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LNA043

Clinical Trial Protocol CLNA043X2202 / NCT03275064

A two-part randomized, placebo-controlled, patient and investigator blinded, Proof of Concept study investigating the safety, tolerability and preliminary efficacy of multiple intra-articular LNA043 injections in regenerating the articular cartilage of the knee in patients with articular cartilage lesions (Part A) and in patients with knee osteoarthritis (Part B)

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Site Operations Manual (SOM)

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

Notification of serious adverse events

Dear Investigator,

You must report a serious adverse event (SAE) (initial or follow-up) to Novartis as summarized below. Refer to Section 9.2 of the protocol for SAE criteria and additional requirements. See also page 2 of the Site Operations Manual for further details on the method of reporting a SAE.

- Complete SAE report
- Submit SAE report to Novartis Chief Medical Office & Patient Safety (CMO&PS) **within 24 hours after awareness of the SAE**
- Notify the Novartis Medical Lead
- The fax number(s) and email address(es) are located in the Site Operations Manual.

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List of abbreviations

ACI	Autologous Chondrocyte Implantation
ACR	American College of Rheumatology
ADA	Anti-Drug Antibody
ADL	Activities of Daily Living
AE	adverse event
AESIs	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANGPLT3	angiopoietin-like 3 protein
AST	aspartate aminotransferase
BMI	Body Mass Index
BP	Blood Pressure
BUN	blood urea nitrogen
CFR	U.S. Code of Federal Regulation
CK	creatinine kinase
CMO&PS	Chief Medical Office & Patient Safety
COAR	Clinical Operations, Analytics & Regions
CR-MSCs	Cartilage Resident Mesenchymal Stem Cells
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTC	Common Toxicity Criteria
CV	coefficient of variation
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EoS	End of study
FIH	First in human
GAG	Glycosaminoglycans
GCP	Good Clinical Practice
GLP	Good laboratory practice

GGT	Gamma-glutamyl transferase
h	hour
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	human immunodeficiency virus
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i.a.	intra-articular
i.v.	intravenous
IA	Interim Analysis
IB	Investigator's Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICRS	International Cartilage Repair Society
IEC	Independent Ethics Committee
IG	Immunogenicity
IHC	Immunohistochemistry
IN	Investigator Notification
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine System
JSW	Joint Space Width
K&L	Kellgren and Lawrence
kg	kilogram(s)
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LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MMRM	Mixed Model Repeated Measures
MRI	Magnetic Resonance Imaging
MSC	mesenchymal stem cells

NIRT	Novartis Interactive Response Technology
NSAIDs	Nonsteroidal anti-inflammatory drugs
OA	Osteoarthritis
PA	posteroanterior
PCR	Protein-creatinine ratio
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PoC	Proof of Concept
PoM	Proof of Mechanism
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QoL	Quality of Life
RBC	red blood cell(s)
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
sCR	serum creatinine
SD	standard deviation
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
TKR	Total Knee Replacement
ULN	upper limit of normal
WBC	white blood cell(s)
WHO	World Health Organization
WOCBP	Women of child bearing potential

Pharmacokinetic definitions and symbols

Ae0-t	Amount of drug (or defined metabolite) excreted into the urine from time zero to time 't' where t is a defined time point after administration [mass units or % of dose]
AUC0-t	The area under the plasma (or serum or blood) concentration-time curve from time zero to time 't' where t is a defined time point after administration [mass x time / volume]
AUCinf	The area under the plasma (or serum or blood) concentration-time curve from time zero to infinity [mass x time / volume]
AUClast	The area under the plasma (or serum or blood) concentration-time curve from time zero to the time of the last quantifiable concentration [mass x time / volume]
AUCtau	The area under the plasma (or serum or blood) concentration-time curve from time zero to the end of the dosing interval tau [mass x time / volume]
AUCtau,ss	The area under the plasma (or serum or blood) concentration-time curve from time zero to the end of the dosing interval tau at steady state [mass x time / volume]
Cav,ss	The average steady state plasma (or serum or blood) concentration during multiple dosing
CL	The systemic (or total body) clearance from plasma (or serum or blood) following intravenous administration [volume / time]
CL/F	The apparent systemic (or total body) clearance from plasma (or serum or blood) following extravascular administration [volume / time]
CLr	The renal clearance from plasma (or serum or blood) [volume / time]
Cmax	The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume]
Cmax,ss	The observed maximum plasma (or serum or blood) concentration following drug administration at steady state [mass / volume]
Cmin,ss	The lowest plasma (or serum or blood) concentration observed during a dosing interval at steady state [mass / volume]
F	Bioavailability of a compound. Fabs is the absolute bioavailability, i.e. the fraction (or percentage) of the administered extravascular dose systemically available. Frel is the relative bioavailability, i.e. the bioavailability relative to a reference
MRT	Mean residence time determined as AUMCinf/AUCinf following intravenous administration [time]
Racc	The accumulation ratio
T1/2	The terminal elimination half-life [time]

T1/2,acc	The effective half-life based on drug accumulation at steady state [time]
Tmax	The time to reach the maximum concentration after drug administration [time]
Vss	The volume of distribution at steady state following intravenous administration [volume]
Vz	The volume of distribution during the terminal elimination phase following intravenous administration [volume]
Vz/F	The apparent volume of distribution during the terminal elimination phase following extravascular administration [volume]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Any drug(s) (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
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)
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.
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.
Patient	An individual with the condition of interest
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
Screen Failure	A subject who is screened but is not treated or randomized
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 drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
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	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

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Protocol synopsis

Protocol number	CLNA043X2202
Title	A two-part, randomized, placebo-controlled, patient and investigator blinded, Proof of Concept study investigating the safety, tolerability and preliminary efficacy of multiple intra-articular LNA043 injections in regenerating the articular cartilage of the knee in patients with articular cartilage lesions (Part A) and in patients with knee osteoarthritis (Part B).
Brief title	Study of safety, tolerability and preliminary efficacy of multiple intra-articular LNA043 injections in patients with articular cartilage lesions (Part A) and in patients with knee osteoarthritis (OA) (Part B).
Sponsor and Clinical Trial Phase	Novartis Phase 2
Intervention type	Biologic
Study type	Interventional
Purpose and rationale	The purpose of this study is to assess the efficacy, safety and tolerability of multiple intra-articular (i.a.) injections of LNA043, in regenerating the articular surface in patients with cartilage lesions of the knee. This study aims to establish Proof of Concept (PoC), namely regeneration of the articular cartilage, in order to provide information on the potential clinical utility of LNA043, with the ultimate goal of replacing current surgical procedures for cartilage repair with an injectable, less invasive regenerative therapy. Both lesions of the femoral condyles and patella will be considered, in order to address a broad population and maximize the clinical relevance of this study (Part A). In Part B patients with medial femoral disease will be enrolled to evaluate the efficacy of LNA043.
Primary Objective(s)	To assess the efficacy of multiple i.a. injections of LNA043 in regenerating the articular cartilage tissue To assess safety and local tolerability of multiple i.a. injections of LNA043
Secondary Objectives	To assess the extent of the repair cartilage tissue following multiple i.a. injections of LNA043 To evaluate systemic and local PK of LNA043 following multiple i.a. injections of LNA043 To assess the potential immunogenicity of LNA043
Study design	This is a non-confirmatory, two-part, randomized, placebo-controlled, patient and investigator blinded study
Population	The study population will be comprised of approximately 60 male and female patients with symptomatic partial thickness (ICRS grade II-IIIA) cartilage lesions of one knee in Part A, and approximately 75 male and female patients with knee OA (Kellgren&Lawrence score of 2-3) in Part B. In total, approximately 135 patients are expected to be randomized into the study.

Key Inclusion criteria	• **Part A:** Patient is ≥18 and ≤55 years old at time of screening. **Part B**: Patient is ≥18 and ≤75 years old at time of screening. • **Part A:** Patient has a body mass index (BMI) <30 kg/m^2 at screening, for patients with a BMI >30 but ≤ 33 kg/m^2, eligibility will be decided by consultation with the sponsor. **Part B**: Patient has a body mass index (BMI) ≤35 kg/m^2 at screening. • **Part A ONLY:** Patient has a symptomatic, single, articular cartilage defect of one knee, grade II or IIIA according to the ICRS classification, localized to either the femoral condyles/femoral trochlea or to the patella, based on MRI or arthroscopy performed within 9 months before screening visit and confirmed by screening 3T MRI. • **PART A ONLY:** Patient has an onset of pain and impairment of function between two (2) months and two (2) years before screening. • Commercially Confidential Information • **Part B ONLY:** Diagnosis of femorotibial OA in the target knee • **Part B ONLY:** K&L grade 2 or 3 OA of the knee with minimum Joint Space Width (JSW) 2.00-4.00 mm at screening • **Part B ONLY:** History of pain due to OA in the target knee for at least 6 months at screening
Key Exclusion criteria	• Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 15 days after stopping of investigational drug. • **Part A:** Regular smokers (> 5 cigarettes/day). Urine cotinine levels will be measured during screening for all patients. Regular smokers will be defined as any patient who reports tobacco use of > 5 cigarettes/day and/or who has a urine cotinine ≥ 500 ng/mL. **Part B:** Regular smokers (> 10 cigarettes/day). • **PART A ONLY:** Patient has radiologically apparent degenerative joint disease in the target knee as determined by Kellgren and Lawrence grade ≥2 based on X-ray evaluation performed within 9 months from screening. • Patient has had surgical treatment of the target knee using mosaicplasty, microfracture, meniscectomy >50% (Note: prior diagnostic arthroscopy with debridement and lavage, <50% meniscectomy, lateral release, patellar realignment, medial patellofemoral ligament reconstruction are acceptable if performed at least 2 months prior to screening; anterior cruciate ligament reconstruction is acceptable if performed 12 months prior to screening, or less if restoration of joint function is evident, and agreed by the sponsor). • Patient has an unstable target knee joint (including but not limited to posttraumatic or congenital laxity) or insufficiently reconstructed ligaments based on medical history and physical examination by the investigator. • **PART A ONLY:** Patient has patellofemoral dysplasia Dejour Grade B-D based on X-ray or MRI evaluation • Patient has malalignment (valgus- or varus-deformity) in the target knee ≥ 5° (Part A) or > 7.5° (Part B) based on X-ray evaluation at screening. In suspected cases, the mechanical axis must be established radiographically through complete leg imaging during standing and in postero-anterior (PA) projection.

