscales: 1) pain severity during various positions or movements ("WOMAC Pain"), 2) severity of joint stiffness ("WOMAC Stiffness"), and 3) difficulty performing daily functional activities ("WOMAC Function"). The 24 items will be scored with a numeric rating scale using 11-box horizontal scale, with the left end marked as "none" and the right end marked as "extreme". The recall period is 48 hours. Appropriate translations of the entire WOMAC® version 3.1 questionnaire (11-box numerical scale version) will be used. For administration of the questionnaire, instructions in the WOMAC 3.1 User's Guide should be followed. This version of WOMAC questionnaire has been validated also for remote capture using mobile technology (Bellamy et al 2010). The WOMAC will be collected using a handheld device and tablet.

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will be collected CCI

Short Form 12 Health Survey (SF-12)

The SF-12 is one of the most commonly used generic health-related quality of life (HRQL) measures in patients with hip or knee disorders. The SF-12 has a lower responder burden compared to SF-36 and has been validated for use in knee OA trials (Gandhi et al 2001). The SF-12 contains a subset of 12 items from the SF-36, including one or two items from each of the eight SF-36 scales (Gandek et al 1998). Two items are included from the Physical Functioning and Mental Health scales because these scales have been shown to best predict physical and mental health; two items each are also included from both Role Functioning scales, because these are relatively coarse scales. One item each is included from the remaining four scales. Information from all 12 items is used to construct physical and mental component summary measures. The SF-12 will be collected using a tablet device. In this study, SF-12 v2 Standard will be used.

Patient's Global Assessment of Pain (PGA)

The PGA is commonly used in OA trials (McAlindon et al 2015). Participants will answer the question: "Considering all the ways your osteoarthritis of the knee has affected you during the last 48 hours, select the number that best describes the impact of your knee osteoarthritis on your daily life?" by using an 11-box horizontal scale, with the left end marked as "none" and the right end marked as "extreme". The PGA will be collected using a tablet device.

Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC)

The PGIS and PGIG provide a responsive and readily interpretable measure of participant's assessments of the clinical importance of their improvement or worsening of their knee pain during functional performance outcome assessments over the course of the clinical trial (Dworkin et al 2005). Participants will answer questions about their perception of disease activity by using a 4-point and a 5-point scale, for PGIS and PGIC, respectively. PGIS and PGIC will be collected using a tablet device after performance based tests during visits at Weeks [redacted] (only PGIS), CCI [redacted]. PGIS and PGIC questions are reported in Section 16.5. PGIS and PGIC will be assessed only when a local language version for the site/country is available.

Widespread Pain Index (WPI) and Symptom Severity Scale (SS scale)

WPI and SS scale will be collected only at Screening Visit 2 with a tablet to exclude participants with fibromyalgia, according to recent criteria by the American College of Rheumatology (Wolfe et al 2010). The use of both scales allows for highly accurate identification and differentiation of fibromyalgia patients.

Performance Outcomes (PerfO)

A series of performance-based tests, according to the OARSI guideline "Recommended performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis" (Dobson et al 2013), will be performed at baseline and at Weeks CCI [redacted]. These tests are intended for use by both clinicians and researchers as performance outcome measures and are viewed as complementary to established self-report measures such as questionnaires. The guideline describes a Core set and a Recommended set

of tests. The Core set includes: 30 second chair stand test, 4×10m fast-paced walk test, and stair climb test. The Recommended set includes the Core set plus timed up & go test and 6 minutes walking distance test.

With the aim of minimizing participants' burden and in consideration of potential operational challenges in implementing all tests in a large multi-center study, only 30 second chair stand test, 4×10m fast-paced walk test, and 6 minutes walking distance test will be performed. Further details on the execution of the tests are described in the OARSI guideline, provided as a separate manual.

8.5.1.1 CCI

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The objectives of the CCI . This information is not otherwise collected in the trial with other assessments.

A total sample size of CCI study participants is planned for CCI . Details regarding the CCI

CCI

Patients who have consented to the CCI

8.5.2 Pharmacokinetics

Pharmacokinetic (PK) samples will be collected at the time points defined in the Assessment Schedule (Table 8-1), footnotes 14 and 15) in all participants. Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing and shipment.

LNA043 PK will be measured only in participants administered LNA043 and will be determined by a validated immuno-capture and LC-MS/MS method; the anticipated Lower Limit of Quantification (LLOQ) is 10 ng/mL in serum.

The endogenous ANGPTL3 will be measured in all participants and will be determined by a validated ligand binding assay; the anticipated LLOQ is 39.7 pmol/L in serum.

Concentrations will be expressed in mass per volume units.

Concentrations below the LLOQ will be reported as "zero" and missing data will be labeled as such in the Bioanalytical Data Report.

PK samples remaining after completion of the determination of parent may be used for exploratory assessment of metabolites or other bioanalytical purposes (e.g., cross check

between different sites, stability assessment). Given the exploratory nature of the work, the analytical method used for those assessments will not be validated.

Due to a limited PK sampling, only summary statistics of measured PK concentrations will be reported, and no further PK parameters will be determined in this study.

8.5.3 Biomarkers

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), at study sites in all participating countries except China.

Serum, urine and synovial fluid biomarkers studied may include, but are not limited to surrogate biomarkers of cartilage tissue turnover:

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- CCI
- CCI
- CCI

CCI

- CCI
- CCI

Provided that LNA043 has demonstrated repair activity by hyaline cartilage formation in damaged articular cartilage in preclinical and early human studies, serum, urine and synovial fluid biomarkers of extracellular matrix remodeling may be studied. The goal is to further characterize the mechanism of action of the drug in participants with moderate to severe knee OA, and to identify potential associations with response to treatment with LNA043 and disease progression.

