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Novartis Research and Development

LNA043

Clinical Trial Protocol CLNA043A12203 / NCT04814368

A randomized, four-arm, canakinumab placebo-controlled, participant, investigator and sponsor-blinded study investigating the safety, tolerability and efficacy of intra-articular canakinumab followed by intra-articular LNA043 in patients with knee osteoarthritis

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List of abbreviations

ADA	Anti-Drug Antibody
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANGPTL3	Angiopoeitin-like Protein 3
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
CCI	[redacted]
BUN	Blood Urea Nitrogen
CC	Chondrocalcinosis
CDISC	Clinical Data Interchange Standards Consortium
CMO&PS	Chief Medical Office and Patient Safety
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-Reactive Protein
CCI	[redacted]
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DCE-MRI	Dynamic Contrast Enhanced MRI
DIN	Drug Inducted Nephrotoxicity
DMOAD	Disease Modifying Osteoarthritis Drug
ECG	Electrocardiogram
EDC	Electronic Data Capture
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	First in Human
fJSW	Fixed Joint Space Width
FMA	Femoral Medial Anterior
FMC	Femoral Medial Central
FMP	Femoral Medial Posterior
FSH	Follicle Stimulating Hormone
GAG	Glycosaminoglycan
GBCA	Gadolinium-Based Contrast Agent
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GGT	Gamma-Glutamyl Transferase
CCI	[redacted]
GLP	Good Laboratory Practice
GLDH	Glutamate Dehydrogenase

h	Hour
HA	Hyaluronic Acid
HBsAg	Hepatitis B virus Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
hsCRP	high sensitivity C-Reactive Protein
i.a.	intra-articular
i.v.	Intravenous
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICRS	International Cartilage Regeneration and Joint Preservation Society
IEC	Independent Ethics Committee
IG	Immunogenicity
IL	Interleukin
IN	Investigator Notification
INR	International Normalized Ratio
CCI	[redacted]
IRB	Institutional Review Board
IRT	Interactive Response Technology
KL	Kellgren-Lawrence
KOOS	Knee injury and Osteoarthritis Outcome Score
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
MCID	Minimal Clinically Important Difference
mL	Milliliter(s)
MRI	Magnetic Resonance Imaging
NOACs	New Oral Anticoagulants
NRS	Numerical Rating Scale
NSF	Nephrogenic Systemic Fibrosis
OA	Osteoarthritis
OTC	Over-the-Counter
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic(s)
CCI	[redacted]
PK	Pharmacokinetic(s)

PoC	Proof of Concept
PoM	Proof of Mechanism
PRN	Pro re nata (Lat. as needed)
PRO	Patient Reported Outcomes
PT	Prothrombin time
CCI	[redacted]
q4wx3	Dose administration every four weeks, three times
QMS	Quality Management System
QoL	Quality of Life
QTcF	QT Interval corrected by Fridericia's Formula
s.c.	Subcutaneous
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SI	Signal Intensity
SNP	Single Nucleotide Polymorphism
SUSAR	Suspected Unexpected Serious Adverse Reaction
TA	Treatment Arm
TB	Tuberculosis
TFC	Tibiofemoral Compartment
ULN	Upper Limit of Normal
UTI	Urinary Tract Infection
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent
WOMAC	Western Ontario and McMaster Universities Arthritis Index
WPI	Widespread Pain Index

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the trial
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a trial participant
Cohort	A specific group of participants fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal trial validity, and/or evaluate comparative effects of the investigational drug
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical trial data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from source data/documents used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug/ treatment	The drug whose properties are being tested in the study
Ktrans	A measure of capillary permeability obtained using dynamic contrast-enhanced (DCE) MR perfusion. It is calculated by measuring the accumulation of gadolinium-based contrast agent in the extravascular-extracellular space.
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.

Patient-Reported Outcome (PRO)	A measurement based on a report that comes directly from the patient about the status of a participant's health condition without amendment or interpretation of the patient's report by a clinician or anyone else
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Randomization	The process of assigning trial participants to investigational drug or control/comparator drug using an element of chance to determine the assignments in order to reduce bias
Randomization number	A unique identifier assigned to each randomized participant
Re-screening	If a participant fails the initial screening and is considered as a Screen Failure, he/she can be invited once for a new Screening visit after medical judgment and as specified by the protocol
Remote	Describes any trial activities performed at a location that is not the investigator site where the investigator will conduct the trial, but is for example a home or another appropriate location
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC) /	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

Amendment 02 (08-Dec-2022)

Amendment rationale

This amendment is generated to clarify permissible re-screening scenarios and to specify the required period of contraception use for women of child-bearing potential after the last investigational drug administration. The amendment also describes an Informed Consent Form used for healthy volunteers during the MRI qualification process, if required by local regulations.

The previous protocol version allowed re-screening of patients based on case-by-case agreement between the investigator and sponsor. To avoid subjective or inconsistent interpretations, the protocol now describes more specific scenarios when re-screening is permissible.

The protocol has been updated to align with the Summary of Product Characteristics (SmPC) of Ilaris® (canakinumab) which states that women of child-bearing potential should use an effective contraceptive method for up to 3 months after the last dose.

CCI [redacted] The hsCRP inclusion criterion has been updated accordingly (criterion 11), CCI [redacted]. The previous threshold of ≥2.0 mg/L has been established for evaluation of cardiovascular risks and therefore less applicable to this study.

Chondrocalcinosis has been removed from the examples of exclusionary conditions (exclusion criterion 8) because it was contradictory to Section 8.2, which correctly describes that information about chondrocalcinosis will be collected as part of the participant's baseline characteristics.

An inconsistency in the previous protocol version between Section 5.1 (inclusion criterion 10), Section 5.2 (exclusion criterion 18) and Table 6-3, with regards to the prohibition period for glucosamine, chondroitin and other nutraceuticals with cartilage-related effect, has been corrected by consistently refer to 4 weeks from Day 1.

If allowed by local regulations, a healthy volunteer MRI scan may be collected during set-up for the imaging qualification of an investigator site. For this purpose, a separate Informed Consent Form has been created and made available to the imaging centers as courtesy in case they do not have their own preferred template.

Minor editorial changes are also made throughout the protocol for increased clarity and consistency.

At the time of amendment, the study is actively recruiting. The first participant was screened on 27 Aug 2021. Seven participants have commenced study treatment.

Screening should continue at a site under the protocol version 01 until applicable approvals have been obtained for the amendment, and all required documents and material have been provided to the site.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

IRBs/IECs

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

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

The changes herein do NOT affect the global model Informed Consent Form. However, if the minimum required period of contraception use after the last investigational treatment dose has been specified in a locally adapted Informed Consent Form, the site must confirm the correct period is stated therein, and if not, ensure a revised version is approved.

Amendment 01 (15-Dec-2021)

Amendment rationale

This amendment is generated CCI [redacted]

An additional secondary objective is introduced in order to investigate differences in pain endpoints between all the four treatment arms (also comparing TA3 vs TA1 and TA3 vs TA4).

CCI [redacted]

The updated visit schedule also allows for an eligibility confirmation prior to the day of first dose, which reduces the participant and site burden compared to discovering potential ineligibility only at Day 1. In addition, the screening period window is prolonged to facilitate visit scheduling.

The inclusion criterion based on the pain diary is simplified to ensure correct and consistent interpretation. Furthermore, the population is broadened to include patients with KL grade 2-4 (previously 2-3), since the KL classification has documented inter-observer variability and the defined ranges for fJSW will avoid the inclusion of too advanced cases.

The necessity of excluding an active or latent tuberculosis (TB) infection, in accordance with the Ilaris® (canakinumab) label, has been emphasized.

Various sections that described mitigation plans in case of a potential SARS-CoV-2 outbreak are updated to a more general scenario of major disruption, such as other pandemics or natural disasters.

Laboratory assessments and CCI [redacted] are updated to reflect current practice in the target population.

The management of assessments when a participant has taken a prohibited pain medication prior to a visit are updated to avoid rescheduling of the entire visit.

The consequence for the individual participant in case of unblinding of the canakinumab treatment is clarified.

Terminology is updated throughout the document to align with the latest Clinical Data Interchange Standards Consortium (CDISC) guidance.

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

The simplifications introduced by this amendment, in particular the eligibility confirmation prior to first dose and the possibility to continue with the majority of assessments despite use of a prohibited pain medication, are expected to have a positive impact on visit compliance, site engagement and participant retention. The added PROs are short and should therefore not

CCI [redacted]

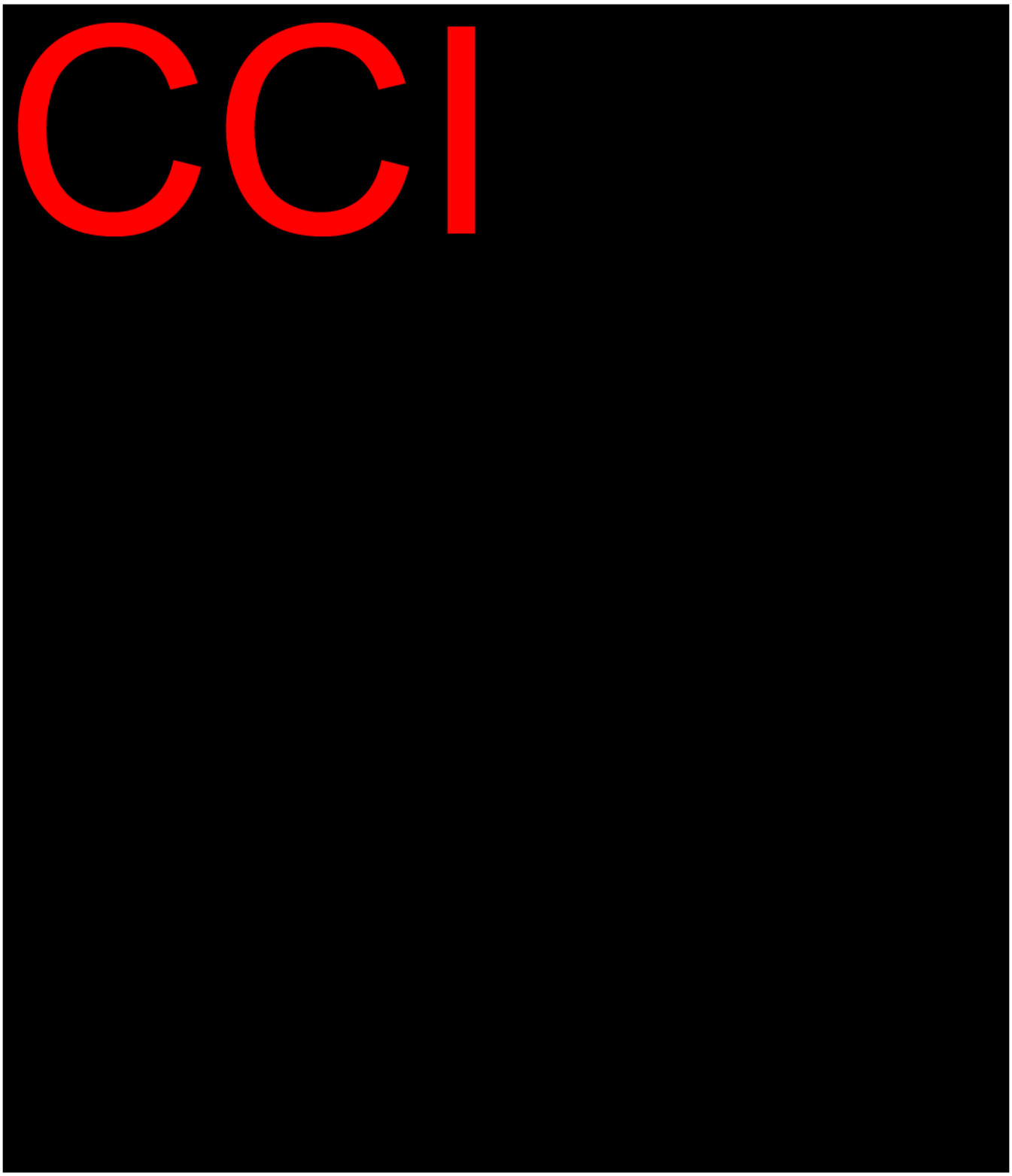
At the time of amendment, the study is actively recruiting. The first participant was screened on 27 Aug 2021. One participant has commenced study treatment.

Screening should continue at a site under the original protocol version until applicable approvals have been obtained for the amendment, and all required documents and material have been provided to the site.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions. The key changes are also listed below.

CCI [redacted]


CCI

IRBs/IECs

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

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

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

Local Amendment 00-HU.01 (23-Nov-2021)

Amendment rationale

This local amendment is created [redacted]

Changes to specific sections are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

Changes to the protocol

[redacted]

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) [redacted]

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

Protocol summary

Protocol number	LNA043A12203
Full Title	A randomized, four-arm, canakinumab placebo-controlled, participant, investigator and sponsor-blinded study investigating the safety, tolerability and efficacy of intra-articular canakinumab followed by intra-articular LNA043 in patients with knee osteoarthritis
Brief title	A safety and efficacy study of anti-inflammatory (canakinumab) and cartilage stimulating drugs (LNA043) injected into the knee joint of participants with knee osteoarthritis (OA)
Sponsor and Clinical Phase	Novartis Phase IIa
Investigation type	Biologic
Study type	Interventional
Purpose and rationale	This is a phase 2a proof of concept study with 4 treatment arms (TA1-4) to establish the effect of LNA043 in patients with symptomatic, knee OA with inflammation, defined by MRI. The chondro-anabolic effect of LNA043 given i.a. has been established in several knee OA studies, but without specifically addressing knee OA with inflammation. The purpose of the current study is • to assess if the effect of i.a. LNA043 can be established in patients with inflammatory knee OA • to assess if a possible negative effect of inflammation on the potential positive effect of LNA043 in cartilage regeneration can be overcome by combination treatment with an anti-inflammatory therapy (i.a. canakinumab) • to assess the efficacy of i.a. canakinumab in relieving pain, other clinical symptoms and improving function Current medical treatments of OA focus on addressing pain and there are no chondro-anabolic treatments available to induce cartilage regeneration. LNA043 has shown cartilage anabolic effects in early stages of knee degeneration but it is not known whether LNA043 will be sufficient to expeditiously reduce symptoms and rebuild structure in patients with moderate-severe knee OA, where concurrent intraarticular inflammation is common. In an inflammatory environment, degrading enzymes are abundant and chondrocytes are less responsive to anabolic stimuli due to metabolic shutdown. Inhibiting the inflammation with canakinumab before treating the patient with LNA043 might therefore affect the chondro-anabolic effect.
Primary Objective(s)	This study has two primary objectives; • To assess the efficacy of q4wx3 (dose administration every four weeks, three times) i.a. injections of LNA043 vs. no injections of LNA043, in maintaining or regenerating articular cartilage tissue, by measuring the change from baseline in cartilage volume in the index region by MRI at Day 197 • To assess the efficacy of a single i.a. injection of canakinumab vs. placebo in relieving OA pain, by measuring the change from baseline in Knee injury and Osteoarthritis Outcome Score (KOOS) Pain subscale at Day 85

Secondary Objectives	• To assess the safety and tolerability of q4wx3 i.a. injections of LNA043, a single i.a. injection of canakinumab and a single injection of canakinumab followed by q4wx3 i.a. injections of LNA043 relative to placebo to canakinumab/no LNA043 injections, by evaluating Adverse Events, ECG, vital signs and standard safety laboratory analyses • To assess the potential immunogenicity of q4wx3 i.a. injections of LNA043, by measuring anti-LNA043 antibodies in serum at Day 15, 43, 85, 197 and 365 • To assess endogenous ANGPTL3, and PK of LNA043, after q4wx3 i.a. injections of LNA043 and after a single i.a. injection of canakinumab followed by q4wx3 i.a. injections of LNA043, by measuring ANGPTL3 serum concentrations, ANGPTL3 synovial fluid concentrations and LNA043 PK profile in serum (Cmax, Tmax, AUC) • To assess the efficacy of a single i.a. injection of canakinumab followed by q4wx3 i.a. injections of LNA043 vs. a single i.a. injection of canakinumab, in regenerating articular cartilage; and vs. only q4wx3 ia. injections of LNA043, by measuring the change in cartilage volume and thickness of the index region by MRI at Day 197 and 365 • To assess the efficacy of q4wx3 i.a. injections of LNA043 vs. no injections of LNA043, in maintaining or regenerating articular cartilage, by measuring the change in cartilage thickness of the index region by MRI at Day 197, and the change in cartilage volume and thickness of the index region by MRI at Day 365 • To assess the efficacy of a single i.a. injection of canakinumab vs. placebo to canakinumab, on synovitis, by measuring the change in synovitis level measured from Ktrans by DCE-MRI at Day 85 • To assess the efficacy of a single i.a. injection of canakinumab vs. placebo to canakinumab, in relieving OA pain and improving function over time, by measuring the change in numeric rating scale (NRS) Pain at Day 15, 29, 43, 57, 71 and 85, and the change in KOOS Pain and Function in daily living (ADL) subscales at Day 15, 29, 43, 57, 71 and 85 • To assess the efficacy of a single i.a. injection of canakinumab followed by q4wx3 i.a. injections of LNA043 vs. a single i.a. injection of canakinumab, in relieving OA pain (TA3 vs. TA4), and vs. only q4wx3 i.a. injections of LNA043 (TA3 vs. TA1), by measuring the change in numeric rating scale (NRS) Pain, and change in in KOOS Pain and ADL subscales, at Day 15, 29, 43, 57, 71, 85, 197, 365
Study design	This is a non-confirmatory, randomized, four arm, placebo-controlled, participant, investigator and sponsor blinded (with regards to canakinumab whereas LNA043 treatment is open label) study in patients with knee OA. The study includes a 10 week treatment period during which participants receive a maximum of four i.a. injections into the knee. Participants are followed up until one year after first dose.
Study population	The study population consists of male and female adult patients with mild to moderate radiographic knee OA (KL grade 2-4) with inflammation. The inflammation will be confirmed by elevated hsCRP (≥1.8 mg/L) and observed synovitis on MRI, at screening. Approximately 138 patients are foreseen to be enrolled and randomised in the trial, of which at least 124 are expected to complete the Day 197 evaluation (10% discontinuation rate).