	• **Part B ONLY:** Clinical signs of inflammation in the target knee • **Part B ONLY:** History of knee replacement in either knee • **Part B ONLY:** Presence of severe hip OA conditioning lower limb function • **Part B ONLY:** Nephrotic syndrome and/or significant proteinuria • **Part B ONLY:** History of coagulopathy or medical condition requiring anticoagulation which would preclude knee injection (antiplatelet or anticoagulant treatment [for patients using warfarin, INR to be <3 prior to injection], is allowed)
Study treatment	**Part A:** • Single i.a. injection of 20 mg [LNA043], CCI • Single i.a. injection of placebo to 20 mg [LNA043], CCI **Part B:** • Single i.a. injection of 40 mg [LNA043], CCI • Single i.a. injection of 20 mg [LNA043], CCI • Single i.a. injection of placebo, CCI
Efficacy/PD assessments	**Part A:** • Articular cartilage bi-layer collagen organization evaluated with T2 relaxation times measured in superficial and deep layers by T2 mapping MRI **Part B:** • Change in volume of cartilage defect filling evaluated with MRI
Key safety assessments	• Adverse event monitoring • 3 hours observation period post every i.a. LNA043 administration • Physical examination • Monitoring of laboratory markers in blood and urine
Other assessments	• Commercially Confidential Information
Data analysis	The primary efficacy variable in Part A, articular cartilage bi-layer collagen organization, assessed based on MRI at Week 16 and 28, and the primary efficacy variable in Part B, change from baseline in volume of cartilage defect filling evaluated with MRI at Weeks 28 and 52, will be analyzed using a mixed model with repeated measures (MMRM), including baseline and both time points to compare treatment groups at Week 16 and Week 28
Key words	Articular cartilage, partial thickness cartilage lesion, knee, cartilage regeneration

1 Introduction

1.1 Background

When articular cartilage damage occurs, healing is limited. Currently, there is no approved pharmacological treatment to regenerate durable hyaline cartilaginous tissue, capable of withstanding joint stress and supporting an active life style. Current surgical procedures (*e.g.*, microfracture) typically lead to fibrous, fibrocartilaginous and/or calcified repair tissue with limited biochemical and biomechanical properties. Clinical evidence has also shown that untreated focal defects of the articular cartilage may progress, leading to osteoarthritis (OA) and requiring joint replacement later in life, with potentially unsatisfactory outcomes for the patients and high costs for the community. Therefore, there is a high unmet medical need for more effective and efficient ways of repairing the articular cartilage, in order to intervene earlier, less invasively and stop the disease progression to OA.

Articular cartilage has limited healing potential. During cartilage damage, the number of cartilage resident mesenchymal stem cells (CR-MSCs) increases. CR-MSCs are capable of multi-lineage differentiation, including chondrogenesis, when exposed to an appropriate signaling environment in vitro. The LNA043 program arose from an effort to identify molecules able to target CR-MSCs to undergo differentiation into chondrocytes and facilitate hyaline articular cartilage repair by inducing the production of SOX9, type II collagen and aggrecan, but not inducing fibrosis or osteogenesis. LNA043 is a modified, recombinant version of the human angiopoietin-like 3 (ANGPTL3) protein, comprising its C-terminal domain. LNA043 acts directly on CR-MSCs and articular chondrocytes through binding to α5β1 and αVβ3 integrins (RGD class) on the cell surface to transmit its anabolic repair effects on cartilage cells. These events promote the formation of articular cartilage extracellular matrix proteins in mature chondrocytes and in CR-MSCs while supporting re-growth of CR-MSCs.

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Considering the previous CCI clinical experience, and the lack of a disease-modifying treatment for these patients, a favorable benefit/risk ratio is anticipated for the patients included in the present study.

The most relevant data for the present study are summarized in the sections below. For detailed information, please refer to the Investigator's Brochure.

1.2 Nonclinical data

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1.3 Clinical data

1.3.1 Human safety and tolerability data

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In Part A of the ongoing PoC LNA043X2202 study, no deaths, drug-related SAEs or discontinuations due to adverse events were reported following weekly repeat doses of 20mg with cut-off date 31-Jan-2020. A higher incidence of study drug-related AEs was reported for LNA043 (Table 1-1). The 3 severe AEs for LNA043 were headache and 2 back pain, while the one for placebo was hypertension. Commercially Confidential Information

Table 1-1 Overall incidence of AE in LNA043X2202 Part A

AEs, Subjects with AEs	LNA043 20 mg N=43 nE, nS (%)	Placebo N=15 nE, nS (%)	Total N=58 nE, nS (%)
AEs, Any	51, 23 (53.5)	10, 7 (46.7)	61, 30 (51.7)
AEs of mild toxicity	27, 16 (37.2)	5, 4 (26.7)	32, 20 (34.5)
AEs of moderate toxicity	21, 13 (30.2)	4, 4 (26.7)	25, 17 (29.3)
AEs of severe toxicity	3, 3 (7.0)	1, 1 (6.7)	4, 4 (6.9)
Study drug-related AEs	17, 10 (23.3)	1, 1 (6.7)	18, 11 (19.0)
Serious AEs	1, 1 (2.3)	0	1, 1 (1.7)
AEs leading to discontinuation of study treatment	0	0	0

A higher incidence of joint swelling (9.3% vs 0%) and arthralgia (11.6% vs 6.7%) is reported for LNA043 (Table 1-2). 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. This is also consistent with the AE-incidence of i.a. hyaluronans and of similar i.a. biologics (e.g., sprifermin) (Hochberg et al 2019). No AEs compatible with hypersensitivity reactions have been reported. No anti-LNA043 antibodies were detected in any of the tested samples.

Table 1-2 Incidence of AE in LNA043X2202 Part A by preferred term (greater or equal to 2 events)

	LNA043 20mg N= 43 n (%)	Placebo N= 15 n (%)	Total N= 58 n (%)
Subjects with at least one AE(s)	23 (53.5)	7 (46.7)	30 (51.7)
Arthralgia	5 (11.6)	1 (6.7)	6 (10.3)
Headache	5 (11.6)	1 (6.7)	6 (10.3)
Joint Swelling	4 (9.3)	0	4 (6.9)
Back Pain	2 (4.7)	1 (6.7)	3 (5.2)
Upper Respiratory Tract Infection	2 (4.7)	1 (6.7)	3 (5.2)

1.3.2 Human pharmacokinetic data

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1.3.3 Human pharmacodynamic data

The CLNA043X2201 study is completed and has been performed in patients undergoing Autologous Chondrocyte Implantation (ACI) to treat a cartilage lesion. LNA043 was administered i.a. right after the end of the first surgery and the donor site was monitored with Magnetic Resonance Imaging (MRI) at 4- and 12-week to detect cartilage regeneration at this site. Both the extent of tissue growth and the quality of tissue composition were evaluated with 7 Tesla MRI. 7 Tesla MRI scanners are needed to perform a compositional evaluation of the proteoglycan component of the cartilage extracellular matrix. Analysis of data showed that, at both time points, tissue compatible with early hyaline cartilage was detected at the donor site. Most of the cartilage regeneration occurred within the first 4 weeks, with a minimal further improvement from 4 to 12 weeks, suggesting a longer pharmacodynamic (PD) effect of LNA043.

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1.4 Study purpose

The purpose of this two-part study is to assess the efficacy, safety and tolerability of multiple intra-articular (i.a.) injections of LNA043, in regenerating the articular surface in patients with cartilage lesions of the knee (Part A) and knee osteoarthritis (Part B).

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In Part A, this study aims to establish Proof of Concept (PoC), namely regeneration of the articular cartilage, in order to provide information on the potential clinical utility of LNA043, with the ultimate goal of replacing current surgical procedures for cartilage repair with an injectable, less invasive regenerative therapy. Both lesions of the femoral condyles and patella will be considered, in order to address a broad population and maximize the clinical relevance of this study. In Part B, this study aims at further evaluating the cartilage anabolic activity of LNA043 in a more severe knee OA population, and at testing the potential benefit of a higher dose of LNA043 administered i.a. monthly instead of weekly. This study will support the further development of LNA043 in a broader clinical setting and with different dose regimens.