CCI

CCI

In particular, CCI

Serum samples may also be used to look for protein markers that may be associated with treatment response or predict response to treatment.

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

DNA sampling / Pharmacogenetics

The study includes an optional genetic research component which requires a separate informed consent signature if the participant agrees to participate. As permitted by local governing regulations and by IRB/IEC, it is required as part of this protocol that the Investigator presents these options to the participant.

The purpose of genetic research may be to better understand the safety and efficacy of LNA043, or to learn more about human diseases, or to help develop ways to detect, monitor and treat diseases.

As technology changes over time, the most appropriate technology will be used at the time the exploratory genetic research is performed. This may include the study of the entire genome.

Laboratory manuals will be provided with detailed information on sample collection, handling, and shipment.

To maximize confidentiality, all samples and the information associated with the samples will be double-coded to prevent the exposure of the participant's information and identity. This double-coding process allows Novartis to go back and destroy the sample at the participant's request. In addition, sample information is stored in one secured database while genetic data is stored in an independent secured database.

8.5.3.1 Additional biomarker assessments

This clinical study may include additional, optional biomarker components on available samples or imaging data, and could be used for exploratory hypothesis generation (e.g., discovery-based research).

8.5.4 Imaging

Standard, short-film X-ray of the knees at 10° of flexion will be performed during screening and during the study at Weeks [redacted], 104, [redacted]. Standardization will be ensured by means of a Synaflex leg holder and central reading. These X-rays will be used to measure JSW with both fixed location and minimal JSW methods.

In order to complement the primary and secondary qMRI endpoints assessing cartilage thickness in the target knee, a series of exploratory analyses will be performed. The analyses below will provide an alternative measurement of the articular cartilage and assess the other tissues of the knee joint.

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

The methods for assessment and recording for both X-ray and MRI are specified in the imaging charter.

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.

8.5.5 Other Assessments

8.5.5.1 Actigraphy

Actigraphy is a well-established, widely-accepted and validated technology, commonly used for physical activity assessment (Farr et al 2008).

Participants will be provided with a medical-grade wrist-worn actigraphy sensor and will be instructed to wear the sensor CCI [redacted] as indicated in Table 8-1. The wrist actigraphy sensor should be worn on the non-dominant hand. Before wearing the wrist-based actigraphy sensor, participants will be trained in placement and use of the sensor by site staff prior to first use and afterward as needed. Participants will bring back the actigraphy sensor to each visit for data transfer as indicated in Table 8-1.

This wrist actigraphy sensor will assess physical activity and mobility parameters. Data will be processed by the vendor centrally, and the daily summary data will be sent electronically to Novartis.

Detailed instructions concerning the actigraphy sensors will be provided to the Investigators and participants in the Actigraphy Manual prior to using the actigraphy sensor.

Actigraphy will not be performed at sites where Health Authority and/or IRB/IEC did not approve Actigraphy assessments, if the device is not available on site for logistics or other reasons, or in case the Investigator confirms that the patients should be exempted.

8.5.5.2 Gait assessment

The optional gait assessment (at selected sites only) will be performed using the BSP, which consists in a series of wearable digital devices. Study participants at selected sites will be invited to participate in the gait assessment, except those who meet any of the following exclusion criteria:

- Body weight > 120 kg at Screening Visit 1
- Shoe size: < 34 or > 47 (EU), < 4.5 or > 11.0 (US) at Screening Visit 1

Participants will be asked to perform a battery of instrumented physical performance tests while wearing the BSP to measure a series of gait parameters, which could include: gait speed, cadence, stride length and knee dynamic loading parameters. These gait parameters will be extracted from the raw data collected at site in the backend post-data collection by Novartis.

All the Investigators in gait assessment should follow further instructions as described in the Gait Assessment Manual. Participants will be instructed how to complete the gait assessment by the Investigators.

On November 18th, 2022, it was communicated to study investigators participating in the optional gait assessment that the exploratory gait assessment was terminated with immediate

effect due to low enrolment, and, therefore, they would no longer have the gait assessments completed at the follow-up visits.

8.5.5.3 Total Knee Replacement (TKR) and Virtual Knee Replacement (VKR)

TKR is a relevant outcome in osteoarthritis trials (Maillefert et al 2005). Assessing disease progression by TKR is dichotomous and will be analyzed both as incidence and time to event in this trial. However, overall the number of OA participants who reach this endpoint within an OA trial is usually small, and important disparities in TKR by race, gender, socioeconomic status, access to care, surgeon preference, and health care systems limit its use in OA trials (Manno et al 2012).

In order to overcome the limitation and biases of TKR, the concept of VKR has been pursued. VKR is a composite score, including both clinical (WOMAC) and structural criteria (JSW). Participants meeting criteria for this composite score could be considered as reaching a stage with sustained pain, reduced function, and evidence of X-ray progression, where a TKR would be warranted, although not necessarily occurring.

8.5.5.4 CCI

CCI will be collected CCI as indicated in Table 8-1. CCI to be recorded include CCI

8.5.5.5 Trial Feedback Questionnaire (TFQ)

This study is including an optional questionnaire, the "Trial Feedback Questionnaire" for trial participants to provide feedback on their clinical trial experience. Individual trial participant responses will not be reviewed by Investigators. Responses may be used by the sponsor (Novartis) to understand where improvements can be made in future clinical trial processes. This questionnaire does not ask questions about the trial participant's disease, symptoms, treatment effect, or AEs, and, therefore is not considered as trial data.