Key Inclusion criteria	• Male or female patients 40 to 80 years of age, inclusive • Diagnosis of primary tibiofemoral knee OA by standard American College of Rheumatology (ACR) clinical and radiographic criteria • Moderate to severe OA pain (corresponding to NRS Pain ≥5 to ≤9) in the target knee, confirmed by; CCI • KOOS pain subscale <60 for the target knee at Screening 1, Screening 2 and Screening 4 • Radiographic disease KL grade 2 to 4 knee OA and joint space width (JSW) 2.0-4.0 mm (men) or 1.5-3.5 mm (women) in the medial TFC in the target knee, confirmed by X-ray at Screening 1 • Active synovial inflammation, defined as moderate (score 9-12) or severe (score ≥13) as per contrast-enhanced MRI (CE-MRI) of the whole knee for synovitis detection from 11 sites at Screening 3

Key Exclusion criteria	• History of, or planned, following surgical interventions;
	  • Knee replacement (partial or total) in either knee
	  • Arthroscopy or lavage in either knee, within 6 months prior to Screening 1 or planned during the study
	  • Any other previous surgical intervention in the target knee, or within 12 months prior to Screening 1 or planned during the study for the contralateral knee, including mosaicplasty, microfracture, meniscectomy >50% or osteotomy
	• Onset of symptoms, or diagnosis, of primary osteoarthritis in other than the knee joints less than 3 months prior to Screening 1
	• Moderate to severe pain in the contralateral knee for the majority of days in the last 3 months prior to Screening 1, as per patient judgment
	• Unable or unwilling to undergo MRI, or having contraindications to MRI (e.g., metallic implants, metallic foreign bodies, pacemaker, defibrillator), or having contraindications to the use of gadolinium-based agents (e.g. patients with previous severe allergic/anaphylactoid reaction to a gadolinium-based contrast agent, moderate to severe renal disease, or acutely deteriorating renal function)
	• Malalignment >7.5° in the target knee (either varus or valgus)

Study treatment	• LNA043 10 mg, CCI injection, open label bulk supply CCI • Canakinumab 150 mg/1 mL, solution for injection (1 mL), open label bulk supply CCI • Canakinumab 0 mg/1 mL, placebo to canakinumab solution for injection (1 mL), open label bulk supply CCI In addition, it is imperative to harmonize and document participants' pain medication as it can potentially confound results. Therefore, only the use of paracetamol/acetaminophen, up to 3000 mg/day, alone or in combination with low dose codeine, e.g. co-codamol, is allowed as basic (non-rescue) medication for pain control regardless of the origin of the pain, up until Day 197. This medication is referred to as "basic pain medication" and the

	investigator will either be supplied with the basic pain medication or source it locally and be reimbursed by the sponsor for its cost, depending on the country.
Treatment of interest	Participants will be assigned to one of the following 4 treatment arms (TA) in a ratio of 1:2:1:2: • TA1: Single i.a. injection of placebo to canakinumab followed by q4wx3 i.a. injections of 40 mg LNA043 • TA2: Single i.a. injection of placebo to canakinumab • TA3: Single i.a. injection of 600 mg canakinumab followed by q4wx3 i.a. injections of 40 mg LNA043 • TA4: Single i.a. injection of 600 mg canakinumab
Efficacy assessments	• Cartilage volume and thickness by conventional 3T MRI • Synovitis level by Dynamic Contrast-Enhanced MRI (DCE-MRI) • Knee injury and Osteoarthritis Outcome Score (KOOS); Pain and Function in daily living (ADL) subscales • Numerical Rating Scale (NRS) Pain
Pharmacokinetic assessments	• Systemic (serum) concentration of endogenous ANGTPL3, and LNA043 • Local (synovial fluid) concentration of endogenous ANGPTL3
Key safety assessments	• Adverse event monitoring • Physical examinations • Monitoring of laboratory markers in blood and urine • ECG • Vital signs
Other assessments	
Data analysis	The analysis for primary endpoints will be carried out using a mixed effect model for repeated measures (MMRM). The model will include baseline as fixed covariate, treatment, timepoint, treatment * timepoints as fixed effects and participant as random effect. An unstructured covariance will be assumed; if not possible, other appropriate covariance structures will be explored such as Autoregressive (AR(1)), Compound symmetry, etc. A two-sided 90% confidence interval for the treatment effect will be formed. A statistically significant difference (one-sided p-value <0.05) between active drug and placebo at Day 85 (for ACZ) and Day 197 (for LNA) will be considered as a positive result. Similar MMRM models as for the primary endpoints will be used for analysis of secondary efficacy endpoints.

	Demographic and other baseline data, safety assessments and immunogenicity will be listed and summarized descriptively. Pharmacokinetic parameters for LNA043 will be calculated, and listed and summarized descriptively. Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.
Key words	Osteoarthritis; Knee osteoarthritis; Inflammation; Synovitis; Cartilage regeneration; Dynamic Contrast-Enhanced MRI; DCE-MRI; Disease-Modifying Osteoarthritis Drugs; DMOAD

1 Introduction

1.1 Background

Osteoarthritis (OA), a slowly progressive disease with a multifactorial pathophysiology, is one of the most common chronic health conditions in adults, and a leading cause of pain and disability (OARSI 2016). Currently, there are only few symptomatic therapies other than joint replacement surgery, and no structure-modifying drugs are available to date (Lohmander and Roos 2019). Due to the demographic changes in an ageing society, the prevalence of OA will steadily increase, posing a significant burden on global health-care systems (OARSI 2016). The knee joint is the most common weight-bearing joint affected by OA. Current medical treatments of OA focus on addressing pain, but there are no chondro-anabolic treatments available to induce cartilage regeneration, so called disease-modifying OA drugs (DMOADs). Eventual joint failure requiring surgical joint replacement is common, with over a million such operations annually in the United States (Williams et al 2015, Wolford et al 2015).

The role of Angiopoietin-like protein 3 (ANGPTL3) in chondrogenesis is a novel discovery made at Novartis. LNA043 is a modified human ANGPTL3 protein with chondrogenic and chondroprotective effects. So far, LNA043 has shown cartilage anabolic effects in early stages of knee degeneration in a proof of mechanism (PoM) study (LNA043X2201) in patients with cartilage lesions and in a proof of concept (PoC) study (LNA043X2202) in patients with early OA. However, it is not known whether a chondro-anabolic agent like LNA043 will be sufficient to expeditiously reduce symptoms and rebuild structure in symptomatic knee OA patients with intra-articular inflammation.

Such inflammation is present in 30-50% of OA patients with moderate-severe disease in acute flare phases of cartilage degradation and/or as chronic low-grade inflammation. Moreover, inflammation is actively involved in the pathophysiology of OA and the progression of the disease even in the absence of overt symptoms. Especially in later stages of OA, intra-articular inflammation is common. Unfortunately, intra-articular corticosteroids (IACS), the current standard of care for inflamed OA joints, have been shown to have long-term detrimental effects on articular cartilage, accelerating disease progression. In addition, data on the potential benefit and its duration after IACS are of low quality and inconsistent (Jüni et al 2015).

The inflammation is driven by a plethora of pro-inflammatory cytokines (e.g., IL-1β, TNFα) and chemokines (e.g., CCL5, IL-8) that are present in joint tissues, synovium, synovial fluid and cartilage of OA patients. These inflammatory mediators downregulate cartilage matrix production by chondrocytes and increase production of matrix-degrading enzymes (MMPs, ADAMTS) by chondrocytes and synovial cells, leading to the breakdown and loss of the cartilage matrix (van den Bosch 2019, Berenbaum 2013).

IL-1β inhibits chondrocyte and progenitor cells anabolic activity and upregulates catabolic enzymes and osteogenic markers *in vitro*. In an inflammatory environment, degrading enzymes are abundant and chondrocytes are less responsive to anabolic stimuli due to metabolic shutdown. In addition, strong evidence exists that IL-1 plays a critical role in OA (Wang et al 2015). Previous clinical trials of IL-1 inhibition in OA have been disappointing in terms of pain reduction (Chevalier et al 2009, Cohen et al 2011, Fleischmann et al 2019,

CACZ885C2201 (unpublished data)). These studies included patients with clinical and radiographic OA, whereas in the current protocol, only patients with knee OA with inflammation are to be included. Furthermore, in support of the current trial design, a post-hoc analyses of the CANTOS trial (ACZ885M2301) showed that the anti-IL-1β antibody canakinumab given s.c. quarterly reduced the incidence of hip or knee joint replacement, and the incidence of OA related adverse events in myocardial infarction patients selected for high sensitivity C-reactive protein (hsCRP) (Schieker et al 2020). These results support the concept of IL-1β inhibition for OA treatment in patients with increased hsCRP levels.

1.2 Purpose

This is a phase 2a proof of concept study with 4 treatment arms (TA1-4) to establish the effect of LNA043 in patients with symptomatic, knee OA with inflammation, defined by MRI. The chondro-anabolic effect of LNA043 given i.a. has been established in several knee OA studies, but without specifically addressing knee OA with inflammation.

The purpose of the study is

- to assess if the effect of i.a. LNA043 can be established in patients with inflammatory knee OA
- to assess if a possible negative effect of inflammation on the potential positive effect of LNA043 in cartilage regeneration can be overcome by concurrent treatment with an anti-inflammatory therapy (i.a. canakinumab)
- to assess the efficacy of i.a. canakinumab in relieving pain, other clinical symptoms and improving function

2 Objectives and endpoints

Study objectives and endpoints are listed in Table 2-1 below. Where an objective describes a change, it implicitly refers to change compared to the baseline defined in Section 3.

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To assess the efficacy of q4wx3 i.a. injections of LNA043 vs. no injections of LNA043, in regenerating articular cartilage tissue (TA1 vs. TA2)	• Change in cartilage volume in the index region measured by MRI at Day 197
• To assess the efficacy of a single i.a. injection of canakinumab vs. placebo in relieving OA pain (TA4 vs. TA2)	• Change in Knee injury and Osteoarthritis Outcome Score (KOOS) Pain subscale at Day 85

Objective(s)	Endpoint(s)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To assess the safety and tolerability of q4wx3 i.a. injections of LNA043, a single i.a. injection of canakinumab and a single injection of canakinumab followed by q4wx3 i.a. injections of LNA043 (TA1, TA3, TA4) relative to placebo to canakinumab/no LNA043 injections (TA2)	• Systemic and local Adverse Events (AEs) Electrocardiograms (ECGs) Vital signs Hematology, blood chemistry and urinalysis
• To assess the potential immunogenicity of q4wx3 i.a. injections of LNA043 (TA1 and TA3)	• Anti-LNA043 antibodies in serum, at Day 15, 43, 85, 197 and 365
• To assess endogenous ANGPTL3, and PK of LNA043, after q4wx3 i.a. injections of LNA043 and after a single i.a. injection of canakinumab followed by q4wx3 i.a. injections of LNA043 (TA1 and TA3)	• ANGPTL3 serum concentrations ANGPTL3 synovial fluid concentrations LNA043 PK profile in serum (Cmax, Tmax, AUC)
• To assess the efficacy of a single i.a. injection of canakinumab followed by q4wx3 i.a. injections of LNA043 vs. a single i.a. injection of canakinumab, in regenerating articular cartilage (TA3 vs. TA4) and vs. only q4wx3 ia. injections of LNA043 (TA3 vs. TA1)	• Change in cartilage volume and thickness of the index region measured by MRI at Day 197 and Day 365
• To assess the efficacy of q4wx3 i.a. injections of LNA043 vs. no injections of LNA043, in maintaining or regenerating articular cartilage (TA1 vs. TA2)	• Change in cartilage thickness of the index region measured by MRI at Day 197 Change in cartilage volume and thickness of the index region measured by MRI at Day 365
• To assess the efficacy of a single i.a. injection of canakinumab vs. placebo to canakinumab, on synovitis (TA4 vs. TA2)	• Change in synovitis level measured from Ktrans by Dynamic Contrast Enhanced MRI (DCE-MRI) at Day 85
• To assess the efficacy of a single i.a. injection of canakinumab vs. placebo to canakinumab, in relieving OA pain and improving function over time (TA4 vs. TA2)	• Change in numeric rating scale (NRS) Pain at Day 15, 29, 43, 57, 71, 85 Change in KOOS Pain and Function in daily living (ADL) subscales at Day 15, 29, 43, 57, 71, 85
• To assess the efficacy of a single i.a. injection of canakinumab followed by q4wx3 i.a. injections of LNA043 vs. a single i.a. injection of canakinumab, in relieving OA pain (TA3 vs. TA4), and vs. only q4wx3 i.a. injections of LNA043 (TA3 vs. TA1)	• Change in numeric rating scale (NRS) Pain at Day 15, 29, 43, 57, 71, 85, 197, 365 Change in KOOS Pain and Function in daily living (ADL) subscales at Day 15, 29, 43, 57, 71, 85, 197, 365
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
CCI	

Objective(s)	**Endpoint(s)**
CCI	

Objective(s)	Endpoint(s)
CCI	

2.1 Primary estimands

Not applicable.

2.2 Secondary estimands

Not applicable.

3 Study design

This is a non-confirmatory, randomized, four arm, placebo-controlled, participant, investigator and sponsor blinded (with regards to canakinumab whereas LNA043 treatment is open label) study in patients with knee OA with inflammation.

The study consists of four screening visits (Screening 1-4), of which Screening 2 and 4 can be performed remotely, and then four treatment visits, at Day 1, 15, 43 and 71. Upon completion of the 10-week treatment period, participants will enter a follow-up period with visits at Day 85, Day 197 and Day 365, i.e. participants will be followed up until one year after the first dose. The Day 365 visit is the End of Study (EoS) visit.

Following their informed consent, participants will be assessed for eligibility at the first of four screening visits (Screening 1). Screening 1 can be arranged up to 42 days prior to Day 1. If eligible at Screening 1, the participant should switch any ongoing pain medications to the provided Basic Pain Medication, see Section 6.1.2.

The purpose of the second screening visit (Screening 2) CCI [redacted] Screening 2 can be performed remotely, i.e. as a telephone or online visit.

The third screening visit (Screening 3) is dedicated to the MRI assessment and should only be performed if the participant qualifies based on all assessments at Screening 1 and Screening 2. Screening 3 should be arranged as close to but no later than 14 days prior to Day 1, to establish an imaging baseline but still allow sufficient turnaround time for the central imaging evaluation.

The fourth and last screening visit (Screening 4) CCI [redacted]. Screening 4 should be performed within maximum five days from first dose (Day 1) and may be performed remotely.

To mitigate potential SARS-CoV-2 infections among participants, guidance and requirements provided by the local regulatory authorities will be followed, which could include screening for SARS-CoV-2 by Polymerase Chain Reaction (PCR) or equivalent approved methodology prior to admission at the investigator site for any overnight stays (if applicable) following local site-specific SOPs.

Once eligibility has been confirmed at Screening 4, participants will be randomized to one of the four treatment arms shown by Figure 3-1 according to a 1:2:1:2 ratio. Participants will then on Day 1 receive an i.a. injection of either canakinumab 600 mg, or matching placebo. Fourteen days later, participants randomized to treatment arms 1 or 3 will receive i.a. injections of LNA043 40 mg every 4 weeks, on Day 15, 43 and 71, with two intermediate follow up remote visits (on-site attendance not needed), on Day 29 and 57. The LNA043 treatment regimen is abbreviated 'q4wx3'.

Participants randomised to TA 2 and 4 will attend the same visits but will not receive further study drug beyond the injection on Day 1, except analgesic treatment defined in Section 6.1.2. The canakinumab treatment is placebo controlled and blinded to participants and investigators whereas the LNA043 treatment is open label.