2 Study objectives and endpoints

2.1 Primary objective(s)

Primary objective(s)	***Endpoints related to primary objective(s)***
• To assess the efficacy of multiple i.a. injections of LNA043 in regenerating the articular cartilage tissue	• Articular cartilage bi-layer collagen organization evaluated with T2 relaxation times measured in superficial and deep layers by T2 mapping Magnetic Resonance Imaging (MRI) at Week 16 and 28 (Part A) • Change in cartilage volume/thickness in the index region at Week 28 and 52 (Part B)
• To assess safety and local tolerability of multiple i.a. injections of LNA043	• Systemic and local Adverse Events • Electrocardiograms (ECGs) • Vital signs • Hematology, blood chemistry, urinalysis

2.2 Secondary objective(s)

Secondary objective(s)	***Endpoints related to secondary objective(s)***
• To assess the extent of the repair cartilage tissue following multiple i.a. injections of LNA043	• Change in volume of cartilage defect filling evaluated with MRI at Week 16 and 28 (Part A) • Articular cartilage bi-layer collagen organization evaluated with T2 relaxation times measured in superficial and deep layers by T2 mapping Magnetic Resonance Imaging (MRI) at Week 28 and 52 (Part B)
• To evaluate systemic and local PK of LNA043 following multiple i.a. injections of LNA043	• Serum and synovial fluid PK profile of LNA043 and ANGPTL3
• To assess the potential immunogenicity of LNA043	• Presence and characterization of anti-LNA043 antibodies in serum at Day 1, Day 15, Day 50, Day 106 and Day 190 (Part A) and Day 1, Day 29, Day 57, Day 85, Day 113, Day 197 and Day 365 (Part B)

2.3 Exploratory objective(s)

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3 Investigational plan

3.1 Study design

3.1.1 Part A

This is a non-confirmatory, randomized, placebo-controlled, patient and investigator blinded study in patients with a partial thickness cartilage lesion of the knee.

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Following their informed consent, patients will be assessed for eligibility at the screening visit. Whenever possible, the MRI should be performed in advance, or immediately after eligibility assessment on the same day of screening within the screening period (Day -35/-5). Safety laboratory assessments should be performed as close as possible to dosing Day 1.

Investigators may perform an unscheduled visit between Screening and first treatment on Day 1 if deemed to confirm eligibility of the subject, or verify safety.

On Day 1, eligible patients will receive either an i.a. injection of LNA043 (20 mg CCI) or matching placebo (CCI) according to a 3:1 randomization ratio. CCI

At each treatment visit, safety and pharmacokinetics will be assessed as detailed in the Assessment schedule (Table 8-1). The investigator will schedule telephone calls with the patient approximately 48 hours after each study drug administration, and two weeks after the last injection, for follow-up assessment of safety. In case of safety concerns, the patient will return to the hospital for assessment and follow-up.

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The EOS visit assessments should be performed also in case of premature patient discontinuation for any reason (except in case of consent withdrawal).

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3.1.2 Part B

This is a non-confirmatory, randomized, placebo-controlled, patient and investigator blinded study in patients with K&L 2-3 knee OA.

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Following their informed consent, patients will be assessed for eligibility at the screening visit. Investigators may perform an unscheduled visit between Screening and first treatment on Day 1 if deemed to confirm eligibility of the subject, or verify safety.

Screening X-ray will be evaluated by the central reader for eligibility. Baseline MRI will be performed after eligibility has been verified. On Day 1, eligible patients will receive a CCI i.a. injection of either LNA043 20 mg, LNA043 40 mg, or matching placebo according to a 1:1:1 randomization ratio. Commercially Confidential Information During the treatment period, safety and pharmacokinetics will be assessed as detailed in the Assessment schedule (Table 8-2). Patients will be monitored on site 3 hours after the i.a. injections. The investigator will schedule telephone calls with the patient approximately 48 hours after each study drug administration for follow-up assessment of safety. In case of safety concerns, the patient will return to the clinical site for assessment and follow-up.

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3.2 Rationale of study design

The design of this study addresses the primary objective of cartilage healing in patients with articular cartilage defects of the knee and knee OA and takes into account (i) the clinical need; (ii) clinical and preclinical data on LNA043; (iii) current practice with intra-articular injectable drugs; and (iv) the burden on patients with articular cartilage lesions and knee OA. The combination of MRI with cartilage-specific pulse sequences (Juras et al 2016a) Commercially Confidential Information will ensure appropriate evaluation of LNA043 effect, from both a morphological and a functional standpoint.

The study has been designed as patient and investigator blinded in order to ensure that b h investigators and patients remain in a state of equipoise, so that a putative difference betw n the treated and control groups can be interpreted as an effect of study treatment. To evalu e potential unconscious bias at the patient level, patients will be asked at EoS, which treatment they believe they have received. Since the assessment of the envisioned endpoints is independent of the investigator, a comparable evaluation at the investigator level is not planned.

3.2.1 Part A

- Randomization will be 3:1 (treatment:placebo), in order to reduce the number of people exposed to placebo, who will not have the chance for therapeutic benefit.
- Regarding the patient population, both lesions to the patella and to the femoral condyles/trochlea will be addressed. This will allow us to examine LNA043's effect in these two patient groups, characterized by different clinical, morphological and biomechanical features, and by a differential response to surgical procedures (Filardo et al 2014), in order to better inform further development of LNA043. Accordingly, randomization will be stratified by type of lesion (femoral condyle/trochlea or patella).

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- A follow-up period at Week 52 (48 weeks after the last study dose) is considered adequate to evaluate cartilage healing and to better understand the kinetics of cartilage growth, durability of the regenerated tissue and long-term efficacy in this population. (Le Graverand-Gastineau 2010, Raynauld et al 2004)
- Inclusion criteria (*e.g.*, BMI<33, age range 18-55 years), and a limited range of lesion depth (partial thickness lesions), corresponding to grade II-IIIA according to the International Cartilage repair Society (ICRS) classification) (Brittberg and Winalski 2003), have been selected in order to ensure homogeneity in a small patient sample.

3.2.2 Part B

- Based on the positive results of the CLNA043X2201 study and of this ongoing CLNA043X2202 study (Part A), a broader patient population of knee OA with high medical need patient population is now being evaluated in part B.
- The patient population of knee OA K&L 2-3 with JSW 2.00-4.00mm has been selected based on the post-hoc analysis of the FORWARD trial (Gühring et al 2019),

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- The MRI data collected at different time points will allow for the evaluation of the short- and long-term effect of one monthly cycle of i.a. treatment with LNA043 and a comparison between the 2 doses tested (20 mg and 40 mg). Meanwhile, since the image analysis will cover well-defined regions the articular cartilage throughout the knee as has been done in part A, results from part B, especially those obtained from the 20 mg group, may also be compared with the results from part A to evaluate the potential added benefit of the monthly dosing regimen in the index region (as defined in part B) vs the damaged region (as defined in part A).
- The monthly dosing regimen (x 4) has been selected based on the results of the FIH clinical study, which suggests a long PD effect of LNA043.

3.3 Rationale for dose/regimen, route of administration and duration of treatment

3.3.1 Part A

The dose of LNA043 given in this study will be 20 mg, by i.a. injection

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In conclusion, clinical experience to date with LNA043 indicates that this compound is safe and well-tolerated. A dose of 20 mg has been selected for repeat dosing, once weekly for four weeks, based on safety and feasibility, and in order to maximize the likelihood of delivering a sustained, pharmacodynamic effect on cartilage repair in the knee. Moreover, the proposed dose regimen is also consistent with current non-operative practices for the symptomatic treatment of cartilage lesions, including *e.g.*, i.a. hyaluronan injections which are administered up to five times once-weekly.

3.3.2 Part B

Part B of this study aims to assess a potential incremental treatment benefit of 20 mg/knee vs 40 mg/knee dose CCI . Based on the available clinical data, the 40 mg/dose in Commercially Confidential Information , might have favorable risk-benefit profile compared to the single and repeated weekly dosing regimens tested up to date.

The proposed dosing regimen takes into account that:

- LNA043 displayed a favorable safety profile with no significant drug related safety signals, up to the maximum evaluated dose of 40 mg/knee in the FIH SAD study.
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- Up to date understanding of dose-response characteristics of LNA043 in the targeted population is limited. However, dose dependency of PD responses in the FIH SAD study indicate that the 40 mg/knee dose may be associated with an incremental treatment benefit without major safety and tolerability concerns.
- Importantly, the PD results from FIH SAD, showed upregulation of chondrogenic genes for up to 21 days, indicating lasting effects and monthly dosing regimen seem to be more appropriate to fully elicit potential treatment benefit of LNA043.

In summary, the less frequent, once-monthly administration of LNA043 up to 40 mg/knee is not expected to be associated with an increased safety/tolerability risk but potentially lead to an incremental treatment benefit for treated patients. Importantly, Part B of the study provides essential information for further optimization of the dosing regimen.

3.4 Rationale for choice of comparator

No cartilage-anabolic compound able to promote cartilage healing has been approved so far. Therefore, the comparator will be placebo.

Placebo contains the same formulation and excipients as the investigational drug, without the active agent. Additionally, the study will be performed with identical standard of care procedures in both the control and investigational drug arms.

3.5 Purpose and timing of interim analyses/design adaptations

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3.6 Risks and benefits

It is not known whether there will be a benefit for the patients participating in this study. However, data from the completed and ongoing studies demonstrate a cartilage anabolic activity of LNA043, with the potential to regenerate the articular cartilage of the knee. No disease modifying therapy exists as standard of care for patients with articular cartilage damage, including from osteoarthritis. Therefore, no such therapies will be withheld by joining this study. The risk to patients in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, and stopping rules.

Invasive, study-specific procedures include synovial fluid aspiration and i.a. injection of LNA043: as with any intra-articular injection, a risk of iatrogenic infection exists. Recent reports found infection rates following i.a. injection of steroids between 1 in 3000 and 1 in 50,000 (Lavelle et al 2007). However, few orthopedists and rheumatologists have encountered a case of poststeroid 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 supposed to be considerably lower.

Sterile technique will be used in all phases of drug reconstitution and administration to further reduce the risk of infection. Potential adverse effects may include local reactions at the site of injection, such as local pain, swelling or inflammation. Potential adverse events will be monitored clinically. Synovial fluid aspiration will be performed at the same time as the i.a. injection of LNA043, with no additional harm or discomfort for the patient. Systemic concentrations following i.a. administration to the patients studied in the FIH study remained <300 ng/mL and within the physiologic range for circulating concentrations of ANGPTL3. In addition, based on the current data available, LNA043 is not expected to persistently bind to or block its receptors.