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

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

Participants may voluntarily discontinue study treatment (refuse study treatment but continue with study participation) or completely discontinue from the study (no further study participation) for any reason, at any time.

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

Study treatment must be discontinued under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of certain prohibited treatment as per the prohibited treatment section (Section 6.2.2)
- Any situation in which study participation might result in a safety risk to the participant
- Following emergency unblinding for safety reason(s)
- TKR in either knee
- Any surgery to the target knee
- Any trauma to the target knee that can have an impact on cartilage growth, according to Investigator's judgement
- Emergence of the following adverse events:
  - Hypersensitivity reaction / anaphylaxis
  - Hemarthrosis
  - Septic arthritis
  - Any laboratory abnormalities that in the judgment of the Investigator, taking into consideration the participant’s overall status, prevents the participant from continuing participation in the study

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

Discontinuation of study treatment does not require the subject to be discontinued from the study and all ongoing visit assessments.

Participants 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 'Withdrawal of Informed Consent' section). Where possible, they should return for the assessments indicated in the Assessment Schedule. 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 participant/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

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

After 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

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

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

9.1.2 Withdrawal of informed consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time.

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

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

and

No longer wishes to receive study treatment

and

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

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

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

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

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

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

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

Novartis/Sponsor will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent/oppose to the use of their data/biological samples, the Investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g., dates of telephone calls, registered letters, etc. A participant should

not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This 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 the participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a prematurely withdrawn participant. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The Investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their Week 260 visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision. In case of an early study termination, each participant will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them.

All participants who received at least one study treatment should have a safety follow-up visit (EOS) conducted at least 6 months after the last injection of study treatment, unless assessments at discontinuation visit were performed at least 6 months after the last injection of study treatment. The information collected is kept as source documentation. All AEs, SAEs and concomitant medications reported during this time period must be reported as described in Section 10.1. Documentation of attempts to contact the participant should be recorded in the source documentation.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

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

- they induce clinical signs or symptoms

- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participants with the underlying disease. Alert ranges for laboratory and other test abnormalities are included in Section 16.1 and Section 16.2.The Investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

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

For participants who sign the pre-screening ICF, AEs occurring after the signature of this consent will be captured only if they meet the definition of serious adverse event as outlined in Section 10.1.2 and are reported to be causally related to pre-screening study procedures (e.g., blood sampling). The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

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 classification of AEs is severity grading of Mild, Moderate, or Severe.

   Mild: usually transient in nature and may require only minimal treatment or therapeutic intervention and generally not interfering with normal activities

   Moderate: sufficiently discomforting to interfere with normal activities but poses no significant or permanent risk of harm to the participant.

   - Severe: interrupts daily activities or significantly affects clinical status or may require intensive therapeutic intervention.

With respect to the possible knee-related AEs, the following guidance on grading is provided:

Table 10-1 Guidance on grading of knee-related AEs

AE term	Mild	Moderate	Severe
Arthralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL
Arthritis	Mild pain with inflammation, erythema, or joint swelling	Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADL	Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; limiting self care ADL
Joint effusion	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; invasive intervention indicated

Joint range of motion decreased	<=25% loss of ROM (range of motion); decreased ROM limiting athletic activity	>25 - 50% decrease in ROM; limiting instrumental ADL	>50% decrease in ROM; limiting self-care ADL

2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e., progression of the study indication) the assessment of causality will usually be 'Not suspected', unless there is reasonable probability that the study drug/procedure led to a worse progression of the knee OA (in intensity or time course). The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of treatment groups, not on a single participant.
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met.
5. Action taken regarding with study treatment.
6. Treatment of the AE, if any.
7. Its outcome.

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

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

Adverse event recording for each participant should be continued for at least 180 days following the last dose of study treatment, or end of study visit (EOS), whichever is longer.Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g., continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Adverse event training for CCI [redacted]

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

10.1.2 Serious adverse events

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

- Fatal
- Life-threatening

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

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

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All 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.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 180 days following the last dose of treatment, or EOS, whichever is longer, must be reported to Novartis Safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events. Any SAEs experienced after the 180-day period after EOS should only be reported to Novartis Safety if the Investigator suspects a causal relationship to study treatment. Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site.

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 one must be reported separately as a new event.

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, Novartis may urgently require further information from the Investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with the same study treatment that this SAE has been reported.

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

Only data related to SAEs causally related to pre-screening study procedures (X-ray, knee examination) will be collected. All other data related to pre-screening will only be recorded in source documentation.

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

10.1.4 Pregnancy reporting

Pregnancies

To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Live births will be followed-up to 12 months of age to collect information on any abnormalities which were not apparent at the time of birth.

Pregnancy should be recorded and reported by the Investigator to Novartis. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship between the study treatment and any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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, including misuse or abuse, must be reported on the AE (or SAE, if the event meets the definition of an SAE) CRF

within 24 hours of Investigator's awareness.

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

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

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

The following two categories of abnormalities / adverse events have to be considered during the course of 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 CRFs

Please refer to Table 16-1 in Section 16.1 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 GGT) to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include, based on Investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining

more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

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

10.2.2 Renal safety monitoring

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

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

Abnormal renal event findings must be confirmed after ≥24 hours but ≤ 5 days after first assessment.

Once a participant is exposed to study treatment, renal laboratory alerts or renal safety events should be monitored and followed up by the Investigator or designated trial staff as summarized in Section 16.2.

Every renal laboratory trigger or renal event as defined in Table 16-3 should be followed up by the Investigator or designated personnel at the trial site as summarized in Table 16-4.