Conventional 3T MRI will be performed at four visits: Screening 3, Day 85, Day 197 and Day 365. DCE-MRI will be collected at two visits: Screening 3 and Day 85.

Pain assessments are collected throughout the study, and via a pain diary up until Day 85. In addition, the participant should complete the pain diary for one week prior to the Day 197 and Day 365 visits.

CCI [redacted] Blood samples for LNA043 PK and IG analysis will be collected from all participants who are randomized to receive LNA043 injections (TA1 and TA3) at a limited number of timepoints, and at additional time points for participants who also consent to the optional LNA043 PK collections (see Section 8.5.1).

Participants will return to the investigator site at Day 85, Day 197 and Day 365 for follow up assessments.

Baseline is defined as the assessments collected pre-dose on Day 1, except for MRI for which baseline data will be collected at Screening 3.

Assessments will be performed at visits and time points specified in the Assessment schedule Table 8-1.

Figure 3-1 Study design

4 Rationale

4.1 Rationale for study design

The design of this study addresses the primary objective of assessing the ability of LNA043 to regenerate articular cartilage tissue in patients with symptomatic knee OA with inflammation after injection of placebo or canakinumab i.a. Furthermore, this study is designed to address the co-primary objective in the ability of canakinumab to reduce pain and/or inflammation in patients with symptomatic knee OA with inflammation.

This study takes into account (i) the clinical need; (ii) clinical and preclinical data on LNA043; (iii) clinical and preclinical data on canakinumab; (iv) current practice with i.a. injectable drugs; and (v) the burden on patients with symptomatic knee OA with inflammation. The combination of MRI measuring the cartilage volume in the index region as well as synovitis and well-established PROs such as KOOS (Bekkers et al 2009) will ensure appropriate evaluation of canakinumab and/or LNA043 effects in this inflamed joint environment, from both a morphological (cartilage structure and synovitis) and a functional standpoint. Given the methodological challenge of measuring relevant changes in pain, care has been taken to select potential participants and assessments based on current recommendations for pain assessments in the literature (Dworkin et al 2012, Patel et al 2021).

For the investigation of canakinumab treatment on OA pain the study has been designed as participant, investigator and sponsor blinded in order to ensure that mentioned parties remain in a state of equipoise, so that a putative difference between the treated and control groups can be interpreted as an effect of study treatment. However, placebo to LNA043 will not be used for reasons described in Section 4.3.

CCI [redacted] Patients will nevertheless be followed up for 12 months to pursue the preservation of the cartilage. The pain effect will be investigated after 3 months CCI [redacted].

Inclusion criteria (e.g., elevated hsCRP ≥1.8 mg/L, fJSW 2.0-4.0 mm (men) or 1.5-3.5 mm (women), age 40-80 years, NRS Pain level at CCI [redacted] of ≥5 to ≤9, KOOS level of <60, and signs of synovitis in MRI) have been selected to enrich for patients with knee OA with inflammation.

The participant population with symptomatic, knee OA of the medial compartment, with inflammation fulfilling the inclusion criteria has been selected in order to i) focus on cartilage regeneration in a high-risk population; ii) maximize the relevance of the findings as the medial compartment is the most frequently affected region of the knee in patients with OA (Wise et al 2012); The exclusion criteria of moderate to severe pain in the contralateral knee for the majority of days in the last 3 months prior to Screening 1 has been chosen to minimize bias caused by severe pain from the contralateral knee affecting the reporting of pain from the target knee as well as knee function. Patients aged <40 years are excluded because their knee inflammation is often acute or subacute caused by trauma.

The inclusion of patients with Widespread Pain Index (WPI) ≤4 is to minimize bias potentially affecting the reporting of pain and function by the presence of generalized pain (Yazici et al 2017). Similarly, patients with newly diagnosed OA in other joints, or ipsilateral hip OA/joint replacement surgery, are excluded to minimize bias.

4.2 Rationale for dose/regimen and duration of treatment

The dose of LNA043 in this study will be 40 mg, given by i.a. injection three times at four-weekly intervals.

In the first-in-human study LNA043X2101, following a single i.a. injection of 0.2, 2, 10, 20, or 40 mg, LNA043 demonstrated an acceptable safety profile and was well tolerated, and could not be measured in synovial fluid 7 days post-dose. At the 40 mg dose level, LNA043 was quantifiable in serum up to 8 hours post-dose, but below quantification limit at 2-4 days post-dose.

Weekly i.a. dosing in the dog did not result in accumulation of LNA043 in serum (undetectable or close to the 25 ng/mL lower limit of quantification (LLOQ) at 24h post-dose), and based on the rapid clearance observed so far in human, accumulation in serum is not expected following monthly dosing in humans. The systemic exposure data from the LNA043X2101 study at 40 mg are based on a limited set of time-points (four concentrations per subject above the LLOQ), and accordingly the AUC0-8h of 1460 ng.h/mL should be treated with caution since they are likely to be somewhat under-estimated. CCI [redacted] When comparing the clinical exposure data with those from the rat and dog i.v. dosing studies, there is a substantial systemic safety margin. Thus, the clinical Cmax of 259 ng/mL following a 40 mg dose in humans is 8991-fold lower than the Cmax observed at the 20 mg/kg dose in the 4-week i.v. dog study, and 168-fold lower than the Cmax observed at 5 mg/kg in the 26-week i.v. rat study. The clinical AUC0-8h 40 mg dose of 1460 ng.h/mL following a 40 mg dose is 91-fold lower than the AUC in the dog following a 20 mg/kg dose and 266-fold lower than the AUC in the rat at 5 mg/kg dose level. As stated earlier, however, these multiples should be interpreted with caution.

A dose of 40 mg is expected to deliver a pharmacological effect since in non-clinical efficacy models, effects start to become observable at 2 µg LNA043 in the rat knee (which scales to 560 µg in human, based on body weight) and 100 µg in the dog (equivalent to 700 µg in human). In both disease models, increasing the dose increased the efficacy and a single dose was enough to elicit a significant effect. Human cartilage is known to be thicker and less easily repaired than in animal models, therefore the 40 mg dose level has been selected based on feasibility, safety and tolerability in previous clinical experience, safety margins with respect to animals, and level of desired pharmacology. Recent data in rats indicate that efficacy following a single dose tends to be transient, and that repeat dosing results in more lasting effects. Therefore, the current study is designed to evaluate the effectiveness of three doses, administered every four weeks, at the 40 mg level to a single knee joint per patient.

In conclusion, clinical experience to date with LNA043 indicates that this compound demonstrates an acceptable safety profile and is well-tolerated, see also Section 4.5.2 or the Investigator's Brochure (IB). A dose of 40 mg has been selected for repeat dosing, for three doses, every four weeks, based on safety and feasibility, and in order to maximize the likelihood of delivering a sustained, pharmacodynamic effect leading to cartilage repair in the knee.

The dose of canakinumab given in this study will be 600 mg, as a single i.a. injection. CCI [redacted] The most frequent class of AEs was Infections and infestations, which is consistent with the known safety profile of canakinumab.

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

No cartilage-anabolic compound able to promote cartilage regeneration has been approved to date. The anabolic effect of LNA043 compared to placebo, in a non-inflamed knee OA population, is being investigated in other trials (LNA043X2202, LNA043A12202). To investigate the cartilage regenerative effect of LNA043 in inflamed joints the effect will be measured with MRI in this study. Placebo to LNA043 is omitted to avoid additional i.a. placebo injections and to allow for the investigation of the effect of canakinumab treatment on pain without the confounding effect of additional i.a. injections. The lack of placebo is not expected to impact the MRI analysis (structural endpoints and central reader blinded assessment).

Placebo to canakinumab (TA1 and TA2) contains the same formulation and excipients as the investigational drug, without the active agent.

4.4 Purpose and timing of interim analyses/design adaptations

An interim analysis is planned after all the participants have completed Day 85 in the study. The purpose is to evaluate the primary objective related to the canakinumab treatment, along with an examination of relevant safety data.

A second interim analysis is planned after all the participants have completed Day 197 in the study. The purpose is to evaluate the primary objective related to the LNA043 treatment, along with an examination of relevant safety data.

Additional interim analyses may be conducted to support decision making concerning the current clinical study, the sponsor's clinical development projects in general, or in case of any safety concerns.

Additional information is presented in Section 12.7.

4.5 Risks and benefits

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

Risks associated with LNA043, canakinumab and imaging are described in separate sections below. For risks associated with the over-the-counter (OTC) medications paracetamol, with or without low-dose codeine, reference is made to the prescribing information.

4.5.1 Benefits

It is not known whether there will be a benefit for the patients with symptomatic knee OA with inflammation participating in this study. Preclinical data and data from clinical studies of LNA043 in patients with cartilage damage either in the context of OA or of cartilage injury; CLNA043X2101 (First in Human), CLNA043X2201 (Proof of Mechanism) and ongoing CLNA043X2202 (Proof of Concept) indicate the chondro-anabolic and chondro-protective effects of LNA043 on damaged articular cartilage at both molecular and tissue level. So far, no approved therapy exists as standard of care addressing the unmet medical need of cartilage repair in patients with degenerative cartilage disorders. Therefore, no such therapies will be withheld by joining this study.

Participants will also receive canakinumab and based on previous (post-hoc) analysis, there is an hypothesis that canakinumab can reduce pain in patients with knee OA with inflammation.

4.5.2 Risks associated with LNA043

Invasive, study-specific procedures include synovial fluid aspiration and i.a. injection of LNA043. As with any invasive procedure (i.a. injection), a risk of inflammation/swelling, pain, infection, and/or bleeding exists; for i.a. injections these complications can occur both at the injection site and within the joint space. Recent reports indicate an incidence of 0.04-0.1% of septic arthritis after intra-articular infiltrations (Kjaer Petersen et al 2019, Kemmerer et al 2017, Geirsson et al 2008). In addition, when proper technique (O'Rourke 2020, AWMF S1 Leitlinie 2015) is applied in a healthy population, and when a non-steroidal drug is used, this rate is considerably lower. Proper aseptic technique will be used in all phases of CCI [redacted] and administration to further prevent the above mentioned risks. Potential adverse effects may include local reactions at the site of injection, such as local pain, swelling or inflammation, and 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 participant.

Systemic concentrations of LNA043 following i.a. administration to the participants studied in the FIH study (LNA043X2101) remained <300 ng/mL and within the physiologic range for circulating concentrations of ANGPTL3, the endogenous protein from which LNA043 is derived. 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.

[redacted]

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 intraarticular 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. CCI

To mitigate the possible risk of severe hypersensitivity reactions in humans, participants with a history of hypersensitivity reactions to any of the study treatments or excipients, or to drugs of similar classes, will be excluded from participation in this study. Participants who experience any grade hypersensitivity reaction will not be re-dosed, and the study will be paused and no further dosing will occur pending a full safety review if two or more participants develop an acute allergic reaction of Grade 3 severity or greater, or one or more participants with life-threatening (Grade 4) or fatal acute allergic reaction according to the NCI-CTCAE/v4.03 Criteria within 24 hours following LNA043 administration (i.e., active drug), unless clearly caused by exposure to a known allergen (i.e. peanut allergy).

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

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

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

4.5.3 Risks associated with canakinumab

Systemic concentrations of canakinumab following i.a. administration to the osteoarthritis participants studied in the completed trial ACZ885C2201 were comparable with s.c. injection and are considered not to confer additional safety risks. No additional safety risk is expected from a single local administration.

Canakinumab is associated with an increased incidence of serious infections (see the Reference Safety Information in the canakinumab Investigator's Brochure). Therefore, participants should be monitored carefully for signs and symptoms of infections before, during and after treatment with canakinumab. Physicians should exercise caution when administering canakinumab to participants with infections, a history of recurring infections, or underlying conditions which may predispose them to infections. The presence of latent or active tuberculosis must be excluded before administration.

Over 2,600 patients including approximately 480 children (aged 2 to 17 years) have been treated with canakinumab in interventional studies in Periodic fever syndromes, Still's disease, gouty arthritis, or other IL-1 beta mediated diseases, and healthy volunteers. The most frequently reported adverse drug reactions were infections, predominantly of the upper respiratory tract. The majority of the events were mild to moderate although serious infections were observed. No impact on the type reactions and opportunistic infections have been reported in patients treated with canakinumab. Neutropenia and leukopenia has also been observed with IL-1 inhibitors including canakinumab, with transient decreases to $<1x10^9$/L observed during clinical trials with canakinumab. In addition to experience in approved indications, over 10,000 patients were enrolled in CANTOS study evaluating canakinumab for the prevention of recurrent cardiovascular events among stable post-myocardial infarction patients with elevated C-reactive protein (CRP), with a cumulative exposure of 32662.6 patient-years (21745.1 patient-years for total canakinumab and 10917.5 patient-years total for placebo). No clinically meaningful differences between canakinumab and placebo were observed for most safety topics of interest, apart from an increase in serious infections and of fatal infections/sepsis; however, the overall incidence was low. The pattern of infections was stable over time, with very few confirmed opportunistic infections distributed evenly across the

treatment groups. There was no evidence of tuberculosis reactivation in canakinumab-treated patients.

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.

Live vaccines should not be given concurrently with canakinumab. No data are available on either the effects of live vaccination or the secondary transmission of infection by live vaccines in patients receiving canakinumab. It is recommended that, if possible, pediatric and adult patients should complete all immunizations in accordance with current immunization guidelines 3 months prior to or after initiating canakinumab therapy. On the other hand, the results of a study in healthy adult participants demonstrated that a single dose of canakinumab 300 mg administered subcutaneously did not affect the induction and persistence of antibody responses after vaccination with influenza and glycosylated protein-based meningococcus vaccines. Additionally, there was no evidence of herpes zoster infection related to receipt of herpes zoster live (attenuated) vaccine in 60 patients who received the vaccine after starting treatment with canakinumab in the CANTOS study (20, 16 and 18 patients on 300 mg, 150 mg, and 50 mg, respectively).

The results of a 56-week, open-label study in CAPS patients aged 4 years and younger demonstrated that all patients who received non-live, standard of care childhood vaccinations developed protective levels of antibody. In addition, time to the first infection in patients who were vaccinated within the 3 months prior to baseline, for investigator-reported infections, investigator-reported serious infections and IAC-confirmed infections in the CANTOS study did not show any clinically meaningful differences between the treatment groups. Similar observations were reported for time to the first infection by vaccination within 6 months from baseline.

4.5.4 Risks associated with imaging assessments

An anteroposterior view x-ray of the target and contralateral knees are often performed during the routine evaluation of patients with knee pain, but not always. Consequently, in some participants they will be obtained only for research purposes. The total amount of radiation exposure per participant from these X-rays will be about 100 µSv. This amount of radiation is equivalent to approximately 13.8 days of background exposure (0.3 µSv per hour at sea level). For effective radiation doses under 3 mSv (300 mrem), the risk is considered to be "minimal". Therefore, the radiation exposure in this study involves minimal risk and is necessary to ensure eligibility of patients.

Magnetic resonance imaging (MRI) will be used in this study both for patient selection and follow-up purposes. MRI is a non-invasive radiology technique that has no x-ray radiation exposure. Thus in principle, MRI scans can be repeated in the same patient as often as necessary. The MRI scanning equipment may cause a feeling of claustrophobia in susceptible persons. The presence of metal in the body may also be a safety hazard or affect the MR image quality. For more information, see exclusion criterion in Section 5.2.

In addition, for the sake of synovitis assessments, a gadolinium-based contrast agent (GBCA) will be administered as an i.v. bolus during each DCE-MRI session. There is recent evidence of gadolinium deposition in brain tissues following use of GBCAs. Although no symptoms or diseases linked to gadolinium accumulation in the brain have been identified, health authorities took a precautionary approach (e.g., EMA/625317/2017), noting that data on the long-term effects in the brain are limited. This led to the suspension of several linear GBCAs and the recommendation that another class of GBCAs known as macrocyclic agents be used as an alternative solution, as they are deemed more stable and have a lower propensity to release gadolinium than linear agents. Although this is highly debated, the current belief is that such agents, especially the linear gadolinium agents, may also increase the risk of a rare but serious disease called nephrogenic systemic fibrosis (NFS). To prevent this risk and in accordance with recommended guidance (e.g., The Royal College of Radiologists 2019, Magnevist® Prescribing information 2018), people with severe kidney failure, patients with previous severe allergic/anaphylactoid reaction to a GBCA; patients with moderate to severe renal disease or acutely deteriorating renal function, who would be at risk of nephrogenic systemic fibrosis, must be excluded from participating in this study.

4.5.5 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected from each participant over a period of approximately 13 months. The approximate volumes are mentioned in the ICF. Additional samples may be required for safety monitoring.

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

A summary blood log is provided in the laboratory manual. Instructions for sample collection, processing, storage and shipment information are also available in the laboratory manual.

See Section 8.5.2.9 on the potential use of residual samples.