Being a modified protein, hypersensitivity and/or immunogenicity to LNA043 may occur.

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In the completed and ongoing clinical studies, no case of local or systemic hypersensitivity reactions have been observed, and no patient developed ADA after a single or multiple intra-articular injection of 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 will be monitored, as well as any potential reactions related to such antibodies, such as antibody-mediated arthropathy or impact on lipid metabolism or renal function, will be monitored closely with the corresponding safety plan in place.

Based on a comprehensive analysis of all safety data from both completed and ongoing preclinical and clinical studies, there is no evidence to suggest that treatment with LNA043 increases the risk of hypersensitivity in humans.

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In order to mitigate this risk in humans, patients with a history of hypersensitivity reactions to any of the study treatments or excipients or to drugs of similar chemical classes will be excluded from participation in this study. Study drug administration will be administered at locations with emergency care facilities, and patients are required to undergo observation for three hours post-injection prior to leaving the site, to ensure their safety. Patients who experience any Grade hypersensitivity reaction must not be re-dosed.

Women of child bearing potential will be informed that taking the investigational drug may involve unknown risks to the fetus if a pregnancy was to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the subject will not reliably comply, they should not be entered in the study.

Risks of imaging procedures

For screening purposes, a standing long leg view of the lower limbs and a Merchant view of the patello-femoral joint are required. These are often performed during the routine evaluation of patients with knee pain, but not always. Consequently, in some patients they will be obtained only for research purposes. The total amount of radiation exposure per subject from these X-rays will be about 100 µSv. This amount of radiation is equivalent to approximately

13.8 days of background exposure (approx. 0.3 µSv per hour at sea level). For effective radiation doses under 3 mSv (300 mrem), the risk is considered to be "minimal". Therefore, the radiation exposure in this study involves minimal risk and is necessary to ensure eligibility of patients.

The only imaging technique used in this study for follow-up purposes is MRI. 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 patient as often as necessary. The MRI scanning equipment may cause a feeling of claustrophobia in susceptible persons. The presence of metal in the body may also be a safety hazard or affect a MRI image quality. For more information, see exclusion criterion 11.

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

Covid-19 risk assessment

Novartis is committed to supporting the safety and well-being of our study participants, investigators, and site staff. All local regulations and site requirements should be applied in the countries that are affected by the COVID-19 pandemic. The Novartis clinical trial team will review the situation in each participating country and work with Investigators to continue to ensure the safety of participants during the conduct of the trial.

A benefit/risk assessment has been made and has been determined to not significantly change for the participants that are planned to be enrolled in the proposed clinical trial. As the COVID-19 situation evolves, Investigators must use their best judgement to minimize risk to participants during the conduct of the study.

3.6.1 Blood sample volumes

A maximum of 227 mL of blood is planned to be collected in each part over a period of up to 61 weeks, from each subject as part of the study. Samples for monitoring of any safety findings would be in addition to this. This is not considered to be a risk for this population.

Timings of blood sample collection are outlined in the Assessment Schedule, Table 8-1 and Table 8-2.

A summary blood log is provided in the Site Operations Manual, together with instructions for all sample collection, processing, storage and shipment information.

See Section 8.9 regarding the potential use of residual samples.

4 Population

Part A

In Part A, the study population will be comprised of male and female patients with partial thickness cartilage lesions of one knee. A total of approximately 60 patients will be enrolled in the study and randomized. Randomization will be stratified by type of lesion (femoral condyle or patella). At least 48 patients are expected to complete the study (20% drop out rate). Additional patients may be enrolled if the dropout rate will exceed 20%.

The investigator must ensure that all patients included in the study meet the eligibility criteria. No additional criteria should be applied by the investigator, in order that the study population will be representative of all eligible patients. Patient selection is to be established by checking through all eligibility criteria at screening and before dosing. 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 patient from enrollment into the study.

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Part B

In Part B, the study population will be comprised of male and female patients with knee OA (K&L 2-3). A total of approximately 75 patients will be enrolled in the study and randomized. At least 69 patients are expected to complete the study (10% drop out rate). Additional patients may be enrolled if the dropout rate will exceed 10%. The investigator must ensure that all patients included in the study meet the eligibility criteria. No additional criteria should be applied by the investigator, in order that the study population will be representative of all eligible patients. Patient selection is to be established by checking through all eligibility criteria at screening and before dosing. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site.

In total, 135 patients are expected to be randomized into the study.

Deviation from any entry criterion excludes a patient from enrollment into the study.

4.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any study-related assessment is performed.
2. Able to communicate well with the investigator, to understand and comply with the requirements of the study.
3. **Part A:** Patient is ≥18 and ≤55 years old at time of screening.

   Part B: Patient is ≥18 and ≤75 years old at time of screening.
4. **Part A:** Patient has a body mass index (BMI) <30 kg/m^2 at screening. For patients with a BMI >30 but ≤ 33 kg/m^2, eligibility has to be confirmed by consultation with the sponsor.

   Part B: Patient has a body mass index (BMI) ≤35 kg/m^2 at screening.
5. **Part A ONLY:** Patient has a symptomatic, single, partial thickness articular cartilage defect of one knee, grade II or IIIA according to the ICRS classification, localized to either the femoral condyles/femoral trochlea or to the patella, based on MRI or arthroscopy performed within 9 months before screening visit and confirmed by screening 3T MRI.
6. **Part A ONLY:** Patient has an onset of pain and impairment of function between two (2) months and two (2) years before screening.
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8. **Part B ONLY:** Diagnosis of femorotibial OA in the target knee by standard American College of Rheumatology (ACR) criteria at study start (clinical AND radiographic criteria)
9. **Part B ONLY:** Patient has a K&L grade 2 or 3 OA of the knee as detailed below according to Schiphof et al (2008)) with JSW 2.00-4.00 mm CCI

10. **Part B ONLY:** Patient must have symptomatic disease predominantly in one (the index) knee, with minimal or no symptoms in the contralateral knee. Symptomatic disease is defined as having pain in the knee more than 50% of the days during the last 3 months from screening, according to PI's evaluation.

4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study:

1. Use of other investigational drugs within 5 half-lives of enrollment, or until the expected pharmacodynamic effect has returned to baseline, whichever is longer.
2. History of hypersensitivity to any of the study treatments or excipients or to drugs of similar chemical classes.
3. History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study such as:
    - Concomitant clinically significant cardiac arrhythmias, e.g. sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
    - Personal history or family history of long QT syndrome or Torsades de Pointes
4. History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result.
5. Chronic infection with Hepatitis B (HBV) or Hepatitis C (HCV). A positive HBV surface antigen (HBsAg) test, or if standard local practice, a positive HBV core antigen test, excludes a patient. Patients with a positive HCV antibody test should have HCV RNA levels measured. Patients with positive (detectable) HCV RNA should be excluded.
6. History of malignancy of any organ system (other than localized basal or squamous cell carcinoma of the skin or *in-situ* cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
7. Pregnant or nursing (lactating) women.
8. 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 and for 15 days after stopping of investigational drug. Highly effective contraception methods include:
    - Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 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 patients on the study the vasectomized male partner should be the sole partner for that patient.
    - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

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

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

9. **Part A:** Regular smokers (> 5 cigarettes or equivalent use of tobacco products per day in the previous 3 months). Urine cotinine levels will be measured during screening for all patients. Regular smokers will be defined as any patient who reports tobacco use of > 5 cigarettes or equivalent/day and/or who has a urine cotinine ≥ 500 ng/mL.

   Part B: Regular smokers (> 10 cigarettes or equivalent use of tobacco products per day in the previous 3 months).

10. **Part A:** Use of prohibited medications:

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    Part B: Use of prohibited medications:

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11. Patient has a known autoimmune disease susceptible to immunosuppressive treatment, inflammatory arthropathy (including but not limited to rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, CPPD, gout), active acute or chronic infection of the joint, Lyme disease involving the knee, systemic cartilage disorder, or a known systemic connective tissue disease.
12. Patient unable to undergo MRI or presents absolute contraindications to MRI (e.g., metallic implants, metallic foreign bodies, pacemaker, defibrillator).
13. Commercially Confidential Information
14. **Part A ONLY:** Patient has radiologically apparent degenerative joint disease in the target knee as determined by Kellgren and Lawrence grade ≥2 based on X-ray evaluation performed within 9 months from screening.
15. Patient has had surgical treatment of the target knee using mosaicplasty, microfracture, meniscectomy >50% (Note: prior diagnostic arthroscopy with debridement and lavage, <50% meniscectomy, lateral release, patellar realignment, medial patellofemoral ligament reconstruction are acceptable if performed at least 2 months prior to screening; anterior cruciate ligament reconstruction is acceptable if performed 12 months prior to screening, or less if restoration of joint function is evident, and agreed by the sponsor).

16. Patient has an unstable target knee joint (including but not limited to posttraumatic or congenital laxity) or insufficiently reconstructed ligaments based on medical history and physical examination by the investigator.
17. **Part A ONLY:** Patient has patellofemoral dysplasia Dejour Grade B-D based on X-ray or MRI evaluation.
18. **Part A:** Patient has malalignment (valgus- or varus-deformity) in the target knee ≥ 5° based on X-ray evaluation. In suspected cases, the mechanical axis must be established radiographically through complete leg imaging during standing and in PA projection.