10.2.3 Data Monitoring Committee

An independent (of the study and LNA043 development program) DMC will review cumulative, semi-blinded safety data continuously and at scheduled at least semi-annual (every 6 months) meetings. The DMC will review SAEs as individual cases and will also be able to review summaries of non-serious adverse events and laboratory data for patterns and trends. All SAEs occurring in this study will be reported to the DMC in a timely manner. The DMC will review data relating to those events and treatment information in a semi-blinded manner at the level of treatment arm. The Independent Statistician and Independent Programmer will receive semi-blinded treatment codes per treatment arm (e.g., A, B, C and D) according to the applicable and documented Novartis procedures. Thus, all analysis outputs sent to the DMC will be semi-blinded, and the Independent Statistician and Independent Programmer will remain partially blinded to the actual treatment assignments. The Independent Statistician will provide electronic reports to the DMC and then communicate with the DMC as needed. To enhance the integrity and credibility of the trial, procedures will be implemented to ensure that the DMC has sole access to information from the clinical trial regarding unblinded or semi-blinded results.

Based on their review and clinical judgement, the DMC will recommend appropriate action to the study team which may include stopping the trial completely, modifying the trial, stopping a dose arm, modifying a dose arm or proceeding as per protocol.

Details on the organization and function of the DMC will be described in the DMC charter.

11 Data Collection and Database management

11.1 Data collection

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

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

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

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

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

11.2 Database management and quality control

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

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

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

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

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made

available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

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

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

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

12 Data analysis and statistical methods

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

Summary statistics for continuous variables will include N, mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum. Summary statistics for discrete variables will be presented in the number and percent of participants in each category.

Unless otherwise specified, p-values will be presented as two-sided p-values and two-sided confidence intervals will be displayed. The default level of significance will be set to 5%.

Efficacy and safety data will be presented by the following treatment groups:

- LNA043 CCI mg CCI , Cycle every CCI

- LNA043 CCI mg CCI and CCI , Cycle every CCI
- LNA043 CCI mg CCI , Cycle every CCI
- LNA043 CCI mg CCI followed CCI later (after first injection) by CCI , Cycle every CCI
- Placebo CCI , Cycle every CCI

The baseline value is defined as the last assessment prior to first dose administration. If the scheduled baseline assessment value is missing, the screening value will be used instead.

12.1 Analysis sets

The following analysis sets will be used in this study:

The Randomized Analysis Set (RAS) consists of all randomized participants. Unless otherwise specified, mis-randomized participants (mis-randomized in IRT) will be excluded from the RAS.

Mis-randomized participants are defined as those participants who were mistakenly randomized into the IRT prior to the site confirming all eligibility criteria had been met and to whom no study medication was given. Mis-randomized participants are treated as screen failures.

The Full Analysis Set (FAS) comprises all participants in the RAS to whom study treatment has been assigned by randomization. According to the intent to treat principle, participants will be analyzed according to the treatment they have been assigned to during the randomization procedure.

The Safety Set includes all participants who received at least one dose of study treatment. participants will be analyzed according to the study treatment received.

The PK analysis set will include all participants who received study drug, have at least one available valid (i.e., not flagged for exclusion) PK (LNA043) concentration measurement, and for whom there are no protocol deviations with impact on PK data.

The ANGPTL3 analysis set will include all participants who have at least one available valid (i.e., not flagged for exclusion) ANGPTL3 concentration measurement.

The IG analysis set will include all participants who received study drug, have at least one available valid (i.e., not flagged for exclusion) IG measurement, and for whom there are no protocol deviations with impact on IG data.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for the FAS and 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 selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized separately by system organ class and preferred term, by treatment group.

12.3 Treatments

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

The number of visits with active and placebo injections received will be presented by treatment group. The duration of exposure to study treatment will also be summarized by treatment group.

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

12.4 Analysis of the primary endpoint(s)/estimand(s)

12.4.1 Definition of primary endpoint(s)/estimand(s)

The primary efficacy variable is change from baseline in cartilage thickness in the cMTFC at Week 104 determined by qMRI of the target knee in participants with knee OA. The analysis of the primary variable will be based on the FAS population.

12.4.2 Statistical model, hypothesis, and method of analysis

The null statistical hypothesis being tested is that there is no difference between each of the LNA043 regimens versus Placebo in the mean change from baseline in cartilage thickness of the cMTFC at Week 104.

Let μ_j denote the mean change from baseline in cartilage thickness of the cMTFC at Week 104 for treatment regimens $j, j = 0, 1, 2, 3$ or 4 where

- 0 corresponds to Placebo
- 1 corresponds to LNA043 CCI mg CCI, Cycle every CCI
- 2 corresponds to LNA043 CCI mg CCI and CCI, Cycle every CCI
- 3 corresponds to LNA043 CCI mg CCI followed CCI later (after first injection) by CCI, Cycle every CCI
- 4 corresponds to LNA043 CCI mg CCI, Cycle every CCI

In statistical terms, H_j: $\mu_j \leq \mu_0$, H_{Aj}: $\mu j > \mu_0$,

H_1: LNA043 CCI mg CCI, Cycle every CCI is not different to Placebo with respect to mean change from baseline in cartilage thickness of the cMTFC at Week 104

H_2: LNA043 CCI mg CCI and CCI, Cycle every CCI is not different to Placebo with respect to mean change from baseline in cartilage thickness of the cMTFC at Week 104

H_3: LNA043 CCI mg CCI followed CCI later (after first injection) by CCI, Cycle every CCI is not different to Placebo with respect to mean change from baseline in cartilage thickness of the cMTFC at Week 104

H_4: LNA043 CCI mg CCI, Cycle every CCI is not different to Placebo with respect to mean change from baseline in cartilage thickness of the cMTFC at Week 104

The primary analysis will be conducted using mixed-effect model repeated measures (MMRM) which is valid under the missing at random (MAR) assumption, with treatment and analysis visit as factors and baseline score as a covariate in the model. Treatment by analysis visit and baseline score by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for this model. The significance of the treatment effects for LNA043 regimens at Week 104 will be determined from the pairwise comparisons using the Dunnett test performed between LNA043 regimens and placebo at α =0.05.