4.6 Rationale for Public Health Emergency mitigation procedures

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

5 Study Population

The study population consists of male and female adult patients with symptomatic mild to moderate radiographic knee OA (Kellgren-Lawrence (KL) grade 2-4) with inflammation. The inflammation will be confirmed by elevated hsCRP (≥1.8 mg/L) and observed synovitis on MRI, at Screening 2.

Approximately 138 patients are foreseen to be enrolled and randomised in the trial, of which at least 124 are expected to complete the Day 197 evaluation per protocol (10% discontinuation rate). Additional patients may be enrolled if the discontinuation rate exceeds 10%.

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

The suffix a, b, c, etc., in the numbering of criteria in Section 5.1 and Section 5.2 denotes the number of times the criterion text has been updated compared to the initial protocol version (insignificant changes that do not alter the actual requirements are not counted).

5.1 Inclusion criteria

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

1. Written informed consent must be obtained before any assessment is performed
2. Able to communicate well with the investigator at Screening 1, to understand and comply with the requirements of the trial
3. Male or female patients 40 to 80 years of age, inclusive
4. Body weight of at least 50 kg and body mass index (BMI) within the range of 18.0 - 35.0 kg/m^2
5. Diagnosis of primary tibiofemoral knee OA by standard American College of Rheumatology (ACR) clinical and radiographic criteria (Altman et al 1986)
6. Moderate to severe OA pain (corresponding to NRS Pain ≥5 to ≤9) in the target knee for the majority of days in the last 3 months prior to Screening 1, as per patient judgment

7a. Primary source of pain throughout the body is due to OA in the target knee, and Widespread Pain Index (WPI) score of ≤4, at Screening 1

8a. Moderate to severe OA pain (corresponding to NRS Pain ≥5 to ≤9) in the target knee, confirmed by

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9a. KOOS pain subscale <60 for the target knee at Screening 1, Screening 2 and Screening 4

10a. Current use of analgesic therapy, including PRN (as needed) use, for control of local pain in the target knee

- Patients taking glucosamine, chondroitin, or any other nutraceutical with potential activity on cartilage repair must be willing to discontinue use from Screening 1.

11a. High sensitivity C-reactive Protein (hsCRP) ≥1.8 mg/L

12a. Radiographic KL grade 2 to 4 knee OA and joint space width (JSW) 2.0-4.0 mm (men) or 1.5-3.5 mm (women) in the medial tibiofemoral compartment (TFC) in the target knee, confirmed by X-ray at Screening 1

13a. Contrast-enhanced MRI (CE-MRI) diagnosed moderate or severe knee synovitis based on an established synovitis scoring system (moderate score 9-12 or severe score ≥13) (Guermazi et al 2011), at Screening 3. Only patients with clinical suspicion of synovitis (e.g. warmth, swelling/bulge sign or patellar tap sign, as per investigator judgment) should undergo CE-MRI.

5.2 Exclusion criteria

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

1a. History of, or planned, following surgical interventions;

- Knee replacement (partial or total) in either knee
- Arthroscopy or lavage in either knee, within 6 months prior to Screening 1 or planned during the study
- Any other previous surgical intervention in the target knee, or within 12 months prior to Screening 1 or planned during the study for the contralateral knee, including mosaicplasty, microfracture, meniscectomy >50% or osteotomy

2. Onset of symptoms, or diagnosis, of primary OA in other than the knee joints less than 3 months prior to Screening 1

3. Moderate to severe pain in the contralateral knee for the majority of days in the last 3 months prior to Screening 1, as per patient judgment

4a. Unable or unwilling to undergo MRI, or having contraindications to MRI (e.g., metallic implants, metallic foreign bodies, pacemaker, defibrillator), or having contraindications to the use of gadolinium-based agents (e.g. patients with previous severe allergic/anaphylactoid reaction to a gadolinium-based contrast agent, moderate to severe renal disease, or acutely deteriorating renal function)

5. Malalignment >7.5° in the target knee (either varus or valgus)

6. Unstable target knee joint (including, but not limited to, posttraumatic or congenital laxity) or insufficiently reconstructed ligaments based on medical history and/or physical examination by the Investigator

7a. Any diagnosis of systemic inflammatory arthritis or connective tissue disease, established by anamnestic information, clinical signs and symptoms with laboratory or imaging markers, including but not limited to rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, gout, Paget's disease, systemic lupus erythematosus or other systemic condition that might confound assessment of OA (e.g. fibromyalgia)

8b. Any diagnosis of local conditions affecting the target joint, established by anamnestic information, or clinical signs and symptoms with laboratory or imaging markers, including but not limited to septic arthritis, reactive arthritis, recurrent clinical episodes of pseudogout, articular fracture, or other local conditions that might confound assessment of OA

9a. Symptomatic patello-femoral pain in the target knee as per the Investigator's examination

10. Ipsilateral hip OA or hip prosthesis recently implanted (within 1 year prior to Screening 1) or hip replacement on either side planned within the study period

11. History of coagulopathy (hemophilia, von Willebrand disease, Factor X deficiency, etc) or medical condition requiring anticoagulation treatment that would preclude knee injection
    - Note: Low-dose aspirin (<325 mg) or anticoagulant management (cumarinics, heparin, direct oral anticoagulants) is allowed as per local practice and as long as INR <3 before the planned first injection. Suspension of new oral anticoagulants (NOACs; e.g., apixaban, dabigatran, rivaroxaban, and edoxaban) before i.a. injection should be assessed by the treating physician, based on local prescribing information.

12a. Metabolic or genetic abnormalities associated with arthropathy, e.g., arthrogryposis multiplex congenita, hemophilia, neurogenic arthropathy, hypermobility or hyperelasticity syndromes

13a. Uncontrolled hypertension, defined as systolic blood pressure (SBP) >160 mmHg and/or diastolic blood pressure (DBP) >100 mmHg at Screening 1

14. History or current diagnosis of ECG abnormalities indicating significant safety risk 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), history of familial long QT syndrome or known family history of Torsades de Pointes

15a. Any known active infections, including skin or knee infections, or suspected or confirmed immunocompromised state, including but not limited to evidence of active or latent tuberculosis (TB), chronic or active hepatitis B or C, known history of, or testing positive for, HIV infection

16. Skin infection, or wound, at the investigational product administration site

17. Total WBC count <3,000/µL, neutrophils <1,500/µL, hemoglobin <8.5 g/dL (85 g/L) or platelet count <100,000/µL

18b. Use of the following prohibited medications (within the period defined below prior to planned Day 1):

- Any local i.a. treatment into the knee, including but not limited to hyaluronic acid, viscosupplementation and corticosteroids (12 weeks)
- Diacetylrhein or centrally acting analgesics (12 weeks)
- Any biological drug (26 weeks)
- Any previous exposure to LNA043
- Long-term treatment (>14 days) with oral corticosteroids >5 mg/day (8 weeks)
- Oral glucosamine, chondroitin sulfate, or any other nutraceutical with potential activity on cartilage repair (4 weeks)
- Any live vaccine (12 weeks)

19. Use of other investigational drugs within 5 half-lives from Screening 1, or until the expected pharmacodynamic (PD) effect has returned to baseline, whichever is longer; or longer if required by local regulations

20. History of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes

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

22a. Any diagnosed psychiatric condition that includes, but is not limited to, a history of mania, bipolar disorder, psychotic disorder, schizophrenia, or schizoaffective disorder, depression or anxiety which may jeopardize patient safety, pain perception or compliance with study procedures, as judged by the investigator

23. History of drug abuse or unhealthy alcohol use within the 12 months prior to expected first dose, or evidence of such abuse as indicated by the laboratory assays conducted during screening

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

24. Pregnant or nursing (lactating) women

25b. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception while taking study treatment and for 3 months after the canakinumab/placebo injection, or 15 days after the last LNA043 injection, whichever is later

Highly effective contraception methods include:

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

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

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

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

Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms). Women are considered not of child bearing potential if they are post-menopausal or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or 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. See also Section 8.4.4 (Pregnancy and Assessments of Fertility).

26a. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the patient in case of participation in the study, taking into consideration the patient's medical history, physical examination and/or clinical or laboratory evidence, included but not limited to:

- Autoimmune disease amenable to, or under ongoing, immunomodulatory treatment
- Inflammatory bowel disease, peptic ulcers, gastrointestinal including rectal bleeding
- Major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection
- Pancreatic injury or pancreatitis
- Known active or recurrent hepatic disorder, including but not limited to cirrhosis, hepatitis B and hepatitis C, or abnormal liver function tests (e.g., abnormal alanine aminotransferase/ aspartate aminotransferase (ALT/AST), alkaline phosphatase levels, serum bilirubin, albumin and prothrombine time, where any single parameter >2 times ULN should be considered exclusionary
- Moderate to severe renal impairment, defined as estimated GFR < 50 mL/min/1.73 m^2 by the CKD-EPI formula

- Nephrotic syndrome and/or significant proteinuria, defined as ≥ 3+ at urinalysis dipstick test or protein: creatinine ratio ≥ 1 g/g Cr
- Evidence of urinary obstruction or difficulty in voiding at Screening 1

6 Treatment

6.1 Study treatment

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

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

6.1.1 Investigational and control drugs

Table 6-1 Investigational and control drug

Investigational/ Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)
LNA043 10 mg	CCI [redacted] injection	Intra-articular injection	Open label bulk supply CCI [redacted]	Sponsor (global)
ACZ885 150 mg/1 mL	Solution for injection (1 mL)	Intra-articular injection	Open label bulk supply CCI [redacted]	Sponsor (global)
ACZ885 0 mg/1 mL	Placebo to ACZ885 solution for injection (1 mL)	Intra-articular injection	Open label bulk supply CCI [redacted]	Sponsor (global)

All dose preparations, regardless of the treatment regimen, require CCI [redacted] of the intended investigational/control drug and are prepared in a syringe with a [redacted] mL injection volume. See Section 6.1.3 for a specification of the treatment arms.

Canakinumab is the generic name of ACZ885. The generic name is generally used throughout the protocol and in study documentation but reference to 'ACZ885' may also exist. LNA043 has not been assigned a generic name.

6.1.2 Additional study treatments

It is imperative to harmonize and document participants pain medication as it can potentially confound results. Therefore, only the use of paracetamol/acetaminophen, up to 3000 mg/day,alone or in combination with low dose codeine, e.g. co-codamol, is allowed as basic (non-rescue) medication for pain control, regardless of the origin of the pain, up until Day 197. This medication is herein referred to as "basic pain medication".

The investigator will either be supplied with the basic pain medication or source it locally and be reimbursed by the sponsor for its cost, depending on the country.

At each study visit, participants will be provided with a quantity of the basic pain medication, either the paracetamol/acetaminophen or the paracetamol/acetaminophen plus codeine combination product, that is estimated to be sufficient until the next planned study visit, starting at Screening 1 and until Day 197. As there are 16 weeks between Day 85 and Day 197, a smaller amount of medication will be provided at Day 85 and the participant will be resupplied by the site when needed and as per local arrangement. The investigator and participant can agree to switch from one to the other type of basic pain medication, for example from single compound paracetamol/acetaminophen to the codeine combination product or vice versa, if deemed necessary and provided both types are available to the investigator.

Patients who use other pain medications must be willing to switch to the basic pain medication at Screening 1 (inclusion criterion).

The participant should only use the basic pain medication provided by the investigator, even if s/he uses or purchases the same generic compound privately.

The basic pain medication can be taken at any point in the study, also within 48 hours of a study visit. To the extent possible, no other pain medication should be used up until Day 197 (see Section 6.2.3 Rescue medication).

Participants will be provided with a diary in which they will document their daily pain and the use of (any) pain medication from Screening 1 up to Day 85, plus one week prior to each of the Day 197 and Day 365 visits (see Section 8.3.2). The investigator or delegate should review the pain diary at each visit to ensure the number of returned basic pain medication tablets are reasonable compared to the documented use in the pain diary but full drug accountability will not be monitored.

The use of basic pain medication should be documented in the concomitant medication page of the CRF, including for which indication the medication is taken (e.g., target knee pain, headache, back pain).

Table 6-2 Basic pain medication

Medication (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
Paracetamol/acetaminophen 500mg	Tablet	Oral use	Open label bulk supply	Sponsor (local)
Paracetamol/acetaminophen in combination with low dose codeine; 500/30 mg	Tablet	Oral use	Open label bulk supply	Sponsor (local)

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

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

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

6.1.3 Treatment arms/group

Participants will be assigned at Day 1 to one of the following 4 treatment arms in a ratio of 1:2:1:2:

- TA1: Single i.a. injection of placebo to canakinumab followed by q4wx3 i.a. injections of 40 mg LNA043
- TA2: Single i.a. injection of placebo to canakinumab
- TA3: Single i.a. injection of 600 mg canakinumab followed by q4wx3 i.a. injections of 40 mg LNA043
- TA4: Single i.a. injection of 600 mg canakinumab

6.2 Other treatment(s)

6.2.1 Concomitant therapy

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

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

Medication entries should be specific to 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 patient or, if the patient is already enrolled, to determine if the participant should continue participation in the study.

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

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Topical NSAIDs and topical steroids are allowed during the study.

Low-dose aspirin (<325 mg) are allowed during the study.

Non-pharmaceutical therapies, such as electrotherapy, acupuncture, physiotherapy and chiropractic treatment are allowed during the study but must be reported in the Concomitant medications/Significant non-drug therapies eCRF.

NSAIDs are allowed after Day 197 but should still not be taken within 48 hours from any visit where NRS Pain or KOOS assessments are conducted. See Section 6.2.3 for information on how to proceed in case mentioned medications were taken within 48 hours from the EoS visit.

The investigator must instruct the participant to notify the study site about any new medications and therapies s/he takes or initiates after the participant was enrolled into the study.

6.2.2 Prohibited medication

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

Table 6-3 Prohibited medication

Medication	Prohibition period	Action taken
Local i.a. treatment into the target knee, including but not restricted to hyaluronic acid, viscosupplementation and corticosteroids	12 weeks prior to Day 1 to EoS	Report protocol deviation and discontinue study treatment
Long term treatment (>14 days) with oral corticosteroid >5 mg (topical, intranasal and ophthalmic are permitted)	8 weeks prior to Day 1 to EoS	Report protocol deviation and discontinue study treatment
Any biologic drug	26 weeks prior to Day 1 until EoS	Report protocol deviation and discontinue study treatment
Glucosamine, chondroitin sulfate (oral), or any other nutraceutical with potential activity on cartilage repair	4 weeks prior to Day 1 to EoS	Report protocol deviation
Diacetylrhein	12 weeks prior to Day 1 to EoS	Report protocol deviation and reschedule pain-related assessments* if taken within the last 48 hours from any visit
Acetylsalicylic acid >325 mg/day	Screening 1 to EoS	Report protocol deviation and reschedule pain-related assessments* if taken within the last 48 hours from any visit
Paracetamol/acetaminophen >3000 mg/day	Screening 1 to EoS	Report protocol deviation and reschedule pain-related assessments* if taken within the last 48 hours from any visit
Opioids, including tramadol and transdermal fentanyl patches, except oral low dose codeine combination drugs	Screening 1 to EoS	Report protocol deviation and reschedule pain-related assessments* if taken within the last 48 hours from any visit

Medication	Prohibition period	Action taken
Systemic Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) other than those listed above, including combination drugs with codeine or caffeine Note NSAIDs used as rescue medication (see Section 6.2.3) and topical NSAIDs are permitted	Screening 1 to Day 197, 48 hours prior to EoS	Report protocol deviation and reschedule pain-related assessments* if taken within the last 48 hours from any visit
Centrally acting analgesics, e.g. duloxetine, medical marijuana and CBD oil	12 weeks prior to Day 1 until EoS	Report protocol deviation and reschedule pain-related assessments* if taken within the last 48 hours from any visit
Any live vaccine	12 weeks prior to Day 1 until 12 weeks post Day 1	Report protocol deviation. If prior to Day 1 and still compliant with visit windows, reschedule Day 1 to after the 12 week period, else screen fail the participant and potentially re-screen later.

* NRS Pain, KOOS, CCI [redacted]

If needed, the pain-related assessments should be rescheduled to the first possible time point outside the 48-hour limit (after last intake), also if this pushes the completion to outside the visit window specified in Table 8-1. The rescheduled assessments may be done as a remote contact, in which case the site personnel must remember to provide the PROs to the participant at the current visit. Before the pain assessments are completed at the rescheduled time point, the responsible site staff member should ensure any of the relevant prohibited medications were not taken again within 48 hours of the contact.

6.2.3 Rescue medication

In case the basic pain medication described in Section 6.1.2 is insufficient for pain control, NSAIDs will be allowed for up to 3 days per calendar-week as rescue medication, but must not be taken within 48 hours of any visit where pain related assessments (NRS Pain, KOOS, CCI [redacted] are conducted up until Day 197, included.

Rescue medication will not be provided by the sponsor.