    Part B: Patient has malalignment (valgus- or varus-deformity) in the target knee > 7.5° based on X-ray evaluation. In suspected cases, the mechanical axis must be established radiographically through complete leg imaging during standing and in PA projection.
19. Vulnerable subjects, e.g. subjects kept in detention, soldiers, employees of the sponsor or a clinical research organization, involved in this study
20. History of drug abuse or unhealthy alcohol use within the 12 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays conducted during screening. Unhealthy alcohol use is defined as a history of, or current alcohol misuse/abuse, defined as five or more drinks on the same occasion on each of 5 or more days in the past 30 days.
21. **Part B (ONLY):** Patients with Nephrotic syndrome and/or significant proteinuria (≥ 3+ on dipstick or protein-creatinine ratio ≥ 1 g/g Cr) at screening
22. **Part B (ONLY):** History of coagulopathy or medical condition requiring anticoagulation which would preclude knee injection (antiplatelet or anticoagulant treatment [for patients using warfarin, INR to be <3 prior to injection], is allowed).
23. **Part B (ONLY):** Clinical signs of inflammation (i.e., redness) in the target knee.
24. **Part B (ONLY):** History of knee replacement (unilateral or total) in either knee.
25. **Part B (ONLY):** Presence of severe hip OA conditioning lower limb function according to PI's evaluation.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

5 Restrictions for Study Subjects

During recruitment, screening/informed consent review, the subjects must be informed and reminded of the restrictions outlined in this section.

5.1 Contraception requirements

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if a pregnancy was to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirement during dosing and for 15 days after stopping of investigational drug.

If there is any question that the subject will not reliably comply, the subject should not be entered or continue in the study. Male subjects should be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information. Please refer to exclusion criteria (Section 4.2) for details of contraception requirements for the study.

5.2 Prohibited treatment

Use of the treatments displayed in the table below is NOT allowed in the reported timeframe. If required outside of the definitions of Rescue medication (see Section 6.10), subject has to be discontinued from study drug, but will continue the study until V399.

Table 5-1 Prohibited treatment Part A

Medication	Prohibited period	Action to be taken
Local i.a. treatment into the knee, including but not restricted to viscosupplementation and corticosteroids (impact on tissue repair/confounding of efficacy)	CCI	discontinue study treatment
Corticosteroid use by any route except topical (impact on tissue repair)	CCI	discontinue study treatment
Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin (greater than 100 mg/day) by any route except topical (impact on cartilage tissue repair). See Section 6.10 (Rescue medication) for exceptions	CCI	Must be recorded on the Concomitant medications/ Significant non-drug therapies section of the CRF.
Paracetamol greater than 3000 mg per day (confounding of liver function) See Section 6.10 (Rescue medication) for exceptions	CCI	Must be recorded on the Concomitant medications/ Significant non-drug therapies section of the CRF.
Oral glucosamine, chondroitin sulfate, or any nutraceutical with potential activity on cartilage repair (confounding of efficacy)	CCI	Must be recorded on the Concomitant medications/ Significant non-drug therapies section of the CRF.
Paracetamol and/or NSAIDs are not allowed during seven days before visit 201, 202, 299 and V399 CCI	CCI	PRO to be performed ≥ 7 days post last paracetamol/ NSAID intake, but ≤2 weeks after planned visit date.

Table 5-2 Prohibited treatment Part B

Medication	Prohibited period	Action to be taken
Local i.a. treatment into the knee, including but not restricted to viscosupplementation and corticosteroids (impact on tissue repair/confounding of efficacy)	CCI	discontinue study treatment
Long-term treatment (>14 days) with oral corticosteroids >5 mg/day.	CCI	Must be recorded on the Concomitant medications/ Significant non-drug therapies section of the CRF.
Paracetamol greater than 3000 mg per day (confounding of liver function) See Section 6.10 (Rescue medication) for exceptions	CCI	Must be recorded on the Concomitant medications/ Significant non-drug therapies section of the CRF.
Oral glucosamine, chondroitin sulfate, or any nutraceutical with potential activity on cartilage repair (confounding of efficacy)	CCI	Must be recorded on the Concomitant medications/ Significant non-drug therapies section of the CRF.

Note: The use of oral corticosteroids (≤5 mg/day oral prednisone or equivalent) for an indication other than OA pain will be allowed during the trial. In addition, short-term use of any tapering course of oral corticosteroids for ≤ 14 days will be allowed. Topical corticosteroids are allowed.

5.3 Dietary restrictions and smoking

5.3.1 Part A

No use of > 5 cigarettes per day or equivalent use of tobacco products is allowed during the study until V399.

5.3.2 Part B

No use of > 10 cigarettes per day or equivalent use of tobacco products is allowed during the study until EOS.

5.4 Other restrictions

During 48 hours post injection, subjects should consider only modest exertion of the concerned knee joint and/or leg.

No high-impact physical exercise (e.g. football, basketball, running, contact sports) is allowed from Day 1 until EoS.

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

6 Treatment

6.1 Study treatment

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

6.1.1 Investigational treatment and control drugs

Table 6-1 Overview of study medication

Study drug name	Formulation	Unit dose	Packaging	Provided by
LNA043	Lyophilisate in Vial (LYO)	10mg	Open label bulk supply	Novartis
Placebo to LNA043	Lyophilisate in Vial (LYO)	0mg	Open label bulk supply	Novartis

6.1.2 Additional study treatment

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

6.2 Treatment arms

6.2.1 Part A

Subjects will be assigned to one of the following two treatment arms in a ratio of "3:1"

Study treatments are defined as:

- A: single i.a. injection of 20 mg LNA043, Commercially Confidential Information
- B: single i.a. injection of placebo to 20 mg LNA043, CCI

6.2.2 Part B

Subjects will be assigned to one of the following three treatment arms in a ratio of "1:1:1"

Study treatments are defined as:

- A: single i.a. injection of 20 mg LNA043, Commercially Confidential Information
- B: single i.a. injection of 40 mg LNA043, Commercially Confidential Information
- C: single i.a. injection of placebo Commercially Confidential Information

6.3 Treatment assignment and randomization

After eligibility confirmation, at the first dosing visit (Day 1) (or one day before), subjects will be randomized via Novartis Interactive Response Technology (NIRT) to one of the two (Part A) or three (Part B) treatment arms. The investigator or his/her delegate will log in the NIRT system after confirming that the patient fulfills all the inclusion/exclusion criteria. The NIRT will assign a treatment arm to the patient. The treatment arm information will not be communicated to the caller (investigator or his/her delegate).

Follow the details outlined in the SOM regarding the process and timing of treatment assignment and randomization of subjects.

The investigator will enter the screening number in the eCRF.

Randomization will be stratified by type of lesion (femoral condyle or patella) only in Part A. Randomization will not be stratified in Part B.

6.4 Treatment blinding

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

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

Site staff

With the exception of any unblinded site staff identified below, all site staff (including study investigator and study nurse) will be blinded to study treatment throughout the study.

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

Drug product will be supplied in bulk, so an unblinded pharmacist or delegate who is independent of the study team will be required in order to maintain the blind. After blinded investigator or his/her delegate performs the randomization in NIRT system, the unblinded pharmacist will log into the NIRT system and see the treatment arm assigned to the randomized subject. Appropriate measures must be taken by the unblinded pharmacist to ensure that the treatment assignments are concealed from the rest of the blinded site staff.

Sponsor staff

The following unblinded sponsor roles are required for this study.

Unblinded field monitor(s)

Unblinded clinical staff managing drug re-supply to site

Unblinded sample analyst(s) (PK blood)

The unblinded field monitors are required to review drug accountability and allocation at site. The unblinded monitors will be unblinded through unblinded user access to the NIRT system and review of source documentation compiled by the unblinded pharmacist or delegate, which details treatment allocation to individual subjects. The names of the unblinded monitor(s) are detailed in the Monitoring Plan.

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

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

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

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

Following final database lock all roles may be considered unblinded.

Table 6-2 Blinding Levels (Part A and B)

Role	Time or Event			
	NIRT set-up & go-live	**Randomization & treatment arm assignment & dosing**	**Safety event (single subject unblinded)**	**Interim analysis**
Subjects/Patients	B	B	UI	B
Site staff	B	B	UI	B
Unblinded site staff (see text for details)	B	UI	UI	UI
Drug Supply and Randomization Office	UI	UI	UI	UI
Unblinded sponsor staff (see text for details)	B	UI	UI	UI
Statistician/statistical programmer/data analysts	B	UI	UI	UI
Independent committees used for assessing interim results	NA	NA	NA	NA
All other sponsor staff not identified above	B	B	UI	B*

B Remains blinded

B* blinded at individual level

NA Not applicable

UI Allowed to be unblinded on individual patient level

6.5 Treating the subject

LNA043/placebo (CCI Part A and CCI Part B) will be administered at the study site to the patient via the following route of administration: intra-articular injection. See the pharmacy manual for further details.

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

For Part B only:

Injections to the target knee should not be considered when overlying skin infections, wounds or inflammatory diseases such as psoriasis are present.

After injection, the patient must be advised to:

- Consult a doctor or emergency room immediately in case of severe systemic delayed reactions.
- Observe any local or systemic reactions that may occur subsequently, seek appropriate medical care as needed and inform the attending doctor at the next visit.

Any allergic reactions (both local and systemic) should be recorded before the patient leaves the clinic.

6.6 Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments are not permitted.

6.7 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the NIRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the study 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 NIRT at any time in case of emergency. The investigator will need to provide:

- protocol number
- study drug name (if available)
- subject number.

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

An assessment will be done by the appropriate site personnel and sponsor after an emergency unblinding to assess whether or not study treatment should be discontinued for a given subject and, if applicable, whether the subject can continue into the next trial phase (e.g., an unblinded extension).

6.8 Treatment exposure and compliance

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects treated with LNA043, as detailed in Section 8.7.