12.4.3 Handling of remaining intercurrent events of primary estimand

The primary analysis will account for the different intercurrent events as explained in the following:

- Treatment discontinuations/disruptions for any reason: data will be censored after treatment discontinuation or first disruption for the primary analysis
- Unforeseen non-adherence in the allowed period of permitted concomitant therapies: data collected after non-adherence in the allowed period of permitted concomitant therapies will be used for the primary analysis

The primary MMRM model implicitly imputes missing data under a missing at random assumption. For analyses, if all post-baseline values are missing then these missing values will not be imputed and this participant will be removed from the analysis, i.e., it might be that the number of participants providing data to the analysis is smaller than the number of participants in the FAS.

12.4.4 Handling of missing values not related to intercurrent event

The primary MMRM model implicitly imputes missing data under a missing at random assumption.

12.4.5 Supplementary analysis

The target population, the primary variable and the summary measure of the supplementary estimand for the supplementary estimand are the same as for the primary estimand. Differently from the primary estimand, the intervention effect for this supplementary estimand is the effect in a treatment policy scenario where participants would not be able to always adhere to study treatment regimen.

The estimation method is the same as for the primary estimand except that data after study treatment discontinuation/disruption for any reason in all treatment arms will be included and missing data will be imputed.

12.4.6 Sensitivity analyses for primary endpoint/estimand

The following sensitivity analysis will be performed for the primary estimand, to assess the robustness of the estimation in the presence of deviations from the assumptions specified in the primary analysis.

The same analysis of covariance (ANCOVA) model as for the primary estimation will be adopted. Intercurrent events will be handled in the same way as in the primary analysis. In the

first step, missing data after study treatment discontinuation/disruption will be imputed in the same way as for the primary analysis. Subsequently, for the active treatment arms these imputed values will be further worsened via the application of increasingly large penalties specified via a sensitivity parameter according to the tipping point method (Permutt 2016).

12.5 Analysis of secondary and safety endpoints/estimands

12.5.1 Efficacy Endpoints

The analysis for all secondary efficacy endpoints will be based on the FAS population.

The change from baseline at Week 104 for the following variables will be analyzed using a similar MMRM model as in the primary analysis:

- WOMAC pain
- WOMAC pain walking on flat surface
- WOMAC function
- Cartilage thickness in the total, medial and lateral TFCs
- Physical function (40-meter fast-paced walk test, 30-second chair stand test, 6-minute walking test)

Response at Week 104 for structural progression in the target knee will be evaluated using a logistic regression model with treatment regimen as a factor.

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, Customized MedDRA Query (CMQ) and preferred term.

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

The on-treatment period lasts from the date of first administration of study treatment up to last administration + 6 months.

Adverse events

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

The number (and percentage) of participants with treatment emergent adverse events (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

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

The number (and proportion) of participants with adverse events of special interest will be summarized by treatment.

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

Vital signs

All vital signs data will be listed by treatment group, participant, 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.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, participant, 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/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

Immunogenicity

All immunogenicity results will be listed by treatment group, participant, and visit/time.

The number and percentage of participants with positive immunogenicity results will be tabulated by treatment group. A participant with multiple positive samples is only counted once.

Acute Inflammatory Reactions (AIR)

Incidence of acute inflammatory reactions (AIRs), defined as increase of pain by 3 points on an 11-points NRS (range 0-10) and a self-reported synovial fluid effusion (i.e., joint swelling) within 3 days following i.a. injection documented in the participant eDiary.

12.5.3 DNA

Exploratory DNA studies are designed to investigate the association between genetic factors (genotypes) and clinical assessments (phenotypes) which are collected during the clinical trial. Without prior evidence of a strong association, a number of possible associations are evaluated with exploratory analyses. A range of statistical tests are used for the analyses. Additional data, from other clinical trials, are often needed to confirm associations. Alternatively, if the number of participants enrolled in the study is too small to complete proper statistical analyses, the data may be combined, as appropriate, with those from other studies to enlarge the dataset for analysis.

Data generated on hypothesis-free platforms will be reported separately (e.g., CSR addendum).

12.6 Analysis of the exploratory endpoints/estimands

The following exploratory efficacy variables are planned to be analyzed using the FAS.