Use of rescue medication must be documented by the participant in the pain diary, see Section 8.3.2.

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

6.2.4 Restriction for study participants

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

6.2.4.1 Dietary restrictions and smoking

No cigarettes/use of nicotine products are allowed during the stay at the investigational site.

From Screening 1 to EoS, the participant should not smoke >10 cigarettes per day or use other tobacco products in amounts corresponding to >10 cigarettes per day.

The participant should not consume >2 units alcohol per day in the last 48 hours prior to each study visit.

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

6.2.4.2 Other restrictions

After dosing, physical activity (e.g., climbing stairs, running, bicycling) should be minimized for 72 hours. Normal pace walking is allowed.

No strenuous physical exercise is allowed from 48 hours prior to first dosing until Day 197 (e.g., weight lifting, long-distance running (>3000 m), intensive ball games (football, handball, volleyball and basketball), or tennis on a regular basis >1 time weekly). In general, activities causing heavy loading or rapid movements/rotations of the knee should be avoided.

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

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. The Participant No. consists of the Center Number (Center No.), as assigned by Novartis to the investigative site, with a sequential participant number suffixed to it so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

6.3.2 Treatment assignment, randomization

The following randomization procedure will be used to ensure that treatment assignment is unbiased and concealed from participants and investigator staff.

The study will use a validated Interactive Response Technology (IRT) system for randomizing participants to the treatment arms. After eligibility is confirmed at Screening 4, the investigator or delegate will log in to the IRT system and request the randomization. The participant will be assigned a randomization number which is linked to the treatment arm. The randomization number is different from the participant number described in Section 6.3.1 and is only used for treatment allocation.

The treatment arm information will not be communicated to the blinded requester. The assigned treatment arm will only be communicated to the unblinded pharmacist/nurse.

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

6.4 Treatment blinding

For reasons described in Section 4.3, the LNA043 treatment in this study is open label. As there is no LNA043 placebo treatment arm, participants, investigators, and the sponsor will know from the point of randomisation if a participant is to receive the LNA043 treatment, although it is not disclosed whether the particpant was randomised to TA1 or TA3. The information provided in this section therefore refers to blinding/unblinding with regards to the canakinumab treatment.

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

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

Table 6-4 Blinding levels

Role	Time or Event			
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)	Interim Analysis & dose escalation
Participants	B	B	UI	B
Site staff	B	B	UI	B
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	B	UI	UI
All other sponsor staff not identified above	B	B	UI	UI

B Remains blinded

UI Allowed to be unblinded on individual patient level

6.4.1 Site personnel

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

Unblinding a single participant at site for safety reasons (if necessary for participant management) will occur via an emergency functionality in the IRT system. If the unblinding occurs after the injection at Day 1 and the medical status allows, the participant may continue the study, including the open label treatment LNA043 (if randomized to TA1 or TA3).

Drug product will be supplied in bulk and needs CCI by an unblinded pharmacist/study nurse who is independent of the study team. This unblinded pharmacist/nurse will receive an email from the IRT system with the assigned treatment arm for a randomized participant. Appropriate measures must be taken by the unblinded pharmacist/nurse to ensure that the treatment assignments are concealed from the rest of the site personnel.

If CCI of LNA043 doses is made by a blinded site staff member, the storage and drug accountability documentation of the LNA043 CCI must be kept separate from the canakinumab CCI and documents to avoid accidental unblindings.

6.4.2 Sponsor staff or delegate

The following unblinded sponsor roles are required for this study:

- Unblinded field monitor(s)
- Unblinded clinical staff managing drug re-supply to site
- CCI
- Unblinded sample analyst(s) (hsCRP and CCI

The unblinded field monitors are required to review drug accountability and allocation at site. The unblinded monitors are not provided with a randomization list directly but will be unblinded through review of source documentation compiled by the unblinded pharmacist/nurse, which details treatment allocation to individual participants.

Sponsor clinical staff are required to assist in the management and re-supply of investigational drug product. These individuals are not provided with randomization lists directly, but may be unblinded through communication of drug re-supply needs via the unblinded site pharmacists.

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

For interim analysis purposes, the independent statistician / programmer / modeler will receive unblinded sample data from the sample analysts to report results for review.

All other sponsor staff (study statistician, study programmer, CCI, clinical trial team, decision boards etc.) will stay blinded to treatment assignments (except in the case of a safety event necessitating unblinding) until after the Day 85 interim analysis.

All unblinded sponsor personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure until after the Day 85 interim analysis.

Randomization data and treatment group information must not be disclosed to the central imaging experts conducting the X-ray and MRI read assessments.

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

6.5 Dose escalation and dose modification

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

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all participants treated with LNA043 and canakinumab, as detailed in Section 8.5.2.

Compliance to the treatment regimen is ensured by administration of LNA043 and canakinumab i.a. injections by the investigator. Information on the study treatment administration or any deviation from the dose regimen must be recorded in the Case Report Form (CRF). All CCI [redacted], dispensed syringes for study treatment and potentially returned CCI or syringes must be recorded in the Drug Accountability Log.

Dispensed and returned basic pain medication must be recorded in the source records but it is not applicable to assess compliance because the consumption depends on the participants need for pain relief.

6.6.2 Recommended treatment of adverse events

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

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

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

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

6.6.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required in order to treat the participant safely. Blinding codes may also be broken after a participant discontinues treatment due to disease progression if deemed essential to allow the investigator to select the participant's next treatment regimen, and after discussion and agreement with the sponsor. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition.

Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a participant, s/he must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

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

- protocol number
- study drug name
- participant number

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

See also Section 9.1 for additional information on study or treatment discontinuation.

6.7 Preparation and dispensation

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

The canakinumab treatment is blinded and the solution for i.a. injection must be prepared by an adequately trained unblinded pharmacist/site personnel after the investigator or delegate has randomized a patient and information about the assigned treatment arm has been received from the IRT system. The study medication will be administered by the investigator into the knee joint.

The LNA043 treatment is open label and the solution for i.a. injection can be prepared by any adequately trained pharmacist/site personnel. The study medication will be administered by the investigator into the knee joint.

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

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

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

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

Medication labels will be in the local language and comply with the legal requirements of each country.

The responsible site personnel must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

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

6.7.1.2 Handling of additional treatment

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

6.7.2 Instruction for prescribing and taking study treatment

Both LNA043 and canakinumab treatments will be administered into the knee by the Investigator or appropriately trained delegate with an i.a. injection preferably using the superolateral approach but alternative approaches may be used depending on the investigator site routine. A detailed instruction for drug administration is described in the Pharmacy Manual.

The basic pain medication should be taken according to the package insert and investigator instructions.

7 Informed consent procedures

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

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

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

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

The following informed consents are included in this study:

- Main study consent, which also includes;
  - a subsection that requires a separate signature for the 'Optional Consent for Additional Research' to allow future research on data/samples collected during this study
  - a subsection that requires a separate signature for the 'Optional Consent for additional blood collection' to analyse LNA043 PK at additional time points (provided the patient is randomized to TA1 or TA3)
- As applicable, Pregnancy Outcomes Reporting Consent for female participants
- CCI [redacted]
- As applicable per local regulations and if no other local version is available, consent for healthy volunteer MRI scan, to be used for the imaging qualification of the site

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

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

Declining to participate in the optional assessments CCI [redacted] will in no way affect the participant's ability to join the main research study.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities, i.e. pandemic, epidemic or natural disaster, that may prevent on-site visits and thereby challenge the ability to obtain a standard written informed consent, the Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference). Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

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

Participants might be asked to complete an optional questionnaire to provide feedback on their clinical trial experience. The questionnaire data will be kept anonymized, and will be used to understand where improvement can be made in the clinical trial process. This questionnaire would not ask about the participant's disease or symptoms and therefore will not be considered to be trial data.

8 Visit schedule and assessments

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

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

When the following assessments are scheduled to be performed at the same time point, the order of priority should be as follows:

1. PROs, in the order WPI, NRS Pain, CCI KOOS, CCI [redacted]
2. Pain diary review and basic pain medication review/dispensation
3. ECG
4. Vital signs
5. Blood sampling
6. All other clinical assessments

Other orders of priority to consider are:

- Randomization must occur after eligibility has been re-confirmed at Screening 4.
- Blood and urine collection must be collected pre-dose
- Synovial fluid must be collected prior to the study drug injection.
- Every effort should be made to take the PK samples at the specified time points.
- X-ray, MRI and DCE-MRI can be performed before or after other clinical assessments at a visit, also on a different day if needed for logistical reasons, but should always be done within the visit window.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. Phone calls, virtual contacts (e.g. teleconsult) or visits by site personnel/home nursing service to the participant´s home depending on local regulations and capabilities, can replace on-site study visits where possible, for the duration of the disruption until it is safe for the participant to visit the site again.

The "X" in the table denotes assessments that are to be recorded in the CRF or received electronically from a vendor. The "S" in the table denotes assessments that are only required in the participant's source documentation and do not need to be recorded in the CRF/clinical database.

Table 8-1 Assessment Schedule

Period	Screening			
Visit Name	Screening 1	Screening 2[1]	Screening 3	Screening 4[1]
Days	-42 to -28	-35 to -14	-28 to -14	-5 to -1
Weeks	-6 to -4	-5 to -2	-4 to -2	-1
Time (post-dose)	-	-	-	-
Informed consent	X			
CCI				
Demography	X			
Medical history/current medical conditions	X			
Body Height	X			
Body Weight	X			
Blood Pressure	X			
Pulse rate	X			
Body Temperature	X			
Physical Examination	S			
WPI	X			
NRS Pain	X	X		X
KOOS	X	X		X
CCI				
Electrocardiogram (ECG)	X			
Clinical Chemistry	X			
Hematology	X			
Urinalysis	X			
Coagulation Panel	X			
hsCRP	X			
CCI				
Hepatitis screen	S			

Period	Screening			
Visit Name	Screening 1	Screening 2[1]	Screening 3	Screening 4[1]
Days	-42 to -28	-35 to -14	-28 to -14	-5 to -1
Weeks	-6 to -4	-5 to -2	-4 to -2	-1
Time (post-dose)	-	-	-	-
HIV screen	S			
TB screen	S			
Alcohol Test and Drug Screen	S			
Pregnancy and assessments of fertility	S[3,4]			
X-ray (target knee)	X			
MRI (target knee)			X	
DCE MRI (target knee)			X	
Inclusion / Exclusion criteria	X	X	X[6]	X
Pain diary	X[8]	X		X
CCI				
Basic pain medication dispensation/return	S	S		S
Randomization				X
ACZ885 injection				
LNA043 injection[9]				
CCI				
LNA043 PK[12]				
ANGPTL3 PK				
LNA043 Immunogenicity[10]				
CCI				

Period	Screening			
Visit Name	Screening 1	Screening 2[1]	Screening 3	Screening 4[1]
Days	-42 to -28	-35 to -14	-28 to -14	-5 to -1
Weeks	-6 to -4	-5 to -2	-4 to -2	-1
Time (post-dose)	-	-	-	-
Concomitant medications[17]	X			
Concomitant non-drug therapies[17]	X			
Adverse Events[17]	X			
Study completion information				

Period	Treatment												
Visit Name	ACZ885 Inj.	LNA043 Inj. 1							Remote 1[1]	LNA043 Inj. 2		Remote 2[1]	LNA043 Inj. 3
Days	1	15 ±3							29 ±3	43 ±3		57 ±3	71 ±3
Weeks	0	2							4	6		8	10
Time (post-dose)	0min[2]	0min[2]	20min ±10	60min ±10	120min ±15	240min ±30	8h -2 +4	24h -2 +4	-	0min[2]	60min ±10	-	0min[2]
Informed consent													
CCI													
Demography													
Medical history/current medical conditions													
Body Height													
Body Weight													
Blood Pressure	X	X			X[9]					X			X
Pulse rate	X	X			X[9]					X			X
Body Temperature	X	X								X			X
Physical Examination	S	S											
WPI													
NRS Pain	X	X							X	X		X	X
KOOS	X	X							X	X		X	X
CCI													

Period	Treatment												
Visit Name	ACZ885 Inj.	LNA043 Inj. 1							Remote 1[1]	LNA043 Inj. 2		Remote 2[1]	LNA043 Inj. 3
Days	1	15 ±3							29 ±3	43 ±3		57 ±3	71 ±3
Weeks	0	2							4	6		8	10
Time (post-dose)	0min[2]	0min[2]	20min ±10	60min ±10	120min ±15	240min ±30	8h -2 +4	24h -2 +4	-	0min[2]	60min ±10	-	0min[2]
CCI													
Electrocardiogram (ECG)	X	X											
Clinical Chemistry	X	X								X			
Hematology	X	X								X			
Urinalysis	X	X								X			
Coagulation Panel													
hsCRP	X	X								X			
CCI													
Hepatitis screen													
HIV screen													
TB screen													
Alcohol Test and Drug Screen													
Pregnancy and assessments of fertility	S[5]	S[5]								S[5]			S[5]
X-ray (target knee)													
MRI (target knee)													
DCE MRI (target knee)													
Inclusion / Exclusion criteria													
Pain diary	X	X								X			X
CCI													
Basic pain medication dispensation/return	S	S								S			S
Randomization													
ACZ885 injection	X												
LNA043 injection[9]		X								X			X

Period	**Treatment**												
Visit Name	**ACZ885 Inj.**	**LNA043 Inj. 1**							**Remote 1[1]**	**LNA043 Inj. 2**		**Remote 2[1]**	**LNA043 Inj. 3**
Days	**1**	**15 ±3**							**29 ±3**	**43 ±3**		**57 ±3**	**71 ±3**
Weeks	**0**	**2**							**4**	**6**		**8**	**10**
Time (post-dose)	**0min[2]**	**0min[2]**	**20min ±10**	**60min ±10**	**120min ±15**	**240min ±30**	**8h -2 +4**	**24h -2 +4**	**-**	**0min[2]**	**60min ±10**	**-**	**0min[2]**
CCI													
LNA043 PK[12]		X[11]	X	X	X	X[13]	X[13]	X[13]		X[11]	X		
ANGPTL3 PK	X[11]	X[11]		X[7]						X[11]			
LNA043 Immunogenicity[10]		X[11]								X[11]			
CCI													
Concomitant medications[17]	X												
Concomitant non-drug therapies[17]	X												
Adverse Events[17]	X												
Study completion information													

Period	**Follow-up**		
Visit Name	**Follow-up 1**	**Follow-up 2**	**EoS**
Days	**85 ±3**	**197 ±7**	**365 ±14**
Weeks	**12**	**28**	**52**
Time (post-dose)	**-**	**-**	**-**
Informed consent			
CCI			
Demography			
Medical history/current medical conditions			
Body Height			
Body Weight	X		X
Blood Pressure	X	X	X
Pulse rate	X	X	X
Body Temperature	X	X	X
Physical Examination	S	S	S
WPI			
NRS Pain	X	X	X
KOOS	X	X	X
CCI			
Electrocardiogram (ECG)			X
Clinical Chemistry	X	X	X
Hematology	X	X	X
Urinalysis	X	X	X
Coagulation Panel			
hsCRP	X	X	X
CCI			
Hepatitis screen			
HIV screen			
TB screen			

Period	**Follow-up**		
Visit Name	**Follow-up 1**	**Follow-up 2**	**EoS**
Days	**85 ±3**	**197 ±7**	**365 ±14**
Weeks	**12**	**28**	**52**
Time (post-dose)	**-**	**-**	**-**
Alcohol Test and Drug Screen			
Pregnancy and assessments of fertility	S[3]	S[3]	S[3]
X-ray (target knee)			
MRI (target knee)	X	X	X
DCE MRI (target knee)	X		
Inclusion / Exclusion criteria			
Pain diary	X	X	X
CCI			
Basic pain medication dispensation/return	S	S	
Randomization			
ACZ885 injection			
LNA043 injection[9]			
CCI			
LNA043 PK[12]			
ANGPTL3 PK	X	X	X
LNA043 Immunogenicity[10]	X	X	X
CCI			
Concomitant medications[17]	X		
Concomitant non-drug therapies[17]	X		

Period	**Follow-up**		
Visit Name	**Follow-up 1**	**Follow-up 2**	**EoS**
Days	**85 ±3**	**197 ±7**	**365 ±14**
Weeks	**12**	**28**	**52**
Time (post-dose)	**-**	**-**	**-**
Adverse Events[17]	X		
Study completion information			X

[1] Can be performed as remote visit
[2] Pre-dose (for participants randomized to TA2 or TA4, for whom there is no injection time point on Day 15, assessments should be performed/collected at the same time and order as if an injection would take place)
[3] Serum pregnancy test (if applicable)
[4] FSH analysis (if applicable)
[5] Urine pregnancy test (if applicable)
[6] Only criteria based on MRI
[7] For participants randomized to TA2 or TA4, for whom there is no injection time point, sample should be collected 60 to 180 minutes after collection of the 0 min-sample
[8] Only instructions and dispensation of the diary
[9] Only for participants who were randomized to receive LNA043 (TA1 and TA3)
[10] In case of suspected allergic hypersensitivity, the participant should return to the site for an unscheduled sample collection to assess immunogenicity as near as possible to the event.
[11] Within 2 hours before injection
[12] Only to be collected for participants who receive LNA043 (TA1 and TA3)
[13] CCI [redacted]

[17] Solicited question must be asked by site personnel at all site-and remote visits and unsolicited reports of events or changes must be documented throughout the study without delay

8.1 Screening

8.1.1 Eligibility screening

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

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

8.1.1.1 Pain

Widespread Pain Index (WPI) (Wolfe et al 2010) is assessed at Screening 1 to exclude patients with substantial pain originating from other regions than the target knee, such as fibromyalgia or other undiagnosed diseases.

