

Novartis Institutes for BioMedical Research

LNA043

Clinical Trial Protocol CLNA043X2201

**A randomized, placebo-controlled, patient and investigator blinded, single dose, Proof of Concept study investigating the safety, tolerability and preliminary efficacy of intra-articular LNA043 in regenerating the articular cartilage of the knee at donor sites in patients undergoing autologous chondrocyte implantation**

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## **Site Operations Manual (SOM)**

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

### **Notification of serious adverse events**

**Dear Investigator,**

You must report a serious adverse event (SAE) or serious adverse device effect (SADE) (initial or follow-up) to Novartis as summarized below. Refer to [Section 9.3](#) of the protocol for SAE and SADE criteria and additional requirements. See also page 2 of the Site Operations Manual for further details on the method of reporting a SAE and SADE.

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

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## List of abbreviations

$\gamma$ -GT	Gamma-glutamyl transferase
ACI	Autologous Chondrocyte Implantation
ADE	Adverse device effect
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANGPTL	angiopoietin-like protein
AST	aspartate aminotransferase
B	Blinded
BMI	Body Mass Index
BP	Blood Pressure
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CK	creatinine kinase
CMO&PS	Chief Medical Office & Patient Safety
COAs	Clinical Outcome Assessments
CPPD	Calcium Pyrophosphate Deposition Disease
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTC	Common Toxicity Criteria
CTRД	Clinical Trial Results Database
CV	coefficient of variation
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EOS	End of Study
FDA	Food and Drug Administration

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FIH	First in Human
GAG	Glycosaminoglycan
GCP	Good Clinical Practice
h	Hour
HBV	Hepatitis B
HCV	Hepatitis C
HDL	High-Density Lipoproteins
HIV	human immunodeficiency virus
i.a.	intra articular
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IG	Immunogenicity
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD/IUS	Intrauterine Device or System

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LDH	lactate dehydrogenase
LDL	Low-density Lipoprotein
LFT	Liver function test
LLN	lower limit of normal
LLQ	lower limit of quantification
MABEL	minimum anticipated biological effect level
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
Ms	Microsecond
MOCART	Magnetic resonance Observation of Cartilage Repair Tissue
MRI	Magnetic Resonance Imaging
NCDS	Novartis Clinical Data Standards
NSAID	Non steroidal anti-inflammatory drugs
NIRT	Novartis Interactive Response Technology

OA	Osteoarthritis
o.d.	once a day
PCR	Polymerase Chain Reaction
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PoC	Proof of Concept
PRO	Patient-Reported Outcomes
RBC	red blood cell(s)
RDC	Remote Data Capture
REB	Research Ethics Board
RF	Radiofrequency
RNA	Ribonucleic Acid
s.c.	Subcutaneous
SAE	serious adverse event
SAD	single ascending dose
SADE	serious adverse device effect
SAR	Specific absorption rate
sCR	serum creatinine
SD	standard deviation
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	total bilirubin
TKR	Total Knee Replacement
ULN	upper limit of normal
ULQ	upper limit of quantification
USADE	unanticipated serious adverse device effect
WBC	white blood cell(s)
WHO	World Health Organization
7T MRI	7 Tesla MRI

## Pharmacokinetic definitions and symbols

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

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

## Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up), which applies across all arms of a study.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug” or “test substance”
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Non-investigational medicinal Product (NIMP)	Products which are not the object of investigation (e.g. any background therapy administered to each of the clinical trial subjects, regardless of randomization group, rescue medication, active drug run-ins etc.)
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest

Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
Study treatment	Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), control(s) or non-investigational medicinal product(s)
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study