1. Change from baseline in cartilage thickness in the cMTFC assessed by qMRI of the target knee at Weeks CCI .
2. Change from baseline at Weeks CCI in:
   - WOMAC pain
   - WOMAC pain walking on flat surface response
   - WOMAC function
3. Change from baseline in cartilage thickness in the total, medial and lateral TFCs assessed by qMRI at Weeks CCI .
4. Proportion of participants demonstrating at Week CCI structural progression in the target knee defined as:
   - Change above the SDC of cartilage thickness by qMRI
   - Loss of medial minJSW $\geq$ 0.70 mm from baseline by X-ray
5. Change from baseline in physical function at Weeks CCI :
   - 40-meter (4×10m) fast-paced walk test
   - 30-second chair stand test
   - 6-minute walking test
6. Change from baseline in WOMAC total score at Weeks CCI
7. Change from baseline at Weeks CCI in OA disease activity as assessed by the PGIS.
8. OA disease activity at Weeks CCI as assessed by the PGIC.
9. Change from baseline at Weeks CCI in OA disease activity as assessed by the PGA.
10. Change from baseline at Weeks CCI in QoL using:
    - SF-12 v2 physical component summary
    - SF-12 v2 mental component summary
    - Total SF-12 v2 score
11. CCI at Weeks CCI .
12. Change from baseline at Weeks CCI in the following assessments:
    - CCI
13. Change from baseline to Weeks CCI :
    - Fixed-location medial JSW measured on X-ray
    - Medial minJSW measured on X-ray

14. Change from baseline to Weeks CCI
15. Proportion of participants who achieved WOMAC pain MCI CCI
16. Proportion of participants who achieved WOMAC function MCID CCI
17. Proportion of OMERACT-OARSI responders at Weeks CCI
18. Change from baseline to Weeks CCI in actigraphy-derived metrics such as measures of physical activity and mobility parameters.
19. Change from baseline to Week CCI in BSP derived metrics.
20. Change from baseline in CCI
21. Proportion of participants with TKR at CCI .
22. Proportion of participants fulfilling the criteria for VKR at CCI
23. Change over time in biomarker levels.

Analyses may include summary statistics and listings and as appropriate graphical presentations of the original values and the changes from baseline.

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12.6.1 Pharmacokinetics

LNA043 and ANGPTL3 serum concentration data will be listed by treatment, participant, 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.

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. No pharmacokinetic parameters will be calculated in this study as sparse sampling does not allow valid estimation by non-compartmental analysis.

Modeling of the data may be performed as appropriate. During modeling of the pharmacokinetics of the study drugs, the broad principles outlined in the 'FDA Guidance for Industry: Population Pharmacokinetics' will be followed. As the PK data from the current study may be pooled with data from previous studies, the PK modeling will be described and reported separately.

12.7 Interim analyses

When an interim analysis is performed, designated Novartis staff will be unblinded; however, the blinded core Novartis study team will remain blinded until at least the primary efficacy (Week 104) database lock.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

A total of CCI participants per each group is deemed appropriate to achieve adequate power for the primary and key secondary endpoints for this study.

The mean change from baselin

e in cartilage thickness of the cMTFC for placebo at Week 52 is -0.116 mm with the standard deviation of 0.27 for placebo based on the results of the Galapagos and Servier ROCCELLA Phase 2 study, which enrolled a comparable knee OA population (Bernard et al 2020). Cartilage loss is assumed to be constant over a 2-year period as shown in the sprifermin trial (Hochberg et al 2019), therefore a -0.23 mm mean change from baseline in cartilage thickness of the cMTFC for placebo at Week 104 is used for this study. Assuming that at the very least LNA043 stops further cartilage degradation compared to placebo, a treatment difference of 0.23 mm in favor of LNA043 with a common standard deviation of CCI will be observed at Week 104, a sample size of CCI participants in each treatment group yields approximately CCI power at α =0.05 (one-sided) using Dunnett contrasts (Addplan DF 4.0.9).

12.8.2 Secondary endpoint(s)

As it is also important to show an effect on a clinical endpoint, a sample size calculation was done using the WOMAC pain subscale. It was shown in the EUFLEXXA trial (Altman et al 2009) that a change from baseline at Week 26 using intra-articular saline demonstrated a mean of 16.3 mm with standard deviation of 26.8 on the WOMAC pain subscale. A treatment difference of CCI in favor of LNA043 at Week 104 will need a sample of CCI power at α=0.05 (one-sided) using Dunnett contrasts (Addplan DF 4.0.9). Considering a CCI dropout rate, a sample size of CCI participants in each treatment group will be needed.

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 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, participant recruitment procedures (e.g. advertisements) and any other written information to be provided to participants. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis

monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the Investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

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

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided 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 participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an Investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the Investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

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

14.1 Protocol amendments

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

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

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

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16 Appendices

16.1 Appendix 1: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-1 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*
If ALT or AST abnormal at baseline:	• ALT or AST > 3x baseline AND > 5x ULN
*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; non-infectious hepatitis; benign, malignant and unspecified liver neoplasms ULN: upper limit of normal	

Table 16-2 Follow up requirements for liver laboratory triggers with liver symptoms

ALT	TBL	Liver Symptoms	Action
ALT increase without bilirubin increase:			
If normal at baseline: ALT > 5 x ULN for more than two weeks OR ALT > 8 x ULN	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	• **Interrupt study treatment** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin and CK in 48-72 hours. • Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies. • Study treatment can be restarted if liver enzymes return to baseline.
If elevated at baseline: ALT > 3 x baseline AND > 5x ULN for more than two weeks OR ALT ≥ 5x baseline AND ≥ 8x ULN			
ALT increase with bilirubin increase:			
If normal at baseline: ALT > 3 x ULN	TBL > 2 x ULN (or INR > 1.5) For participants with Gilbert's syndrome:	None	
If elevated at baseline: ALT > 2 x baseline			

ALT	TBL	Liver Symptoms	Action
AND > 3x ULN	Doubling of direct bilirubin		
If normal at baseline: ALT > 3 x ULN	Normal or elevated *	Severe fatigue, nausea, vomiting, right upper quadrant pain*	
If elevated at baseline: ALT > 2 x baseline AND > 3x ULN			
* This situation suggests liver injury based on (i) elevation of ALT, and (ii) the presence of symptoms of liver injury. Even if bilirubin is normal, the presence of liver symptoms indicates potentially severe liver injury.			