Other patient reported outcomes (PROs) for assessing pain are collected for screening purposes as well as for efficacy evaluation, see Section 8.3.2.

The same method of collection as for the PROs described in Section 8.3.2 will be used.

8.1.1.2 Coagulation

Prothrombine Time (PT) and International Normalized Ratio (INR) will be analysed at Screening 1 to evaluate conditions related to impaired coagulation.

8.1.1.3 Screening for Infections

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

All participants will be screened for Hepatitis B Virus Surface Antigen and Hepatitis B Virus Core Antibodies. If positive, Hepatitis B Virus Surface Antibodies and Hepatitis B Virus DNA should be determined.

Screening for Hepatitis C will be based on Hepatitis C Virus Antibodies and if positive, Hepatitis C Virus RNA levels should be determined.

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

Determination of TB status is required before study participation per eligibility criteria and must include a QuantiFERON test performed by the central laboratory. If presence of active or latent TB is established, treatment for TB must have been completed prior to potential re-screening for the study. In case a participant develops TB during the study, the event must be followed up and recorded as an AE in the CRF.

8.1.1.4 Alcohol test, Drug screen, Urine cotinine

Participants will be tested for substances of abuse (e.g. alcohol, amphetamines, barbituates, benzodiazepines, cannabinoids, cocaine and opiates).

Cotinine in urine will not be analysed at screening but the investigator should clarify tobacco use habits for participants who use tobacco products to ensure it is realistic that the patient can comply with the restriction described in Section 6.2.4.1 (nicotine replacement therapies are allowed).

8.1.1.5 Knee X-ray

A target knee X-ray will be performed at Screening 1 to evaluate the KL and medial fJSW eligibility criterion, using a non-fluoro, standardized and quality controlled method, as described in the Imaging Manual. A central reader will analyze the images as described in the Imaging Manual.

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

If a patient has been screened for a similar trial with the same conventional X-ray projections, the images acquired during screening can be used within 6 months of the X-ray date, provided the patient confirms there are no significant changes in local symptoms since the initial image was taken.

8.1.2 Information to be collected on screening failures

A participant who signs an informed consent form and subsequently found ineligible prior to randomization will be considered a screen failure.

The reason(s) for the screen failure should be recorded on the appropriate Case Report Form. The visit date, demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data need to be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see Section 10.1.3 for SAE reporting details).

A participant who is randomized and fail to start treatment, e.g. when randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

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

8.1.3 Re-screening

It is permissible to re-screen a participant if the initial screen failure reason is logistical by nature, e.g., a patient who becomes unavailable due to family emergencies, or if the screen failure reason is considered transient, e.g. ongoing minor infection or insufficient washout of prohibited medication. Such re-screening may occur once the screen failure reason is considered resolved.

Re-screening is also permissible, one time only, if the screen failure reason is insufficient level of OA, provided the anamnesis and physical examination indicate a true and sustained deterioration of the participant's OA compared to the status at the initial screening. Such re-screening must not be performed sooner than 6 months from the initial screening. Insufficient level of OA progression refers to the inclusion criteria for target knee pain, hsCRP, JSW and synovitis by MRI.

Eligibility criteria assessed by X-ray can be based on the initial screening X-ray results if the re-screening occurs within 6 months of the X-ray date and the patient reports there are no significant changes in local symptoms since the initial image was taken.

Each case of re-screening should be discussed and agreed with Sponsor on a case-by-case basis.

8.2 Participant demographics/other baseline characteristics

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

Participant demographics include age at screening, sex, race, predominant ethnicity (if permitted).

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.

Height will be measured only at Screening 1 to evaluate the BMI eligibility criterion. Relevant medical history/current medical conditions (until informed consent signature date) will be recorded in the eCRF. Where possible, the diagnosis and not symptoms should be recorded.

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

An association between OA and radiographic evidence of chondrocalcinosis (CC) has been recognised for years, and CC may be present in up to 15% of the patients with OA (Ryu et al 2014). However, it is not yet clear to what extent CC is the cause of OA in patients experiencing acute flares of joint pain linked to pseudogout, or if it develops as a result of changes in chondrocyte metabolism or in the extracellular matrix. Because gross calcium depositions in articular cartilage could interfere with the expected treatment effect, CC will be identified as part of the baseline characteristics by MRI at Screening 3, using hypointense foci of a dedicated MRI pulse sequence, e.g., fat saturation gradient recalled echo – Fat Sat GRE –

sequence. A single dose of canakinumab is unlikely to reduce CC and CC is therefore not used as a study endpoint.

8.3 Efficacy

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

Articular cartilage structure (primary endpoint) CCI [redacted] as well as synovitis (secondary endpoint) CCI [redacted] will be evaluated by MRI as described in Section 8.3.1.

Pain (primary endpoint) will be assessed by PROs as described in Section 8.3.2.

8.3.1 Knee MRI

Alterations in normal knee kinematics shift loading from cartilage regions adapted for loading to regions less well suited. This leads to the initiation and progression of degenerative processes consistent with OA in multiple knee areas, potentially even more so in presence of an inflammatory flare. 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 which in turn contribute to a change in its CCI [redacted]

MRI will be obtained from the target knee to i) select patients with synovitis and ii) visualize the cartilage tissue and other structures through the knee. Thus, the imaging protocol will be developed to mainly quantify changes in volume and thickness of cartilage in the index region (i.e. the region where most cartilage damage occurs in OA patients with KL 2-4), but also to detect synovitis and quantify any changes during treatment. The index region is defined as the union of the femoral medial anterior (FMA), central (FMC) and posterior (FMP) cartilage subregions in the knee. CCI [redacted] Overall, these measures will demonstrate the effectiveness of LNA043 in regenerating cartilage in the absence and presence of canakinumab, but also allow verification of the quality of the cartilage newly formed upon treatment. This information should make it possible to predict to what extent the repair is durable over time.

In addition, the assessment of the synovitis level using a dynamic-contrast-enhanced (DCE) MRI approach will demonstrate the effectiveness of canakinumab in reducing knee inflammation and whether this response is correlated with a decrease in pain.

8.3.1.1 Image collection

The acquisition of magnetic resonance images will be performed by a trained MRI professional at each site. The MRI technologist will be blinded to the treatment received by the patient. All participants will be imaged using a clinical MRI 3T scanner, after ensuring there is no contraindications for MRI (such as metallic implants, claustrophobia etc). For each MRI session,

images will be acquired from the target knee as described in the imaging protocol to assess synovitis, cartilage structure[redacted]. Patient setup will ensure correct reproducible positioning of the knee via the use of a footboard device and a cushion in the knee coil as well as sufficient comfort to limit motion artefacts. Scanning sessions, including those using the additional sequences for the additional DCE-MRI measurement (baseline and Day 85), should not exceed one hour to minimize patient burden.[redacted] As the last acquisition in the protocol for synovitis assessment at baseline and Day 85, T1-weighted (T1w) DCE-MR images will be obtained before and after the injection of the GBCA by acquiring a time series of T1w images of the knee with intervals of a few seconds. If necessary, participants may be allowed to take a break between the structural MRI and the DCE-MRI part so that they are not required to lie still in the MRI scanner for the entire time.

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

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

8.3.1.2 Image processing

The image analysis will be performed centrally, as defined in the imaging manual, in order to primarily:

1. Screen for patients with synovitis prior to the LNA043 injection
2. Assess changes in cartilage volume, thickness and[redacted] both in the index region and the rest of the joint
3. Assess changes in the level of synovitis as well as changes in the thickness of the synovial membrane,[redacted]

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.

At screening, a comprehensive semi-quantitative scoring system will be used for the assessment of whole-knee synovitis (Guermazi et al 2011). This analysis will be performed on one of the scans obtained from the DCE-MRI series, ideally the one recorded ~2 minutes after the injection of GBCA, from which the maximal synovial enhancement should be observed. Synovitis will be assessed at 11 sites of the joint and synovial thickness at each of these sites will be scored semi-quantitatively: grade 0 (<2 mm), grade 1 (2–4 mm) and grade 2 (>4 mm) at each site. Whole-knee synovitis will then be assessed by summing the scores from all sites and categorised as follows: 0–4 normal or equivocal synovitis; 5–8 mild synovitis; 9–12 moderate synovitis and ≥13 severe synovitis.

DCE-MRI scans will be used for the longitudinal assessment of synovitis both at baseline and Day 85. During the DCE-MRI acquisition, while the contrast agent is preferentially taken up at

sites with high perfusion (such as the inflamed synovial membrane), a temporal variation of the MRI signal intensity occurs. When the contrast distributes through the intravascular and extravascular spaces, the MR signal intensity in the image volume elements (voxels) of the target tissue changes over time, generating so-called signal intensity (SI) curves. These curves can then be analyzed to derive parameters related to tissue perfusion. The parameter of primary interest will be the volume transfer rate of the GBCA from the blood plasma in synovium, commonly referred to as Ktrans (Riis et al 2017), CCI

Ktrans results are potentially unblinding with regards to the canakinumab treatment and will therefore not be disclosed to blinded sponsor staff until after the database has been frozen for the first interimanalysis at Day 85.

Segmentation of knee articular cartilage will be performed for the measurement of cartilage volume and thickness by using an automated segmentation software (ChondralHealth, Siemens, Erlangen, Germany). The software allows a robust automated segmentation of the femoral, tibial and patellar cartilage as well as the Region-of-Interest analysis. CCI As a result, the complete set of parameters is provided (volumetry and descriptive statistics of quantitative MR parameters). Measured variables will include volumes (in mm^3) and cartilage thickness (in millimeters) separately for 21 knee regions (Femur: medial posterior-FMP, medial central-FMC, medial anterior-FMA, trochlea medial-FTM, trochlea central-FTC, trochlea lateral-FTC, lateral posterior-FLP, lateral central-FLC and lateral anterior-FLA; Tibia: lateral posterior-TLP, lateral central-TLC, lateral anterior-TLA, medial posterior-TMP, medial anterior-TMA and medial central-TMC; Patella: lateral inferior-PLI, lateral central-PLC, lateral superior-PLS, medial inferior-PMI, medial central-PMC, medial superior-PMS). This definition of the subfields is based on a modified ICRS score (Surowiec et al 2014). The automated software will calculate cartilage volume and cartilage thickness within each of these subfields.

Structural and contrast-enhanced MR images will also be analysed for the determination of CCI as described in the literature, e.g CCI .

CCI

CCI

8.3.2 Patient Reported Outcomes (PROs)

The PROs used in this study are WPI (described in Section 8.1.1.1), NRS Pain, KOOS, CCI and a Pain Intensity and Pain Medications Diary. The PROs are completed on paper and transcribed into the CRF by the site staff.

The completion of the full set of PROs is expected to take approximately 35 minutes, with the KOOS being the most time consuming (around 20 minutes), CCI and last the remaining PROs (around 5 minutes combined). The diary is expected to require 1-5 min of the participant's time per day depending on how much pain medication the participant needs to report.

The participant must be given the PRO measure(s) to be completed at the scheduled visit before any other clinical assessments are conducted.

The participant will potentially also complete NRS Pain, KOOS, CCI at home during the remote visits (Screening 2, Screening 4, Day 29 and Day 57). The investigator or delegate should, if applicable, provide the CCI PROs to the participant latest at the preceding visit and remind the participant to complete the questionnaires during the remote visit contact. If completed off-site, the participant should return the completed original questionnaires at the following visit to the investigator site.

The questionnaires should be completed in the language most familiar to the participant. The participant should be given sufficient space and time to complete the PRO measure(s). A participant's refusal to complete all or any part of a PRO measure should be documented in the CRF but should not be captured as a protocol deviation.

The site personnel should check the PRO measure(s) collected on-site for completeness and ask the participant to complete any missing responses.

For PROs completed off-site, a provisional submission of the PROs via verbal communication, fax, email, text-message or other preferred digital method is allowed. If the PROs are completed at home but the answers are needed to evaluate the participant's eligibility, i.e. if NRS Pain and KOOS are completed remotely at Screening 2 and/or Screening 4, the eligibility check can be based on the provisional data as long as they are verified against the completed original at Day 1.

Completed PROs, including any unsolicited comments written by the participant, must be reviewed and assessed by the investigator for responses which may indicate potential AEs or SAEs before any clinical study examinations. If AEs or SAEs are confirmed, study investigators should not encourage the participant to change responses reported in the completed questionnaires. Study investigators must follow reporting instructions outlined in Section 10.

8.3.2.1 NRS Pain

Numerical Rating Scale (NRS) for Pain (Hawker et al 2011) is assessed at regular intervals to confirm eligibility and to evaluate pain status throughout the study.

The NRS Pain instrument has CCI and the participants will be asked to rate CCI

8.3.2.2 KOOS

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

8.3.2.3 CCI

8.3.2.4 CCI

8.3.2.5 CCI

8.3.2.6 CCI

8.3.2.7 Pain Intensity and Pain Medications Diary

Daily assessments of pain intensity (NRS Pain), as well as any pain medication intake will be recorded by the participant in the study specific pain diary, from Screening 1 until Day 85, and again during one week (seven consecutive days) prior to the Day 197 and Day 365 where the seven days should fall within 3 weeks from the visit. Use of prescribed or OTC pain medications will still need to be documented as Concomitant Medications according to Section 6.2.1.

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

At each visit, participants must be provided with a new pain diary that covers at least the period they should complete until the next planned visit. The site personnel should remind the participant about the diary completion around three weeks prior to the planned Day 197 and Day 365.

8.3.3 CCI

8.3.4 Appropriateness of efficacy assessments

For appropriateness of knee MRI parameters, see Section 8.3.1.

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

The NRS pain score is traditionally used to assess pain.

CCI [redacted].

8.4 Safety

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every four weeks or more frequently if needed) for safety monitoring and discussion of the participant´s health status until it is safe for the participant to visit the site again.

8.4.1 Physical examination, vital signs and height/weight

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

For details on AE collection and reporting, see Section 10.1.1.

Table 8-2 Assessments and Specifications

Assessment	Specification
Physical Examination	A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A complete physical examination must be performed at Screening 1 and Day 197. A short physical examination, i.e. with focused examinations as judged by the investigator, can be performed at Day 1, Day 15, Day 85 and Day 365. A knee joint examination will also be performed as part of the physical examination at all timepoints specified in Table 8-1, and includes examination for range of motion, stability, warmth, swelling/bulge sign and patellar tap sign as well as for patellofemoral pain. Targeted physical examinations to elaborate self- reported symptoms, complaints, injection site reactions or post-injection flares as applicable, can be done at any visit. Information for all physical examinations must be included in the source documentation at the investigator site but will not be recorded in the CRF. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant findings made after signing informed consent, which meet the definition of an Adverse Event, must be recorded as an adverse event.
Vital signs	Vital signs will include the collection of body temperature by locally accepted standard method, e.g. digital or infrared sensor and oral, otic, axillary, etc (recorded in °C), blood pressure (BP) and pulse measurements. The same method for measuring the body temperature should be used throughout the study. Systolic and diastolic blood pressure will be measured after the participant has been sitting for five minutes, with back supported and both feet placed on the floor, three times at 3-minute intervals using an automated validated device, e.g. OMRON, with an appropriately sized

Assessment	Specification
	cuff. The mean of the three measurements will be used for evaluations and entered in the eCRF. In case the cuff sizes available are not large enough for the participant's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. If the blood pressure is out-of-range at screening and/or baseline three additional readings can be obtained after approximately 30 minutes, in the manner described above. The mean of the last three readings must be within the ranges provided in the eligibility criteria in order for the patient to qualify. In case of repeated blood pressure assessments, the mean value from both set of measurements (initial and repeat) should be entered in the eCRF.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured. Body mass index (BMI) will be calculated to one decimal using the following formula: BMI =Body weight (kg) /[Height (m)]^2 The Screening visit height measurement will be used for BMI calculations throughout the study.

8.4.2 Laboratory evaluations

In the case where a laboratory range is not specified by the protocol, but a value is outside the reference range, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator (in consultation with the sponsor if needed) and shall be based, in part, upon the nature and degree of the observed abnormality.

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

A central laboratory will be used for analysis of all safety specimens collected except for the potential SARS-Cov-2 tests and urine pregnancy test, which will be performed and read-out locally. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the central laboratory manual.