Withdrawal of study  
consent

Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

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## Protocol synopsis

<b>Protocol number</b>	CLNA043X2201
<b>Title</b>	A randomized, placebo-controlled, patient and investigator blinded, single dose, Proof of Concept study investigating the safety, tolerability and preliminary efficacy of intra-articular LNA043 in regenerating the articular cartilage of the knee at donor sites in patients undergoing autologous chondrocyte implantation.
<b>Brief title</b>	Study of safety and tolerability and preliminary efficacy of LNA043 in patients undergoing autologous chondrocyte implantation.
<b>Sponsor and Clinical Trial Phase</b>	Novartis Phase II
<b>Intervention type</b>	Biologic
<b>Study type</b>	Interventional
<b>Purpose and rationale</b>	The purpose of this Proof of Concept (PoC) study is to assess safety, tolerability and preliminary efficacy of intra articular (i.a.) LNA043 in regenerating the articular cartilage of the knee at the donor sites of the autologous chondrocyte implantation (ACI) procedure, with a hyaline tissue, significantly more often than with placebo. The highest single safe dose of LNA043 of the First in Human CLNA043X2101 study will be used.
<b>Primary Objective(s)</b>	<ul style="list-style-type: none"> <li>To assess the efficacy of a single LNA043 i.a. injection in regenerating hyaline cartilage tissue at the donor sites of patients undergoing autologous chondrocyte implantation (ACI)</li> <li>To assess safety and tolerability of a single LNA043 i.a. injection in patients undergoing ACI</li> </ul>
<b>Secondary Objectives</b>	<ul style="list-style-type: none"> <li>To assess extent and quality of the repair tissue at the donor site before surgery</li> <li>To assess over a longer term the extent and quality of filling of the donor site</li> <li>To evaluate local and systemic pharmacokinetics (PK) of LNA043 following a single i.a. administration</li> <li>To assess the potential immunogenicity of LNA043</li> </ul>
<b>Study design</b>	Randomized, placebo-controlled, patient and investigator blinded, parallel group, 2 cohorts, single dose, 6 month study
<b>Population</b>	Approximately 22 patients (18-50 years of age) undergoing autologous chondrocyte implantation to allow approximately 18 completers, divided as follow: approximately 12 completers in Cohort 1 and approximately 6 completers in Cohort 2. The two cohorts differ only by the dose administered: 20 mg LNA043 or matching placebo in Cohort 1, 40 mg LNA043 or matching placebo in Cohort 2
<b>Key Inclusion criteria</b>	<ul style="list-style-type: none"> <li>Written informed consent must be obtained before any assessment is performed</li> <li>Patient is <math>\geq 18</math> and <math>\leq 50</math> years old at time of screening</li> <li>Patient has a body mass index (BMI) <math>&lt;30 \text{ kg/m}^2</math> at screening</li> <li>Patient has a localized articular cartilage defect of the knee and is scheduled for an ACI procedure</li> </ul>

	<ul style="list-style-type: none"><li>• Able to communicate well with the investigator, to understand and comply with the requirements of the study.</li></ul>
<b>Key Exclusion criteria</b>	<ul style="list-style-type: none"><li>• Patient has radiologically apparent degenerative joint disease in the target knee as determined by Kellgren and Lawrence grade <math>\geq 2</math> based on X-ray evaluation performed within 6 months from screening</li><li>• Patient has unstable knee joint or insufficiently reconstructed ligaments, based on medical history and physical examination by the investigator.</li><li>• Patient scheduled for a concomitant articular surgical procedure (e.g., anterior cruciate ligament reconstruction) other than debridement or partial meniscectomy</li><li>• Patient has malalignment (valgus- or varus-deformity) in the target knee <math>\geq 5^\circ</math> based on X-ray evaluation performed within 6 months from screening.</li><li>• Patient has a known autoimmune disease, inflammatory arthropathy (including but not limited to rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, CPPD, gout), active acute or chronic infection of the joint, recent Lyme disease to the knee, systemic cartilage disorder, or a known systemic connective tissue disease.</li><li>• Patient has had surgical treatment of the target knee using autologous osteochondral transplantation/mosaicplasty within 12 months prior to screening (Note: prior diagnostic arthroscopy with debridement and lavage, meniscal surgery, microfracture, anterior cruciate ligament reconstruction, and extra-articular surgery e.g., high-tibial osteotomy are acceptable).</li><li>• Patient is unable to undergo magnetic resonance imaging (MRI) or presents absolute contraindications to MRI (e.g., metallic implants, metallic foreign bodies, pacemaker, defibrillator).</li><li>• Patient taking medications prohibited by the protocol: corticosteroids by any route (except topical) from 4 weeks prior to screening; nonsteroidal anti-inflammatories or aspirin (greater than 100 mg per day) within 2 weeks prior to screening; paracetamol greater than 3000 mg per day within 2 weeks prior to screening; glucosamine or chondroitin sulfate within 2 weeks prior to screening; any local treatment i.a. into the knee within 3 months from screening.</li><li>• Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 15 days after stopping of investigational drug.</li><li>• Regular smokers (use of tobacco/nicotine products in the previous 3 months <math>&gt; 5</math> cigarettes/day). Urine cotinine levels will be measured during screening for all subjects. Regular smokers will be defined as any subject who reports tobacco use of <math>&gt; 5</math> cigarettes/day and/or who has a urine cotinine <math>\geq 500</math> ng/mL.</li></ul>
<b>Study treatment</b>	<p>Cohort 1:</p> <ul style="list-style-type: none"><li>○ A: single dose of 20 mg LNA043</li><li>○ B: single dose of matching placebo to 20 mg LNA043</li></ul> <p>Cohort 2:</p> <ul style="list-style-type: none"><li>○ C: single dose of 40 mg LNA043</li><li>○ D: single dose of matching placebo to 40 mg LNA043</li></ul>