Compliance to the treatment regimen is ensured by administration of LNA043 i.a. injections by the investigator (or her/his delegates). Information on the study treatment administration or any deviation from the dose regimen must be recorded in the Case Report Form (CRF). All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.9 Recommended treatment of adverse events

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

From the completed and ongoing clinical trials, no case of local or systemic hypersensitivity reactions have been observed with LNA043 to date. Due to the potential risk of serious allergic reactions, immediate access to full resuscitation equipment and drugs must be available, including adrenaline for injection and staff trained in the use thereof (i.e. at locations with emergency care facilities). If symptoms of a systemic reaction, such as urticaria, angioedema or severe asthma occur, symptomatic treatment should be initiated immediately according to local treatment protocols. Study participants in Part A will be monitored at the clinical site for at least 1 (one) hour post intra-articular injection or longer at the discretion of the Investigator to ensure adequate safety monitoring. Study participants in Part B are required to undergo observation for three hours post-injection prior to leaving the site. Patients who experience any Grade hypersensitivity reaction in Part B must not be re-dosed.

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

6.10 Rescue medication

6.10.1 Part A

Paracetamol/acetaminophen up to 3000 mg/day is allowed as rescue medication to treat local pain to the target knee. In case paracetamol/acetaminophen is not effective, NSAIDs will be allowed for up to 3 consecutive days as rescue medication.

Both paracetamol and NSAIDs are not allowed during seven days before any follow-up visit

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

6.10.2 Part B

Paracetamol/acetaminophen up to 3000 mg/day and NSAIDs are allowed as rescue medication to treat local pain to the target knee.

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

6.11 Concomitant treatment

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

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

In the event of an available COVID-19 vaccine in the future, vaccination of study subjects will be permitted during the study duration. The investigator must document their discussion with the subject regarding COVID-19 vaccination in the source documentation, and follow the instructions described above related to the eCRF.

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

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

7 Study completion and discontinuation

7.1 Study completion and post-study treatment

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

Study completion and end of the trial is defined as when the last subject has completed the long-term follow-up (Week 52) 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.

The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 9.2 and the SOM. Documentation of attempts to contact the subject should be recorded in the source documentation.

After study participation, the patients will continue to be treated according to the local standard clinical practice. The investigator must provide follow-up medical care for all subjects who prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

7.2 Discontinuation of study treatment

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7.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject cannot be formally considered lost to follow-up until his/her scheduled end of study (EOS) visit would have occurred.

7.4 Withdrawal of informed consent

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

Withdrawal of consent from the study is defined as when a subject:

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

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

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

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

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

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

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

7.5 Study Stopping rules

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7.6 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. Should this be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests.

In case of an early termination the Sponsor will notify the end of the trial to the national competent authorities and the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) concerned immediately and at the latest within 15 days after the trial is halted, will clearly explain the reasons, and will describe follow-up measures, if any, taken for safety reasons.

8 Procedures and assessments

8.1 Assessment schedule

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Table 8-2 Assessment schedule Part B

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8.2 Informed consent procedures

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

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

Novartis will provide to investigators a proposed informed consent form that complies with the ICHE6 GCP guideline and regulatory requirements and is considered appropriate for this study. The informed consent form will also include a section related to optional future research which will require a separate signature if the subject agrees to future research. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

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

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

8.3 Subject screening

In general, it is permissible to re-screen a subject if s/he fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

Initial screening assessments (i.e. Physical examination, laboratory assessments, ECGs, vital signs, pregnancy test, gait assessment) are valid and can be used in case of re-screening up to 90 days after the initial assessment date if the patients do not report a change in health status.

Initial screening X-Rays and MRIs are valid and can be used in case of re-screening up to 180 days after the initial assessment date if the patients do not report a change in symptoms (qualitative or quantitative).

Information on what data should be collected for screening failures is outlined in the Site Operations Manual.

8.4 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects. 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 also be collected until signature of informed consent. Date of onset of symptoms (Part A), ICRS grading of the lesion (Part A), Commercially Confidential Information cartilage lesion localization (i.e lateral femoral condyle, medial femoral condyle, trochlea, patella – Part A) will be collected in the CRF as baseline characteristics. Details are outlined in the SOM.

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

Hepatitis screen, HIV screen

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

Alcohol test, Drug screen, cotinine test

Subjects will be tested at screening for substances of abuse (e.g., alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates) in Part A and Part B and cotinine concentration in Part A only. Results will be available as source data and will not be recorded within the eCRF.

X-ray

In Part A, X-rays will be performed at screening in case no former examination results are available to confirm eligibility by excluding apparent degenerative joint disease, patellofemoral dysplasia Dejour Grade B-D (optional), and/or valgus- or vagus-deformity of $\geq 5°$ in the target knee.

In Part B, X-rays will be performed at screening for all subjects to confirm eligibility, at the hospital or nearby facility. Commercially Confidential Information

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8.5 Efficacy / Pharmacodynamics

Articular cartilage bi-layer collagen organization (primary endpoint in part A) and articular cartilage volume and thickness (primary endpoint in part B) are evaluated with knee MRI described in Section 8.5.1.

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8.5.1 Knee MRI

Hyaline cartilage is characterized by two main distinct layers between the articular surface and bone interface, marked by orientation of collagen fibrils. Besides the collagen matrix being highly structured, glycosaminoglycans (GAG) are also abundant in hyaline cartilage. In early stages of cartilage degeneration and fibrocartilage, subtle changes typically involve these major constituents of the cartilage solid matrix.

MRI will be obtained from the injured knee to visualize the cartilage tissue either in the femoral, tibial or patellar region depending on the defect location. The imaging protocol was developed to primarily quantify changes in the bi-layer collagen organization, but also cartilage loss and, when visible, sub-chondral bone edema. Details inherent to the image acquisition and analysis can be found in the imaging charter.

8.5.1.1 Image collection

Magnetic Resonance (MR) images acquisition will be performed by a trained MRI professional at the hospital or nearby facility. The MRI radiologist will be blinded to the treatment received by the patient. All patients will be imaged using a clinical high-field MRI scanner. For each MRI session, images will be acquired as described in the imaging protocol to assess bi-layer collagen organization, the extent of cartilage injury (i.e. cartilage volume and thickness in index region) and knee features such as bone marrow edema.

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

8.5.1.2 Image processing

The image analysis will be performed centrally, as defined in the imaging charter, in order to assess changes in cartilage quality in the defective region of articular cartilage (primary endpoint in Part A and secondary endpoint in Part B) as well as in weight-bearing and non-weight-bearing regions of articular cartilage. Other endpoints will include the extent of the repair tissue at the site of injury such as the % of defect filling (secondary endpoint in Part A) or cartilage volume in the index region (primary endpoint in Part B) and knee features such as bone marrow edema.

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.

8.6 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the SOM, with the Assessment Schedule (Table 8-1 and Table 8-2) detailing when each assessment is to be performed.

8.6.1 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/or pelvic exams may be performed. See the SOM for details.

8.6.2 Vital signs

- Body temperature
- Blood pressure (BP)
- Pulse rate

Details on how vital signs should be measured can be found in the SOM.

8.6.3 Height and weight

- Height
- Body weight
- Body mass index (BMI) will be calculated (Body weight (kg) / [Height (m)]^2)

8.6.4 Laboratory evaluations

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

8.6.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (monocytes, eosinophils, basophils, neutrophils, lymphocytes), platelet count, aPTT, and PT/INR will be measured.

8.6.4.2 Clinical chemistry

Sodium, potassium, creatinine, urea, uric acid, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, LDH, GGT, AST, ALT, CK, glucose, total cholesterol, LDL, HDL, triglycerides.

If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

8.6.4.3 Urinalysis

Urine test by dipstick (e.g. Combur9): leucocytes, nitrite, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood/ hemoglobin.

If the dipstick result is positive for protein, nitrite, leucocytes and/or blood the sample will be sent for microscopic analysis of WBC, RBC and casts.

8.6.5 Electrocardiogram (ECG)

Single 12 lead ECGs are collected. The original ECGs, appropriately signed and dated, should be collected and archived at the study site.

ECGs will be performed as outlined in the Assessment Schedule (Table 8-1 and Table 8-2).

Each ECG tracing should be labelled with study number, subject number, date and time, be appropriately signed and dated to confirm review and filed in the study site source documents. For any ECGs with subject safety concerns, two additional ECGs should be performed to confirm the safety finding. QTcF (Fridericia) interval longer than 450 msec for males and 460 msec for females and other clinically significant ECG findings prior to dosing with investigational treatment must be discussed with the Sponsor.

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

The eCRF will contain:

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

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

8.6.6 Pregnancy and assessment of fertility

All pre-menopausal women who are not surgically sterilized will have pregnancy testing. See the Assessment Schedule, Table 8-1 and Table 8-2, for timing of the protocol required pregnancy testing; additional pregnancy testing may be performed to meet local requirements*. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative.

*If additional pregnancy testing is needed per local requirements, those additional results will be kept as source documentation only.

8.6.7 Immunogenicity

IG samples will be collected at the time points defined in the Assessment schedule (Section 8.1 and Section 8.2).

Further details on sample collection, numbering, processing and shipment can be found in the SOM.

8.6.7.1 Immunogenicity analytical method

A validated ligand binding assay will be used for the detection of anti-LNA043 antibodies, and cross-reactivity to ANGPTL3 and ANGPTL4. Positive samples will be further analyzed for presence of neutralizing antibodies using a validated ligand binding assay.

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.

8.7 Pharmacokinetics

Validated bioanalytical assays will be used to determine LNA043 and ANGPTL3 in synovial fluid and serum.