If participants cannot visit the site for safety assessments conducted through the central laboratory, local laboratory collection may be used during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits. If used, relevant documentation should be obtained from the local laboratory to evaluate the validity of the data, considering potential differences in analysis assays, reference ranges, etc. between the local and central laboratories. It must be clear from the final data set which data originate from local laboratory analyses.

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

All abnormal laboratory results must be evaluated for criteria defining an adverse event and reported as such if the criteria are met, see Section 10.1.1. For laboratory related adverse events, follow-up evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant.

Table 8-3 Laboratory evaluations

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Ery. Mean Corpuscular Hemoglobin, Ery. Corpuscular HGB Concentration, Ery. Mean Corpuscular Volume, Platelets, Erythrocytes, Leukocytes, Erythrocytes Cell Morphology, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils) If abnormal results are obtained from Differential, a manual (smear) differential analysis will be performed.
Clinical chemistry	Sodium, Potassium, Magnesium, Phosphate, Bicarbonate, Urea Nitrogen, Creatinine (and GFR), Uric Acid, Chloride, Albumin, Calcium, Alkaline phosphatase, Total Bilirubin, Direct and Indirect Bilirubin, Lactate dehydrogenase (LDH), Gamma-glutamyl-transferase (GGT), AST, ALT, Creatine kinase, HbA1c, Total Protein, Total Cholesterol, LDL Cholesterol, HDL Cholesterol, Triglycerides
Urinalysis	Protein, creatinine, protein:creatinine ratio Macroscopic panel (dipstick): Leukocytes esterase, Nitrite, pH, Protein, Glucose, Ketones, Blood/ Hemoglobin. If the dipstick result is positive for Protein, Nitrite, Leukocytes esterase and/or Blood, the sample will be sent for microscopic analysis.
Pregnancy Test	Serum / Urine pregnancy test, FSH (if applicable) see Section 8.4.4

8.4.3 Electrocardiogram (ECG)

ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. In the case of a series of assessments, ECG should be first assessment obtained while the participant is at rest.

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

Unless auto-calculated by the ECG machine, the investigator must calculate QTcF at the Screening and/or Baseline visit(s) (as applicable) to assess eligibility according to the following formula:

Figure 8-1 QTcF formula

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

Single 12-lead ECGs are collected and results are entered into the appropriate eCRF page.

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

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

8.4.4 Pregnancy and assessment of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Additional pregnancy testing might be performed if requested by local requirements.

If participants cannot visit the site to have serum pregnancy tests during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, urine pregnancy test kits may be used (subject to prior approval from local authorities, as appropriate). Relevant participants can perform the urine pregnancy test at home and report the result to the site. The Investigator should establish a communication process with the participant so that the Site is informed and can verify the pregnancy test results (e.g. following country specific measures).

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

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

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

8.4.5 Appropriateness of safety measurements

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

8.5 Additional assessments

8.5.1 Pharmacokinetics

PK samples will be collected at the time points defined in Table 8-1. Detailed instructions regarding sample collection, numbering, processing and shipment are described in the laboratory manual.

Arrangements should be made to facilitate the logistics for participants who consent to the optional LNA043 PK collections at Day 15, where in particular the 8 and 24 hours post dose collection time points can be challenging for both the investigator site and participants. Depending on local requirements/approvals, participant preference, the investigator site resources or facilities, and subcontracted vendor representation in the region, these arrangements could include one or a combination of the following:

- Ambulant phlebotomist who visits the participant at his/her home for the blood draws
- Participant being domiciled at the investigator site overnight
- Transport arrangements which facilitates the participant's return to the investigator site

In order to better define the PK profile, the timing of the PK sample collection may be altered based on emergent data.

CCI [redacted] LNA043 PK samples will only be obtained from those who received LNA043 treatment. ANGPTL3 samples will be collected and analyzed from all participants in all treatment arms.

Unscheduled PK sample may be collected on request from the sponsor or investigator, if considered useful to investigate an AE.

8.5.1.1 PK analytical method(s)

[LNA043] will be determined by a validated immuno-capture and LC-MS/MS method; the anticipated LLOQ is 10 ng/mL in serum.

[ANGPTL3] will be determined by a validated ligand binding assay; the anticipated LLOQ is 39.7 pmol/L in serum and 51.1 pmol/L in synovial fluid.

CCI [redacted]

Concentrations will be expressed in mass per volume units.

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

PK samples remaining after concentration 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.

For standard pharmacokinetic abbreviations and definitions, see Table 12-1.

The following pharmacokinetic parameters will be determined, in participants with sufficient data, from the serum concentration-time data using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 8 or higher):

- Cmax, Tmax, and AUClast will be determined for LNA043
- Cmax, Cav, and Cmin will be determined for ANGPTL3

The linear trapezoidal rule will be used for AUC calculation.

8.5.2 CCI [redacted]

CCI [redacted]

CCI

8.5.2.1 CCI

CCI

8.5.2.2 CCI

CCI

8.5.2.3 CCI

8.5.2.4 CCI

8.5.2.5 CCI

8.5.2.6 CCI

8.5.2.7 CCI

CCI

8.5.2.8 CCI

CCI

8.5.2.9 CCI

CCI

8.5.3 Immunogenicity

Immunogenicity (IG) samples will be obtained at the time points defined in the Assessment schedule (Table 8-1) and evaluated in all participants in all treatment arms, including the placebo/untreated treatment arms.

In case of suspected allergic hypersensitivity, the participant should return to the site as soon as possible to have samples collected for immunogenicity assessment. Unscheduled post-dose samples should also be collected, in addition to planned pre-dose samples, during scheduled visits in case of suspected allergic hypersensitivity is noticed after the injection of study treatment.

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

The investigator should follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing, and shipment.

8.5.3.1 Immunogenicity analytical method(s)

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

CCI [redacted]

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

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

CCI [redacted]

8.5.4 CCI [redacted]

CCI [redacted]

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

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

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

Study treatment must be discontinued if any of the following circumstances occur for the individual participant:

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment for which discontinued study treatment is mandatory according to Table 6-3
- Any situation in which continued study participation might result in a safety risk to the participant

- Emergence of the following adverse events:
  - SAE suspected to be related to the LNA043 treatment
  - Severe local tolerability reaction
  - Allergic reaction of any severity grade, unless clearly caused by exposure to a known allergen (i.e. peanut allergy).
  - Septic arthritis or haemarthrosis in the target joint
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the participant's overall status, prevents the participant from continued study treatment
- If a liver or renal event occurs, follow guidelines outlined in Section 16.1 and Section 16.2 regarding discontinuation of study treatment.

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason and document this information in the CRF and source records.

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent, see Section 9.1.2. Where possible, they should return for the assessments indicated in Table 8-1 (Assessment schedule), with the exceptions described below. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the participant as specified in Section 9.1.3. This contact should preferably be done according to the study visit schedule.

The following assessments are not expected to be performed for participants who have discontinued study treatment but continue to be followed up as part of the study:

- Participants who discontinue study treatment due to a renal event prior to first LNA043 injection should not perform the DCE-MRI assessment at Day 85
- Participants who discontinue study treatment should not have synovial fluid samples collected for any subsequent visit
- Participants who are randomized to TA1 or TA3 but discontinue study treatment prior to first LNA043 injection should not have blood samples for LNA043 PK analysis collected
- Female participants who become pregnant should not perform any assessment that is considered a risk during pregnancy, including but not limited to MRI scanning

If the participant cannot or is unwilling to attend any further visit(s) as per the assessment schedule, the site personnel should explore the possibility to arrange an unscheduled visit as soon as possible, at which time all of the assessments listed for the final visit (EoS) should be performed. At this final visit, all dispensed pain medication should be returned. If possible, the site personnel should maintain regular telephone contact with the participant, or with a person pre-designated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum and assuming participant consent, the following data should be collected at clinic visits or via telephone/email contact:

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

9.1.1.1 Replacement policy

Additional patients may be enrolled if the discontinuation rate exceeds 10% and if feasible for the study timelines, see Section 5.

9.1.2 Withdrawal of informed consent

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

- Does not want to participate in the study anymore, and
- Does not want any further visits or assessments, and
- Does not want any further study related contacts

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw his/her consent 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 participant are not allowed unless safety findings require communicating or follow-up.

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

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation.

9.1.3 Lost to follow-up

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

9.1.4 Study stopping rules

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

- Three (3) or more participants on active therapy presenting new unexpected SAEs considered related to LNA043 or canakinumab
- Two (2) or more participants presenting acute allergic reactions of severity grade 3, according to the NCI-CTCAE (version 4.03 or higher), within 24 hours following LNA043 administration, unless clearly caused by exposure to a known allergen (e.g., peanut allergy)
- One (1) or more participant presenting life-threatening or fatal acute allergic reaction (severity grade 4 or greater), according to the NCI-CTCAE (version 4.03 or higher), within 24 hours following LNA043 administration, unless clearly caused by exposure to a known allergen (e.g. peanut allergy)
- Two (2) or more participants on active therapy presenting suspected and severe LNA043 treatment related AEs of local origin, as judged by the Investigator and/or the Sponsor
- Two (2) or more participants on active therapy presenting suspected and severe canakinumab treatment related AEs of local origin, as judged by the Investigator and/or the Sponsor

The current SARS-CoV-2 pandemic may pose a challenge to the integrity of trial, protection of participants' rights, safety and wellbeing, as well as the safety of study personnel. Therefore, risk mitigation strategies have been established and will be evaluated on an ongoing basis for the duration of the study, in line with health and governmental authority guidance. If the safety of the participants and study personnel, or integrity of the data collected cannot be guaranteed at any point, the study will be halted.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination can be:

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

In taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a prematurely withdrawn participant. No more treatment with canakinumab or LNA043 should take place after the investigator has been informed of the early study termination. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their EoS 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.

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

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 participants who prematurely withdraw from the study, or must refer them for appropriate ongoing care.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

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

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

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

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events may also be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments (e.g. indicated by comments in the pain diary).

Adverse events must be recorded on the AE CRF under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible):

1. The severity grade, categorized as;
- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities

2. Its relationship to the study treatment and other investigational treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant

3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. Whether it constitutes a SAE, see Section 10.1.2, and which seriousness criteria have been met
5. Action taken regarding study treatment. All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Drug interrupted/permanently discontinued

6. Its outcome

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

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

Adverse event monitoring should be continued for at least 60 days following the last dose of study treatment.

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

Information about adverse drug reactions for the investigational drug can be found in the IB.

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

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

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

10.1.2 Serious adverse events

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

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

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

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

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

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

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

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days after the last study visit must be reported to Novartis immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

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

otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

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

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

Any SAEs experienced after the 30-day period after the last study visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment, unless otherwise specified by local law/regulations.

10.1.4 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 the pregnancy consent form to allow the investigator to ask about her pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed 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 should be recorded and reported by the investigator to the Novartis CMO&PS. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

Investigational treatment errors and uses outside of what is foreseen in the protocol will be recorded as protocol deviations irrespective of whether or not associated with an AE/SAE and reported to CMO&PS only if associated with an SAE.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

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

See Table 16-1 in Section 16.1 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-2. Liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and G-GT) should be repeated to confirm elevation.

- These liver chemistry repeats will be performed using the central laboratory. If results are not available from the central laboratory, the repeats can also be performed at a local laboratory to monitor the safety of the participant. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate CRF.
- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- The investigational drug should be discontinued, if appropriate, as per Section 9.1.1
- The participant should be hospitalized, if appropriate
- Causality assessment of the liver event should be performed
- Thorough follow-up of the liver event should include, based on investigator's discretion:
  - Serology tests, imaging and pathology assessments, hepatologist's consultancy
  - Obtaining a more detailed history of symptoms and prior or concurrent diseases.
  - Obtaining a history of concomitant drug use (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 16-2
  - Imaging such as abdominal US, CT or MRI, as appropriate
  - Obtaining a history of exposure to environmental chemical agents.
  - Considering gastroenterology or hepatology consultations.

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

10.2.2 Renal safety monitoring

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

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

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

Every renal laboratory trigger or renal event as defined in Table 16-4 should be followed up by the investigator or designated personnel at the trial site as summarized in Table 16-5.

11 Data Collection and Database management

11.1 Data collection

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

Participants will be asked to complete PROs on a paper copy. The participant's responses will be transcribed into the eCRF by the site personnel. When a paper copy is used off-site, e.g. at the remote Day 29 and Day 57 visits, the participant should bring or send the completed questionnaire(s) to the site at earliest convenience.

The pain diary will be paper based and should be completed and returned by the participants at each visit up to Day 85, and again one week prior to Day 197 and Day 365. The diary data will be transcribed into the CRF by the site personnel.

Completed paper questionnaires (if any) and diaries will be kept as source documentation at the investigator site and are not to be collected by the sponsor.

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

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

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

11.2 Database management and quality control

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

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

Dates of screenings, randomizations, screen failures, discontinuations and study completion, as well as randomization codes will be tracked using an IRT system.

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

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

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of participant records, the accuracy of data capture/data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. 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 participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the participant's file. The investigator must also keep the original informed consent form signed by the participant (a signed copy is given to the participant).

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

12 Data analysis and statistical methods

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

12.1 Analysis sets

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

The Full Analysis Set (FAS) will include all participants to whom study treatment has been assigned.

The Safety Set will include all participants who received at least one dose of study medication.

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

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

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

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data will be listed and summarized descriptively by treatment group for the FAS.

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

Relevant medical histories and current medical conditions at baseline will be summarized for all participants by treatment group.

12.3 Treatments

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

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

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

This study has two co-primary aims.

The primary aim for canakinumab (TA4) is to assess its efficacy vs. placebo (TA2) in relieving OA pain in participants with symptomatic knee OA with inflammation.

The primary aim for LNA043 (TA1) is to assess its efficacy vs no injection (TA2) in regenerating the articular cartilage in patients with symptomatic knee OA with inflammation after both (TA1 and TA2) have been administered placebo for relieving OA pain.

12.4.1 Definition of primary endpoint(s)

The primary efficacy variable for canakinumab is the change from baseline in KOOS, pain subscale at Day 85.

The primary efficacy variable for LNA043 is the change from baseline in cartilage volume in the index region at Day 197.

12.4.2 Statistical model, hypothesis, and method of analysis

The analysis for primary endpoints will be carried out using a mixed effect model for repeated measures (MMRM).

- The primary efficacy variable for canakinumab, change from baseline in KOOS pain subscale will be analyzed using a mixed effect model for repeated measures (MMRM). The model will include baseline as fixed covariate, treatment, timepoint, treatment * timepoints as fixed effects and participant as random effect. An unstructured covariance will be assumed; if not possible, other appropriate covariance structures will be explored such as Autoregressive (AR(1)), Compound symmetry etc. A two-sided 90% confidence interval for the treatment effect (i.e., canakinumab minus Placebo) at Day 85 will be formed. A statistically significant difference (one-sided p-value <0.05) between active drug and placebo at Day 85 will be considered as a positive result.
- The primary efficacy variable for LNA043, change from baseline in cartilage volume in the index region, will be analyzed using a mixed effect model for repeated measures (MMRM). The model will include baseline as fixed covariate, treatment, timepoint, and treatment * timepoints as fixed effects and participant as random effect. An unstructured covariance will be assumed; if not possible, other appropriate covariance structure will be explored such as Autoregressive (AR(1)), Compound symmetry etc. A two-sided 90% confidence interval for the treatment effect (i.e., LNA043 minus No injection) at Day 197

will be formed. A statistically significant difference (one-sided p-value <0.05) between active drug and no injection at Day 197 will be considered as a positive result.

12.4.3 Handling of missing values not related to intercurrent event

All drug concentrations below the lower limit of quantification (LLOQ) will be reported as "zero" and will be treated as zero for the calculation of PK parameters.

Missing data for MRI outcomes will not be imputed.

Missing data for KOOS will not be imputed.

12.5 Analysis of secondary endpoints/estimands

See Section 2 for secondary objectives of this study.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

The secondary efficacy objectives for LNA043 are as follows:

- To assess the efficacy of q4wx3 i.a. injections of LNA043 after i.a. injection of placebo (TA1) vs q4wx3 i.a. injections of LNA043 after i.a. injection of canakinumab (TA3) in regenerating the articular cartilage in participants with symptomatic knee OA with inflammation. The variables associated with this objective are change from baseline in cartilage volume and change from baseline in cartilage thickness in the index region at Days 197 and 365. Both variables will be analyzed separately using two separate MMRM models. The structure of both MMRM models will be same as the one mentioned in primary analysis of LNA043.
- To assess the efficacy of q4wx3 i.a. injections of LNA043 (TA3) vs no LNA043 injections (TA4) in regenerating the articular cartilage in participants with symptomatic knee OA with inflammation after both trial arms (i.e. TA3 and TA4) have been administered with an i.a. injection of canakinumab to relieve OA pain. The variables associated with this objective are change from baseline in cartilage volume and change from baseline in cartilage thickness in the index region at Days 197 and 365.
  Both variables will be analyzed separately using two separate MMRM models.
  The structure of both MMRM models will be same as the one mentioned in primary analysis of LNA043.
- To assess the efficacy of q4wx3 i.a. injections of LNA043 (TA1) vs no LNA043 injections (TA2) in regenerating the articular cartilage in participants with symptomatic knee OA with inflammation after both trial arms (i.e. TA1 and TA2) have been administered with an i.a. injection of placebo to relieve OA pain. The variables associated with this objective are change from baseline in cartilage volume at Day 365 and change from baseline in cartilage thickness at Days 197 and 365 in the index region.
  Both variables will be analyzed separately using two separate MMRM models.
  The structure of both MMRM models will be same as the one mentioned in primary analysis of LNA043.