16.2 Appendix 2: Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-3 Specific Renal Alert Criteria and Actions

Renal Event	Actions
Confirmed serum creatinine increase 25 – 49%	• Consider causes and possible interventions • Repeat laboratory values within 48 hrs of receipt of abnormal test results. Assess patient for signs and symptoms of illness, AKI, etc. .
Serum creatinine increase ≥ 50 % *	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Repeat laboratory values within 48 hrs of receipt of abnormal test results. Assess patient for signs and symptoms of illness, AKI, etc. • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider referral to nephrologist for diagnosis and management • Consider patient hospitalization and specialized treatment
New onset dipstick proteinuria ≥ 3+ OR Protein-creatinine ratio (PCR) ≥ 1g/g C	• Confirm presence of true proteinuria by quantification: protein:creatinine on first morning void • Consider causes and possible interventions • Assess serum albumin & serum total protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider referral to a nephrologist
New onset hematuria ≥ 3+ on urine dipstick	• Obtain urine microscopy to distinguish hemoglobinuria or myoglobinuria from hematuria • Assess sCr • Exclude infection, trauma, calculi, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder
* Corresponds to KDIGO criteria for Acute Kidney Injury	

Additional specialized assessments are available to assess renal function or renal pathology. *(Note: In exceptional cases, when a nephrologist considers a renal biopsy, it is recommended to make histology images available for evaluation by the RSG to potentially identify project-wide patterns of nephrotoxicity.)*

Whenever a renal event is identified, a detailed patient history and examination are indicated to identify and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (sitting after 5-minute rest, with an appropriate cuff size; consider orthostatic evaluation)

- Signs and symptoms like fever, headache, shortness of breath, cardiac murmur, back or abdominal pain, hepatomegaly, dysuria or hematuria, dependent or periorbital edema
- Changes in body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other diseases or causes, e.g., dehydration due to delirium, tumor lysis

Table 16-4 Renal Event Follow up

FOLLOW-UP OF RENAL EVENTS
· Event resolution: (sCr within 10% of baseline or protein-creatinine ratio (PCR) < 1 g/g Cr, or ACR <300 mg/g Cr), or
· Event stabilization: sCr level with ±10% variability over last 6 months or PCR stabilization at a new level with ±50% variability over last 6 months.
· Analysis of urine markers in samples collected over the course of the DIN event

16.3 Appendix 3: American College of Rheumatology Criteria for the Classification and Reporting of Osteoarthritis of the Knee

Table 16-5 Summary of Criteria for Classification of Idiopathic Osteoarthritis of the Knee*

Clinical and Laboratory	Clinical and Radiographic	Clinical†
Knee pain + at least 5 of 9: • Age > 50 years • Stiffness < 30 minutes • Crepitus • Bony tenderness • Bony enlargement • No palpable warmth • ESR < 40 mm/hour • RF < 1:40 • SF OA	Knee pain + at least 1 of 3: • Age > 50 years • Stiffness < 30 minutes • Crepitus • Osteophytes	Knee pain + at least 3 of 6: • Age > 50 years • Stiffness < 30 minutes • Crepitus • Bony Tenderness • Bony enlargement • No palpable warmth
92% sensitive	91% sensitive	95% sensitive
75% specific	86% specific	69% specific

* Altman et al 1986

ESR = erythrocyte sedimentation rate (Westergren); RF = rheumatoid factor; SF OA = synovial fluid signs of OA (clear, viscous, or white blood cell count < 2,000/mm3).

† Alternative for the clinical category would be 4 of 6, which is 84% sensitive and 89% specific.

16.4 Appendix 4: Guidelines for administering the questionnaires for patient reported outcomes

Before study start

Study coordinators should familiarize themselves with the PRO questionnaire(s) in the study and identify any items where a participant's response might highlight issues of potential concern.

Before completion

1. Subjects should be provided with the correct questionnaire at the appropriate visits and in the appropriate language.
2. Subjects should have adequate space and time to complete the forms.
3. Questionnaire administered at site should be administered before the clinical examination.

During completion

1. Administrator may clarify the questions but should not influence the response.
2. Only one response for each question.
3. Also see "Addressing Problems and Concerns".

After completion

1. Check for completeness and not for content*.
2. Check for multiple responses that were made in error.

*However, any response which may directly impact or reflect the participant's medical condition (e.g., noting of depression) should be communicated by the study coordinator to the Investigator).

Addressing problems and concerns

Occasionally a participant may have concerns or questions about the questionnaires administered. Guidance related to some of the most common concerns and questions are given below.

The participant does not want to complete the questionnaire(s)

Tell the participant that completion of the questionnaire(s) is voluntary. The goal is to better understand the physical, mental and social health problems of participants. Emphasize that such information is as important as any other medical information and that the questionnaire(s) is simple to complete. Suggest that the questionnaire(s) may be different from anything the respondent has filled in the past. If the participant still declines, retrieve the questionnaires. Record the reason for the decline and thank the participant.

The participant is too ill or weak to complete the questionnaire(s)

In these instances, the coordinator may obtain participant responses by reading out loud each question, followed by the corresponding response categories, and entering the participant's response. No help should be provided to the participant by any person other than the designated study coordinator. The coordinator should not influence participant responses. The study coordinator cannot translate the question into simpler language and has to be read verbatim.

The participant wants someone else to complete the questionnaire(s)

In no case should the coordinator or anyone other than the participant provide responses to the questions. Unless specified in the study protocol, proxy data are *not* an acceptable substitute for participant self-report. Participants should be discouraged from asking a family member or friend for help in completing a questionnaire.