PK samples will be collected at the timepoints defined in the Assessment schedule, Table 8-1 and Table 8-2. Follow instructions outlined in the SOM regarding sample collection, numbering, processing and shipment. See Section 8.9 regarding the potential use of residual samples.

In order to better define the PK profile, the timing of the PK sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

PK samples will be obtained from all subjects.

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

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.

8.8 Other assessments

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8.9 Use of residual biological samples

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

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9 Safety monitoring

9.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study until V399 (for Part A) and V499 (for Part B). Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an adverse event irrespective if a clinical event has occurred. See Section 9.5 for an overview of the reporting requirements.

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

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

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

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values that are considered to be non-typical in patients with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for liver and kidney related events are included in Appendix 1 and Appendix 2, respectively.

Adverse events must be recorded on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. the Common Toxicity Criteria (CTC) AE grade (version 4.03).
   If CTC-AE grading does not exist for an adverse event, use:
   - 1 = mild,
   - 2 = moderate,
   - 3 = severe
   - 4 = life threatening* (see Section 9.2 for definition of a serious adverse event (SAE))
     *Note: There may be cases where a CTCAE with a grade of 4 (life-threatening) may not necessarily be an SAE (e.g. certain laboratory abnormalities in the absence of meeting other seriousness criteria).
   - CTC-AE grade 5 (death) is not used, but is collected as a seriousness criteria and also collected in other CRFs (e.g. Study Completion, Death/Survival).
2. its relationship to the study treatment
   - Yes or
   - No
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 9.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding investigational treatment.
   All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - no action taken (e.g. further observation only)
   - investigational treatment dosage increased/reduced
   - investigational treatment interrupted/withdrawn
   - concomitant medication or non-drug therapy given
   - hospitalization/prolonged hospitalization (see Section 9.2 for definition of SAE)
6. its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

Information about common side effects already known about the investigational drug can be found in the IB. Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the investigational drug, the interventions required to treat it, and the outcome.

The investigator must also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

9.2 Serious adverse event reporting

9.2.1 Definition of SAE

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:

- is fatal or life-threatening
- 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 the start of study drug
    - 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
    - social reasons and respite care in the absence of any deterioration in the subject's general condition
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention.

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

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

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. 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 (see Annex IV, ICH-E2D Guideline).

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

All AEs (serious and non-serious) are captured on the CRF; SAEs also require individual reporting to Novartis Drug Safety & Epidemiology (DS&E) as per Section 9.2.2.

9.2.2 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the End of Study (Week 28) or Long term follow-up (Week 52) visit in part A or EOS (Week 52) visit in part B, as appropriate depending on the subject, must be reported to Novartis within 24 hours of learning of its occurrence as described below. Any SAEs experienced after this period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Note: SAEs reported by subjects deemed to be screen failures must be reported to Novartis as outlined here with appropriate information also captured in the CRFs as specified in the Site Operations Manual.

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.

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an IN to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Follow the detailed instructions outlined in the SOM regarding the submission process for reporting SAEs to Novartis. Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.

9.3 Liver safety monitoring

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

Please refer to Table 15-1-Appendix 1 for complete definitions of liver events.

Follow-up of liver events

Every liver event defined in Table 15-1-Appendix 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 15-2-Appendix 1.

- Repeating liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and γGT) to confirm elevation within 48-72 hours.

  These liver chemistry repeats should always be performed using the central laboratory, with the results provided via the standard electronic transfer. If results will not be available from the central laboratory within 24 hours, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results reported on the unscheduled local laboratory CRF.
- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 7.2 (Discontinuation of study treatment), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include:
  - Repeating liver chemistry tests two or three times weekly. Testing should include ALT, AST, ALP, PT/INR, and gGT. If total bilirubin is elevated > 2 x ULN, fractionation into direct and indirect bilirubin is required. To rule out muscular origin of transaminase elevations, CPK should be measured along with liver chemistry tests. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.
    Retesting should be continued up to resolution.
  - Obtaining a more detailed history of symptoms and prior or concurrent diseases.
  - Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
  - Exclusion of underlying liver disease, as specified in Table 15-3.
  - Imaging such as abdominal US, CT or MRI, as appropriate
  - Obtaining a history of exposure to environmental chemical agents.
  - Considering gastroenterology or hepatology consultations.

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

9.4 Renal safety monitoring

9.4.1 Part A

Renal events are defined as one of the following:

- confirmed (after ≥ 24h) increase in serum creatinine of ≥ 25% compared to baseline during normal hydration status
- new onset (≥1+) proteinuria, hematuria or glucosuria; or as a
- doubling in the urinary albumin-creatinine ratio or urinary protein-creatinine ratio (PCR) (if applicable).

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

- Serum creatinine triggers that will require follow up and repeat assessments of the abnormal laboratory parameter
- Urine dipstick triggers that will require follow up and repeat assessments of the abnormal laboratory parameter

Every renal laboratory trigger or renal event must be followed up by the investigator or designated personnel at the trial site. Recommended follow-up assessments are listed in Section 16-Appendix 2.

9.4.2 Part B

Renal events are defined as one of the following:

- confirmed (after ≥ 24h) increase in serum creatinine of ≥ 25% compared to baseline during normal hydration status
- urinary protein-creatinine ratio >1 g/g Cr
- New onset dipstick proteinuria ≥ 3+
- New onset dipstick haematuria ≥ 3+ (excluding menstruation, infection, extreme exercise, or trauma).

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

- Serum creatinine triggers that will require follow up and repeat assessments of the abnormal laboratory parameter
- Urine dipstick triggers that will require follow up and repeat assessments of the abnormal laboratory parameter

Every renal laboratory trigger or renal event must be followed up by the investigator or designated personnel at the trial site. Recommended follow-up assessments are listed in Section 16-Appendix 2.

9.5 Reporting Medication errors including misuse/abuse

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

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

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

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) CRF. Study treatment errors are only to be reported to Novartis CMO&PS department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the adverse event (AE) CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to Novartis CMO&PS. As such, instances of misuse or abuse are also to be reported using the SAE form/CRF.

Table 9-1 summarizes the reporting requirements.

Table 9-1 Summary of reporting requirements for medication errors

Treatment error type	Document in Dose Administration (DAR) CRF	Document in AE CRF	Complete SAE form/CRF
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see Section 9.1 and Section 9.2, respectively.

9.6 Pregnancy reporting

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her pregnancy. To ensure subject 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 for up to 12 months following the birth to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis CMO&PS Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

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

9.7 Early phase safety monitoring

The Investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

10 Data review and database management

10.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of subject records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

Continuous remote monitoring of each site's data may be performed by Novartis. Additionally, a central analytics organization may analyze data and identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the eligibility criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety 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 subjects will be disclosed.

10.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the Contract Research Organization (CRO) working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the SOM and Assessment schedule and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

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

10.3 Database management and quality control

CRO working on behalf of Novartis review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to CRO working on behalf of Novartis who will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant 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.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization data about all study drug(s) dispensed to the subject will be tracked using the Novartis Interactive Response Technology (NIRT) database. The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via NIRT 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.

The occurrence of any protocol deviations will be determined. After these 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. Any changes to the database after that time can only be made by joint written agreement between the COAR Analytics NIBR Franchise Head and the relevant NIBR TA Head.

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10.4 Data Monitoring Committee

Not required.

10.5 Adjudication Committee

Not required.

11 Data analysis

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

11.1 Analysis sets

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

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

The PK analysis set will include all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received LNA043 and with no protocol deviations that impact on PK data.

The primary pharmacodynamic (PD) analysis set will include all subjects with available PD data. The secondary PD analysis set will include all subjects with available PD data and no protocol deviations with relevant impact on PD data. Details of which protocol deviations have impact on PD data will be provided in the Statistical Analysis Plan (SAP).

11.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and subject.

11.3 Treatments

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

11.4 Analysis of the primary variable(s)

11.4.1 Variable(s)

The primary efficacy variable is the articular cartilage bi-layer collagen organization evaluated with MRI at Week 16 and 28 (part A) and change from baseline in cartilage volume/thickness in the index region, assessed based on MRI at Weeks 28 and 52 (part B).

The primary safety variables are:

- Systemic and local Adverse Events
- ECGs
- Vital signs
- Hematology, blood chemistry, urinalysis

11.4.2 Statistical model, hypothesis, and method of analysis

The primary efficacy variables will be analyzed using the secondary PD analysis set and the primary safety variables using the safety analysis set.

11.4.2.1 Part A

The primary efficacy variable, articular cartilage bi-layer collagen organization, assessed based on MRI at Weeks CCI16 and 28, will be analyzed using a mixed model repeated measures (MMRM) analysis of variance model, including baseline and all time points to compare treatment groups at Weeks CCI16 and Week 28. The model will include treatment, timepoint, treatment*timepoint, and type of lesion as fixed effects, subject as a random effect, and baseline measure as a fixed covariate. If deemed appropriate, the endpoint measure data will be transformed to facilitate analysis. 90% two-sided confidence intervals for the treatment effect will be formed at Weeks CCI16 and Week 28. Considering that the time course of response to LNA043 is not known, statistically significant differences between active drug and placebo at either Week 16 or Week 28 will be considered as a positive result.

11.4.2.2 Part B

The primary efficacy variable, change from baseline in cartilage volume/thickness in the index region, assessed based on MRI at Weeks 28 and 52. will be analyzed using a mixed model repeated measures (MMRM), including baseline and all time points to compare treatment

groups at Week 28 and Week 52. The model will include baseline measure, treatment, timepoint, treatment*timepoint as fixed effects, participant as a random effect. 90% two-sided confidence intervals for the treatment effect will be formed at Weeks 28 and 52. If deemed appropriate, the endpoint measure data will be transformed to facilitate analysis. Considering that the time course of response to LNA043 is not known, statistically significant differences between active drug (either LNA043 dose) and placebo at either Week 28 or Week 52 will be considered as a positive result.