- To assess the efficacy of a single i.a. injection of canakinumab followed by q4wx3 i.a. injections of LNA043 (TA3) vs a single i.a. injection of canakinumab (TA4) in participants with symptomatic knee OA with inflammation in improving functions of daily living over time. The variables associated with this objective are change from baseline in KOOS pain subscale and Function in daily living (ADL) subscales at Day 15, 29, 43, 57, 71, 85, 197, 365 and it will be analyzed using a MMRM model. The structure of the MMRM model will be same as the one mentioned in primary analysis of LNA043.
- To assess the efficacy of a single i.a. injection of canakinumab followed by q4wx3 i.a. injections of LNA043 (TA3) vs a single i.a. injection of canakinumab (TA4) in participants with symptomatic knee OA with inflammation to relieve OA pain. The variable associated with it is change from baseline in the numeric rating scale (NRS) pain at Day 15, 29, 43, 57, 71, 85, 197, 365 and it will be analyzed using a MMRM model. The structure of the MMRM model will be same as the one mentioned in primary analysis of LNA043.

The secondary efficacy objectives for canakinumab are as follows:

- To assess the efficacy of canakinumab (TA4) vs placebo (TA2) in participants with symptomatic knee OA with inflammation in relieving pain. The variable associated with this objective is change from baseline in KOOS pain subscale at Day 15, 29, 43, 57, 71, 85 and it will be analyzed using a MMRM model. The structure of the MMRM will be same as the one mentioned in primary analysis of canakinumab.
- To assess the efficacy of canakinumab (TA4) vs placebo (TA2) in participants with symptomatic knee OA with inflammation in improving functions of daily living over time. The variable associated with this objective is change from baseline in KOOS function daily living subscale at Day 15, 29, 43, 57, 71, 85 and it will be analyzed using a MMRM model. The structure of the MMRM will be same as the one mentioned in primary analysis of canakinumab.
- To assess the efficacy of canakinumab (TA4) vs placebo (TA2) on synovitis in participants with symptomatic knee OA with inflammation at Day 85. The variable associated with this objective is change from baseline in synovitis level measured from Ktrans by DCE-MRI at Day 85 and it will be analyzed using a MMRM model. The structure of the MMRM will be same as the one mentioned in primary analysis of canakinumab.
- To assess the efficacy of canakinumab (TA4) vs placebo (TA2) in relieving OA pain in participants with symptomatic knee OA with inflammation. The variable associated with it is change from baseline in the numeric rating scale (NRS) pain at Day 15, 29, 43, 57, 71, 85 and it will be analyzed using a MMRM model. The structure of the MMRM will be same as the one mentioned in primary analysis of canakinumab.
- To assess the efficacy of a single i.a. injection of canakinumab followed by q4wx3 i.a. injections of LNA043 (TA3) vs only q4wx3 i.a. injections of LNA043 injections (TA1) in participants with symptomatic knee OA with inflammation in improving functions of daily living over time. The variables associated with this objective are change from baseline in KOOS pain subscale and Function in daily living (ADL) subscales at Day 15, 29, 43, 57, 71, 85, 197, 365 and it will be analyzed using a MMRM model. The structure of the MMRM model will be same as the one mentioned in primary analysis of canakinumab.

- To assess the efficacy of a single i.a. injection of canakinumab followed by q4wx3 i.a. injections of LNA043 (TA3) vs only q4wx3 i.a. injections of LNA043 injections (TA1) in participants with symptomatic knee OA with inflammation to relieve OA pain.
  The variable associated with it is change from baseline in the numeric rating scale (NRS) pain at Day 15, 29, 43, 57, 71, 85, 197, 365 and it will be analyzed using a MMRM model. The structure of the MMRM model will be same as the one mentioned in primary analysis of canakinumab.

12.5.2 Safety endpoints

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

Adverse events

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

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

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.

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

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

Vital signs

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

12-lead ECG

All ECG data will be listed by treatment group, participant 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, participant, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time. Shift tables using the low/normal/high (low and high) classification will be used to compare baseline to the worst on-treatment value.

12.5.3 Pharmacokinetics

LNA043, ANGPTL3, and CCI [redacted] serum and synovial fluid (only ANGPTL3) concentration data will be listed by treatment, participant, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

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

Pharmacokinetic parameters will be calculated for LNA043 at Day 15 as described in Section 8.5.1.1 and will be listed by treatment and participant. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is Tmax where median, minimum, and maximum will be presented.

Pharmacokinetic parameters will be calculated for ANGPTL3 as described in Section 8.5.1.1 and will be listed by treatment and participant. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum.

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Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values.

Table 12-1 Non-compartmental pharmacokinetic parameters

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]
Cav	The average concentration observed in plasma, blood, serum, or other body fluid, defined as AUC over a defined period of time divided by that length of time(mass x volume-1)
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass x volume-1)
Cmin	The minimum (lowest) observed plasma, blood, serum, or other body fluid analyte concentration over a defined period (mass x volume-1)
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)

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

12.5.4 Immunogenicity

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

The number and percentage of participants with positive immunogenicity results will be tabulated by treatment group for both LNA043CCI A participant with multiple positive samples is only counted once.

12.6 Analysis of exploratory endpoints

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12.6.1 CCI

CCI

12.6.2 CCI

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12.6.3 CCI

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12.7 Interim analyses

First interim analysis in the study will be conducted after all the participants have completed Day 85 and the second interim analysis in the study will be conducted after all the participants have completed Day 197.

The purpose of the first interim analysis is to evaluate the primary objective related to canakinumab and the purpose of the second interim analysis is to evaluate the primary objective related to LNA043. In both interim analyses, relevant safety data will be analyzed.

Additional interim analyses may be conducted to support decision making concerning the current clinical study, the sponsor's clinical development projects in general or in case of any safety concerns.

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

The clinical team may communicate interim results (e.g. evaluation of PoC criteria or information needed for planning/modifying another study) to relevant Novartis teams for information, consulting and/or decision purposes.

Interim results may be used to prepare abstracts to scientific meetings. This would typically require investigator input to abstract preparation. Every attempt will be made to assure that the investigator will not have access to individual participant data, but rather will review aggregate, summary data.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

For LNA043, a positive treatment effect is indicated by an increase in volume in the index region and in this study we hope to detect a difference of 100 mm^3. CCI [redacted] a total of 23 evaluable participants per arm will provide more than 80% power, with a 1-sided alpha of 0.05, to detect 100 mm^3 difference between LNA043 and no injection at Day 197.

For canakinumab, a positive treatment effect is indicated by an increase in KOOS pain score and in this study we hope to detect a difference of 12 points. CCI [redacted]. Thus, assuming a standard deviation of 20 points, a total of 46 evaluable participants per arm will provide more than 80% power, with a 1-sided alpha of 0.05, to detect 12-point difference between canakinumab and placebo at Day 85.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

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

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement

to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

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

For details on the Novartis publication policy including authorship criteria, the investigator should consult the Novartis publication policy training materials that will be provided at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

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

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

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

14 Protocol adherence

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

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

14.1 Protocol amendments

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

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

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

15 References

References are available upon request

Altman R, Asch E, Bloch D, et al (1986) Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum. p. 1039-49.

AWMF S1 Leitlinie (2015) «Intraartikuläre Punktionen und Injektionen: Hygienemaßnahmen», Registernummer 029 – 006. Available from: <https://www.awmf.org/uploads/tx_szleitlinien/ 029-006l_S1_Hygiene_intraartikulaere_ Punktionen_und_Injektionen_2015-08_01-abgelaufen.pdf>. Accessed on (27 July 2021).

CCI [redacted]

Bayer Healthcare Pharmaceuticals (2018) Magnevist injection; Prescribing information p. 1-14. Viewed on 25 November 2020.

Bekkers JE, de Windt TS, Raijmakers NJ, et al (2009) Validation of the Knee Injury and Osteoarthritis Outcome Score (KOOS) for the treatment of focal cartilage lesions. Osteoarthr. Cartil. p. 1434-9.

Berenbaum F (2013) Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthr. Cartil. p. 16-21.

CCI [redacted]

Chevalier X, Goupille P, Beaulieu AD, et al (2009) Intraarticular injection of anakinra in osteoarthritis of the knee: a multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum. p. 344-52.

Cohen SB, Proudman S, Kivitz AJ, et al (2011) A randomized, double-blind study of AMG 108 (a fully human monoclonal antibody to IL-1R1) in patients with osteoarthritis of the knee. Arthritis Res. Ther. p. R125.

CCI [redacted]

Dworkin RH, Turk DC, Peirce-Sandner S, et al (2012) Considerations for improving assay sensitivity in chronic pain clinical trials: IMMPACT recommendations. Pain; 153(6):1148-58.

EMA/625317/2017; European Medicines Agency (2017) EMA's final opinion confirms restrictions on use of linear gadolinium agents in body scans p. 1-4. Viewed on 25 November 2020.

CCI [redacted]

Fleischmann RM, Bliddal H, Blanco FJ, et al (2019) A Phase II Trial of Lutikizumab, an Anti-Interleukin-1α/β Dual Variable Domain Immunoglobulin, in Knee Osteoarthritis Patients With Synovitis. p. 1056-1069.

CCI [redacted]

Geirsson ÁJ, Statkevicius S, Víkingsson A (2008) Septic arthritis in Iceland 1990–2002: increasing incidence due to iatrogenic infections. Ann Rheum Dis; 67:638-43.

Guermazi A, Roemer FW, Hayashi D, et al (2011) Assessment of synovitis with contrast-enhanced MRI using a whole-joint semiquantitative scoring system in people with, or at high risk of, knee osteoarthritis: the MOST study. Ann. Rheum. Dis. p. 805-11.

CCI [redacted]

CCI [redacted]

Hawker GA, Mian S, Kendzerska T, et al (2011) Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken) p. S240-52.

CCI [redacted]

Jüni P, Hari R, Rutjes AWS, et al (2015) Intra - articular corticosteroid for knee osteoarthritis. Cochrane Database of Systematic Reviews, Issue 10. Art. No.: CD005328. DOI: 10.1002/14651858.CD005328.pub3. Accessed 30 August 2021.

Kemmerer M, Gramlich Y, Walter G, et al (2017) Infections of large joints – diagnostics and therapeutic strategy. OUP; 1:031-6.

Kjær Petersen S, Jensen Hansen IM, Asmussen Andreasen (2019) Low frequency of septic arthritis after arthrocentesis and intra-articular glucocorticoid injection. Scandinavian Journal of Rheumatology; 48(5):393-7.

CCI [redacted].

Lohmander LS, Roos EM (2019) Disease modification in OA - will we ever get there? Nat Rev Rheumatol p. 133-135.

CCI [redacted]

CCI [redacted]

O'Rourke K (2020) Approach to Aspiration and Injections. ACR Virtual Rheumatology Practicum. doi:10.1136/ard.2007.077131 Via ACR

Osteoarthritis Research Society International (2016) Osteoarthritis: a serious disease. White paper submitted to the U.S. Food and Drug Administration, viewed 16 December 2019 p. 1-103.

Patel KV, Amtmann D, Jensen MP, et al (2021) Clinical outcome assessment in clinical trials of chronic pain treatments. Pain Rep; 6(1):e784.

Riis RGC, Henriksen M, Klokker L, et al (2017) The effects of intra-articular glucocorticoids and exercise on pain and synovitis assessed on static and dynamic magnetic resonance imaging in knee osteoarthritis: exploratory outcomes from a randomized controlled trial. Osteoarthr. Cartil. p. 481-491.

Roos EM, Engelhart L, Ranstam J, et al (2011) ICRS Recommendation Document: Patient-Reported Outcome Instruments for Use in Patients with Articular Cartilage Defects. Cartilage p. 122-36.

Ryu K, Iriuchishima T, Oshida M, et al (2014) The prevalence of and factors related to calcium pyrophosphate dihydrate crystal deposition in the knee joint. Osteoarthritis Cartilage p. 975-9.

Schieker M, Conaghan PG, Mindeholm L, et al (2020) Effects of Interleukin-1β Inhibition on Incident Hip and Knee Replacement : Exploratory Analyses From a Randomized, Double-Blind, Placebo-Controlled Trial. Ann Intern Med p. 509-515.

CCI [redacted]

Surowiec RK, Lucas EP, Fitzcharles EK, et al (2014) T2 values of articular cartilage in clinically relevant subregions of the asymptomatic knee. Knee Surg Sports Traumatol Arthrosc p. 1404-14.

Terpstra SES, van der Velde JHPM, de Mutsert R, et al (2021) The association of clinical and structural knee osteoarthritis with physical activity in the middle-aged population: the NEO study. Osteoarthritis Cartilage; 24:S1063-4584(21)00845-1.

The Royal College of Radiologists (2019) Guidance on gadolinium-based contrast agent administration to adult patients p. 1-23. Viewed on 25 November 2020.

CCI [redacted]

Wang X, Hunter D, Xu J, et al (2015) Metabolic triggered inflammation in osteoarthritis. Osteoarthr. Cartil. p. 22-30.

Williams SN, Wolford ML, Bercovitz A (2015) Hospitalization for Total Knee Replacement Among Inpatients Aged 45 and Over: United States, 2000-2010. NCHS Data Brief p. 1-8.

Wise BL, Niu J, Yang M, et al (2012) Patterns of compartment involvement in tibiofemoral osteoarthritis in men and women and in whites and African Americans. Arthritis Care Res (Hoboken) p. 847-52.

Wolfe F, Clauw DJ, Fitzcharles MA, et al (2010) The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken) p. 600-10.

Wolford ML, Palso K, Bercovitz A (2015) Hospitalization for total hip replacement among inpatients aged 45 and over: United States, 2000-2010. NCHS Data Brief p. 1-8.

Yazici Y, McAlindon TE, Fleischmann R, et al (2017) A novel Wnt pathway inhibitor, SM04690, for the treatment of moderate to severe osteoarthritis of the knee: results of a 24-week, randomized, controlled, phase 1 study. Osteoarthr. Cartil. p. 1598-1606.

van den Bosch MHJ (2019) Inflammation in osteoarthritis: is it time to dampen the alarm(in) in this debilitating disease? Clin. Exp. Immunol. p. 153-166.

16 Appendices

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

Table 16-1 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	• ALT or AST >5×ULN • ALP >2×ULN (in the absence of known bone pathology) • Total bilirubin >3×ULN (in the absence of known Gilbert syndrome) • ALT or AST >3×ULN and INR >1.5 • Potential Hy's Law cases (defined as ALT or AST >3×ULN and Total bilirubin >2×ULN [mainly conjugated fraction] without notable increase in ALP to >2×ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST >3×ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity
If ALT or AST abnormal at baseline:	• ALT or AST >3xbaseline or >300 U/L (whichever occurs first)

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

	ALT	TBL	Liver Symptoms	Action
ALT increase without bilirubin increase:				
	If normal at baseline: ALT > 3xULN **If elevated at baseline:** ALT >2xbaseline or >300 U/L (whichever occurs first)	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	• **No change to study treatment** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH (if available) in 48-72 hours. • Follow-up for symptoms.
	If normal at baseline: ALT >5xULN for more than two weeks **If elevated at baseline:** ALT >3xbaseline or >300 U/L (whichever occurs first) for more than two weeks	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	• **Interrupt study drug** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH (if available) in 48-72 hours. • Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies. • Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
	If normal at baseline: ALT >8xULN	Normal	None	
ALT increase with bilirubin increase:				
	If normal at baseline: ALT > 3 xULN **If elevated at baseline:** ALT >2xbaseline or >300 U/L (whichever occurs first)	TBL >2xULN (or INR >1.5) For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
	If normal at baseline: ALT >3xULN **If elevated at baseline:** ALT >2xbaseline or >300 U/L (whichever occurs first)	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	

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

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

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

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

Table 16-4 Specific Renal Alert Criteria and Actions

Renal Event	Actions
Confirmed serum creatinine increase 25 – 49%	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase ≥50 %* **OR if <18 years old, eGFR 35 mL/min/1.73 m^2**	• 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	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

Table 16-5 Renal Event Follow Up

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 ACR <300 g="" li="">) • 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