<b>Efficacy/PD assessments</b>	<ul style="list-style-type: none"><li>• Cartilage glycosaminoglycan (GAG) content and bi-layer collagen organization based on 7 Tesla MRI (7T MRI)</li><li>• International Cartilage Repair Society (ICRS) II histology scoring system</li><li>• Percentage (%) of donor site filling based on 7T MRI</li></ul>
<b>Key safety assessments</b>	<ul style="list-style-type: none"><li>• Adverse event monitoring</li><li>• Physical examinations</li><li>• Monitoring of laboratory markers in blood and urine</li></ul>
<b>Other assessments</b>	<ul style="list-style-type: none"><li>• Serum PK profile of LNA043 and /AngPTL3</li><li>• <b>Corporate Confidential Information</b></li><li>• Presence and characterization of anti-LNA043 antibodies in serum</li></ul>
<b>Data analysis</b>	The primary efficacy variable, GAG content change and bi-layer collagen organization in the cartilage repair tissue at the donor sites based on 7T MRI at Week 4, and key secondary endpoints, will be analyzed using a mixed model repeated measures (MMRM) analysis of variance model, including all timepoints, to compare treatment groups.
<b>Key words</b>	ACI, cartilage regeneration, 7T MRI

## 1 Introduction

### 1.1 Background

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

Articular cartilage has limited healing potential. During cartilage damage, the number of cartilage resident mesenchymal stem cells (CR-MSCs) increases. CR-MSCs are capable of multi-lineage differentiation, including chondrogenesis, when exposed to an appropriate signaling environment in vitro. The LNA043 program arose from an effort to identify molecules able to target CR-MSCs to undergo differentiation into chondrocytes and facilitate hyaline articular cartilage repair by inducing the production of SOX9, type II collagen and aggrecan, but not inducing molecules involved in fibrosis or osteogenesis.

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LNA043 acts directly on CR-MSCs and articular chondrocytes through binding to  $\alpha 5\beta 1$  and  $\alpha V\beta 3$  integrins (RGD class) on the cell surface to transmit its anabolic repair effects on cartilage cells. These events promote the formation of articular cartilage extracellular matrix proteins in mature chondrocytes and in CR-MSCs while supporting re-growth of CR-MSCs.

The first-in-human single ascending dose (FIH SAD) study initially investigated doses up to 20 mg, and then a further dose escalation to 40 mg was performed. FIH SAD has been performed in primary OA patients who were scheduled for total knee replacement (TKR). LNA043 was administered 1 week prior to surgery and safety, tolerability, pharmacokinetics (PK), immunogenicity data were collected. In summary, (i) no significant drug-related Adverse Events (AE) and Serious Adverse Events (SAE) have been reported up to the highest evaluated single i.a. dose of 40 mg; (ii) LNA043 was rapidly eliminated from the synovial fluid of the knee and the plasma (LNA043 levels were below limit of quantification after 7 days in both samples) and (iii) no anti-drug antibodies (ADA) were detected. Consequently after evaluating the data from the FIH on the 40 mg dose, it has been decided to use it in the CLNA043X2201 study. From a risk-benefit perspective no changes are foreseen. Considering the FIH SAD study results, the 40 mg dose was not associated with any significant drug related AEs or SAEs while the demonstrated dose/response in the pre-clinical studies indicate potential incremental treatment benefit which might be associated with an higher dose of LNA043.