The safety variables will be summarized descriptively by treatment group for part A and part B.

Exploratory variables will be summarized descriptively by treatment group and associations with primary and secondary variables will be explored.

11.5 Handling of missing values/censoring/discontinuations

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Subjects with missing PK concentrations in some but not all periods will be included in a mixed model analysis assuming missing at random.

Missing data for MRI outcomes will not be imputed.

11.6 Summary statistics of safety

Vital signs

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

ECG evaluations

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

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, subject, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Adverse events

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

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A subject with multiple adverse events within a body system is only counted once towards the total of this body system.

The number (and proportion) of subjects with AEs of special Interest (AESI) will be summarized by treatment.

11.6.1 Sensitivity analyses

Not applicable.

11.7 Analysis of secondary variable(s)

Part A

The secondary efficacy variable, change in volume of cartilage defect filling, assessed based on MRI at Week 16 and 28, will be analyzed using a mixed model repeated measures (MMRM) analysis of variance model, including baseline and both timepoints to compare treatment groups at Week 16 and Week 28. The model will include treatment, timepoint, treatment*timepoint, and type of lesion as fixed effects, subject as a random effect, and baseline measure as a fixed covariate. 90% two-sided confidence intervals for the treatment effect will be formed at both Week 16 and Week 28. If deemed appropriate, the endpoint measure data will be transformed to facilitate analysis. Considering that the time course of response to LNA043 is not known, statistically significant differences between active drug and placebo at either Week 16 or Week 28 will be considered as a positive result.

Part B

The secondary efficacy variable, change from baseline in articular cartilage bi-layer collagen organization, assessed based on MRI at Weeks 28 and 52 will be analyzed using a mixed model repeated measures (MMRM). The model will include baseline measure, treatment, timepoint, treatment*timepoint as fixed effects, participant as a random effect. The model will be used to form 90% two-sided confidence intervals for the treatment effect at Weeks 28 and 52. If deemed appropriate, the endpoint measure data will be transformed to facilitate analysis. Considering that the time course of response to LNA043 is not known, statistically significant differences between active drug (either LNA043 dose) and placebo at either Week 28 or Week 52 will be considered as a positive result.

11.7.1 Efficacy / Pharmacodynamics

Not Applicable.

11.7.2 Pharmacokinetics

LNA043 serum and synovial fluid concentration data will be listed by subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, Commercially Confidential Information

Summary statistics will include mean (arithmetic and geometric), Standard Deviation (SD), CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented.
Commercially Confidential Information . A geometric mean will not be reported if the dataset includes zero values. Pharmacokinetic parameters will be calculated as described in Section 8.7 and will be listed by treatment and subject.

11.7.3 Pharmacokinetic / pharmacodynamic interactions

Not Applicable.

11.7.4 Immunogenicity

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

11.7.5 Other assessments

Not Applicable

11.8 Analysis of exploratory variables

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11.9 Sample size calculation

11.9.1 Part A

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A sample size of 36 LNA043 treated patients and 12 Placebo patients (48 patients, 3:1 LNA043:Placebo) will allow for approximately 90% power, with a 1-sided alpha of 0.05, to detect a 20% relative difference between LNA043 and Placebo overall, and CCI . Stated differently, a two-sided 90% confidence interval for the treatment effect will exclude zero with probability 90%.

A 20% relative improvement in T2 mapping between treatments is considered to be potentially clinically meaningful and statistically different than the 10% random variability. So, in the calculations above, an effect size of 0.2/0.18=1.11 is used.

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11.9.2 Part B

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11.10 Power for analysis of key secondary variables

Not applicable

11.11 Interim analyses

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12 Ethical considerations

12.1 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 Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 Responsibilities of the investigator and IRB/IEC

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

For multi-center trials, a Coordinating Investigator will be selected by Novartis around the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

12.3 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

13 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 subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

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.

13.1 Protocol Amendments

Any change 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.

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 9 (Safety Monitoring) must be followed and the Study Lead informed.

14 References

References are available upon request

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15 Appendix 1: Liver Event Definitions and Follow-up Requirements

Table 15-1 Liver Event Definitions

Definition	Thresholds
Potential Hy's law cases	• ALT or AST > 3 × ULN and TBL > 2 × ULN without initial increase in ALP to > 2 × ULN
ALT or AST elevation with coagulopathy	• ALT or AST > 3 × ULN and INR > 1.5 (in the absence of anticoagulation)
ALT or AST elevation accompanied by symptoms	• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash, or eosinophilia
Isolated ALT or AST elevation	• ALT or AST > 8 × ULN • 5 x ULN < ALT/AST ≤ 8 x ULN • 3 x ULN < ALT/AST ≤ 5 x ULN
Isolated ALP elevation	• ALP > 2 × ULN (in the absence of known bone pathology)
Others	• Any clinical event of jaundice (or equivalent term) • Any adverse event potentially indicative of liver toxicity

Table 15-2 Actions required for Liver Events

Criteria	Actions required
Potential Hy's Law case ALT or AST elevation with coagulopathy ALT or AST elevation accompanied by symptoms Isolated ALT or AST elevation > 8 × ULN Jaundice	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete CRFs per liver event guidance
Isolated ALT or AST elevation > 5 to ≤ 8 × ULN	• If confirmed, consider interruption or discontinuation of study drug • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete CRFs per liver event guidance
Isolated ALT or AST elevation > 3 to ≤ 5 × ULN (patient is asymptomatic)	• Monitor liver chemistry tests two or three times weekly
Isolated ALP elevation	• Repeat liver chemistry tests within 48-72 hours • If elevation is confirmed, measure fractionated ALP; if >50% is of liver origin, establish hepatic causality • Complete CRFs per liver event guidance
Any AE potentially indicative of liver toxicity	• Consider study treatment interruption or discontinuation • Hospitalize if clinically appropriate • Complete CRFs per liver event guidance

Table 15-3 Exclusion of underlying liver disease

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-HAV; HBSAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, gGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

16 Appendix 2: Specific Renal Alert Criteria and Actions

Table 16-1 Specific Renal Alert Criteria and Actions for Part A

Criteria	Action required
Serum creatinine (sCr) increase 25 – 49% compared to baseline	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase ≥ 50%	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider hospitalization and specialized treatment
Protein-creatinine or albumin-creatinine ratio increase ≥ 2-fold or new onset dipstick proteinuria ≥ 1+ or Albumin-creatinine ratio ≥ 30 mg/g or ≥ 3 mg/mmol; or Protein-creatinine ratio (PCR)≥ 150 mg/g or >15 mg/mmol	• Consider causes and possible interventions • Assess serum albumin & serum protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset glucosuria on urine dipstick (unless related to concomitant treatment, diabetes)	Assess & document: • Blood glucose (fasting) • Serum creatinine • Urine albumin-creatinine ratio
New hematuria on dipstick	Assess & document: • Urine sediment microscopy • Assess sCr and urine albumin-creatinine ratio • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

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 strongly recommended to make specimen slides available for evaluation by Novartis to potentially identify project-wide patterns of nephrotoxicity.)

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

- Blood pressure assessment (after 5 min rest, with an appropriate cuff size)
- Signs and symptoms such as fever, headache, shortness of breath, back or abdominal pain, dysuria, hematuria, dependent or periorbital edema
- Changes in blood pressure, 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 potential causes of renal dysfunction, e.g., dehydration, hemorrhage, tumor lysis

Table 16-2 Follow-up of renal events for Part A

Action	Follow up
Assess*, document and record in the Case Report Form (CRF) or via electronic data load. Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc) in the CRF.	• Urine dipstick and sediment microscopy • Blood pressure and body weight • Serum creatinine, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output
Monitor subject regularly (frequency at investigator's discretion) until:	• Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline) or • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.

* Urine osmolality: in the absence of diuretics or chronic kidney disease this can be a very sensitive metric for integrated kidney function that requires excellent tubular function. A high urinary osmolality in the setting of an increase in sCr will point toward a "pre-renal" cause rather than tubular toxicity.

Table 16-3 Specific Renal Alert Criteria and Actions for Part B

Renal Event	Actions
Confirmed serum creatinine increase 25 – 49%	Consider causes and possible interventions Follow up within 2-5 days
Serum creatinine increase ≥ 50 % [+]	Consider causes and possible interventions Repeat assessment within 24-48h if possible Consider drug interruption or discontinuation unless other causes are diagnosed and corrected Consider patient hospitalization and specialized treatment
New onset dipstick proteinuria ≥ 3+ OR Protein-creatinine ratio (PCR) ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)	Consider causes and possible interventions Assess serum albumin & serum total protein Repeat assessment to confirm Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria ≥ 3+ on urine dipstick (excluding menstruation, infection, extreme exercise, or trauma)	Assess & document Repeat assessment to confirm Distinguish hemoglobinuria from hematuria Urine sediment microscopy Assess sCr Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation Consider bleeding disorder

[+] 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 slide specimen 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 (after 5-minute rest, with an appropriate cuff size)
- Signs and symptoms like fever, headache, shortness of breath, back or abdominal pain, dysuria or hematuria, dependent or periorbital edema
- Changes in blood pressure, 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 for Part B

FOLLOW-UP OF RENAL EVENTS
Assess, document and record in CRF • Urine dipstick and sediment microscopy evidence of DIN: crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells • Blood pressure and body weight • Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output
Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the CRF
Monitor patient regularly (frequency at investigator's discretion) until - • Event resolution: (sCr within 10% of baseline or PCR < 1 g/g Cr, or albumin-creatinine ratio <300 mg/g Cr) or • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio 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