The participant does not want to finish completing the questionnaire(s)

If non-completion is a result of the participant having trouble understanding particular items, ask the participant to explain the difficulty. Re-read the question for them *verbatim* but do not rephrase the question. If the respondent is still unable to complete the questionnaire, accept it as incomplete. Thank the participant.

The participant is concerned that someone will look at his/her responses

Emphasize that all responses are to be kept confidential. Point out that their names do not appear anywhere on the questionnaire, so that their results will be linked with an ID number and not their name. Tell the participant that his/her answers will be pooled with other participants' answers and that they will be analyzed as a group rather than as individuals. Tell the participant that completed forms are not routinely shared with treating staff and that their responses will only be seen by you (to check for completeness) and by the Investigator. Any response which may directly impact on or reflect their medical condition (e.g., noting of severe depression) will be communicated by the coordinator to the physician.

The participant asks the meaning of a question/item

While completing the questionnaire, some participants might ask the meaning of specific items so that they can better understand and respond. If this happens, assist the participant by rereading the question for them *verbatim*. If the participant asks to interpret the meaning of an item, do not try to explain it, but suggest that he/she use his/her own interpretation of the question. Participants should answer the questions based on what *they* think the questions mean.

General information about all questionnaire(s):

All questionnaires have to be completed by the participants in their local languages using an electronic device. The questionnaires should be completed by the participants in a quiet area free from disturbance, and before any visit assessments. Participants should receive no help from family members; if questions cannot be answered alone (due to problems with reading or understanding), then the doctor or nurse should read the questions and record the participant's

responses without influencing their answers. The information provided is strictly confidential and will be treated as such. If a participant has missed a question or given more than one response per question, then this should be brought to participant. Incomplete questions should not be accepted without first encouraging the participant to complete unanswered questions.

The Investigator must complete the participant/visit information on the electronic device and ensure that the center number, participant's number and initials are identical to the Case Record Form. As there are no source data for this questionnaire, the data queries will be restricted to participant/visit information.

16.5 Appendix 5: Patient Global Impression of Severity and Patient Global Impression of Change

Patient Global Impression of Severity of Knee Pain during 6 Minute Walking Test

Please choose the response below that best describes the severity of your **knee pain** while performing the 6 minutes walking test today.

□ None

□ Mild

□ Moderate

□ Severe

Patient Global Impression of Severity of Knee Pain during 40 meters Fast-Paced Walk Test

Please choose the response below that best describes the severity of your **knee pain** while performing the 40 meters fast-paced walk test today.

□ None

□ Mild

□ Moderate

□ Severe

Patient Global Impression of Severity of Knee Pain during 30-second Chair Stand Test

Please choose the response below that best describes the severity of your **knee pain** while performing the 30-second chair stand test today.

□ None

□ Mild

□ Moderate

□ Severe

Patient Global Impression of Change in Knee Pain during 6 Minute Walking Test

Please choose the response below that best describes the overall change in your **knee pain** while performing the 6 minutes walking test compared to when you started taking the study treatment (select one response).

□ Much better

□ A little better

□ No change

□ A little worse

□ Much worse

Patient Global Impression of Change during 40 meters Fast-Paced Walk Test

Please choose the response below that best describes the overall change in your **knee pain** while performing the 40 meters fast-paced walk test compared to when you started taking the study treatment (select one response).

□ Much better

□ A little better

□ No change

□ A little worse

□ Much worse

Patient Global Impression of Change of Knee Pain during 30-second Chair Stand Test

Please choose the response below that best describes the overall change in your **knee pain** while performing the 30-second chair stand test compared to when you started taking the study treatment (select one response).

□ Much better

□ A little better

□ No change

□ A little worse

□ Much worse

16.6 Blood collection log

Refer to the central laboratory manual for sample collection, preparation and shipping information.

Table 16-6 Sample log: Time schedule for sampling of LNA043 PK, ANGPTL3 and anti-drug antibody

Period	Visit Name	Time (post-dose)	LNA043 PK blood collection			ANGPTL3 blood collection		Anti-drug antibody to LNA043	
			Size (mL)	Dose Ref ID.	Sample No.	Size (mL)	Sample No.	Size (mL)	Sample No.
Core Period	CCI	pre-dose	2	1	101	2	201	3.5	301
		15±5 min*	2	1	102				
		120±15 min	2	1	103	2	202		
	CCI	pre-dose	2	3	104	2	203	3.5	302
		15±5 min*	2	3	105				
		120±15 min	2	3	106	2	204		
	CCI	pre-dose						3.5	303

Period	Visit Name	Time (post-dose)	LNA043 PK blood collection			ANGPTL3 blood collection		Anti-drug antibody to LNA043	
			Size (mL)	Dose Ref ID.	Sample No.	Size (mL)	Sample No.	Size (mL)	Sample No.
	CCI	pre-dose						3.5	304
	CCI	pre-dose							
		15±5 min*	2	7	107				
		120±15 min	2	7	108	2	205		
	CCI	pre-dose						3.5	305
		15±5 min*	2	9	109				
		120±15 min	2	9	110	2	206		
	CCI	pre-dose						3.5	306
	CCI	pre-dose						3.5	307
		15±5 min*	2	13	111				
		120±15 min	2	13	112	2	207		
Extension Period	CCI	pre-dose						3.5	308
	CCI							3.5	309
Extension Period – Follow-up	CCI							3.5	310
Unscheduled			2		1101 1102 1103 1104			3.5	1301 1302 1303 1304

* Post-dose at 15±5 min is at the selected sites only.