Considering the previous pre-clinical and clinical experience, a potentially favorable benefit/risk is anticipated for the patients included in the present study. Potential benefits include (i) better healing of the donor sites; (ii) improved integration of the ACI graft; (iii) reduction in size of the cartilage defect, possibly resulting in a better outcome of the ACI procedure.

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

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#### **1.4 Study purpose**

The purpose of this study is to assess safety, tolerability, pharmacokinetics and preliminary efficacy of a single intra-articular (i.a.) administration of LNA043 in regenerating the articular cartilage of the knee, in a standardized clinical scenario of acute cartilage defect. This study is aimed at establishing Proof of Concept (PoC) and characterizing the mechanism(s) of action of LNA043, in order to provide information on the potential for clinical application, with the ultimate goal of replacing current surgical procedures for cartilage repair. A First In Human (FIH) study was conducted previously and demonstrated safety and tolerability of a single i.a. injection of LNA043. This study will support the further development of LNA043 in other clinical studies, planned to include a multiple i.a. injection regimen.

## 2 Study objectives and endpoints

### 2.1 Primary objective(s)

<i>Primary objective(s)</i>	<i>Endpoints related to primary objective(s)</i>
<ul style="list-style-type: none"><li>• To assess the efficacy of a single LNA043 i.a. injection in regenerating hyaline cartilage tissue at the donor sites of patients undergoing autologous chondrocyte implantation (ACI)</li></ul>	<ul style="list-style-type: none"><li>• Cartilage glycosaminoglycan (GAG) content and bi-layer collagen organization based on 7T MRI at Week 4</li></ul>
<ul style="list-style-type: none"><li>• To assess safety and tolerability of a single LNA043 i.a. injection in patients undergoing ACI</li></ul>	<ul style="list-style-type: none"><li>• Adverse Events</li><li>• ECGs</li><li>• Vital signs</li><li>• Hematology, blood chemistry, urinalysis</li><li>• Physical examination</li></ul>

### 2.2 Secondary objective(s)

<i>Secondary objective(s)</i>	<i>Endpoints related to secondary objective(s)</i>
<ul style="list-style-type: none"><li>• To assess extent and quality of the repair tissue at the donor site before surgery</li></ul>	<ul style="list-style-type: none"><li>• International Cartilage Repair Society (ICRS) II histology scoring system at Week 4</li><li>• Percentage (%) of donor site filling based on 7T MRI at Week 4</li></ul>
<ul style="list-style-type: none"><li>• To assess over a longer term the extent and quality of filling of the donor site</li></ul>	<ul style="list-style-type: none"><li>• Percentage (%) of donor site filling based on 7T MRI at Week 12 and 28</li><li>• Cartilage GAG content and bi-layer collagen organization estimated using 7T MRI at Week 12 and 28</li></ul>
<ul style="list-style-type: none"><li>• To evaluate local and systemic pharmacokinetics (PK) of LNA043 following a single i.a. administration</li></ul>	<ul style="list-style-type: none"><li>• Serum PK profile of LNA043 and AngPTL3, Cmax and AUC</li><li>• Concentration of LNA043 and AngPTL3 in synovial fluid at Week 4</li></ul>
<ul style="list-style-type: none"><li>• To assess the potential immunogenicity of LNA043</li></ul>	<ul style="list-style-type: none"><li>• Presence and characterisation of anti-LNA043 antibodies in serum at Day 1 (predose), Day 8, 29, 85, 197</li></ul>

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### **3      Investigational plan**

#### **3.1    Study design**

This is a non-confirmatory, patient and investigator blinded, randomized, placebo-controlled, parallel group, 2 cohorts, single dose study in patients with cartilage lesions undergoing autologous cartilage implantation (ACI) with the use of an exploratory 7T MRI for efficacy assessment. Approximately 22 patients will be enrolled in the study to allow approximately 18 completers, divided as follows: approximately 12 completers in Cohort 1 and approximately 6 completers in Cohort 2. The two cohorts differ only by the dose administered: 20 mg LNA043 or matching placebo in Cohort 1, 40 mg LNA043 or matching placebo in Cohort 2. Participants will be treated only on one occasion (Day 1) with a single i.a. injection that will be performed under arthroscopic visualization.

Cohort 1 and Cohort 2 will have the same design and will consist of a screening epoch (Day -42/-1); a Day 1 treatment epoch in which an arthroscopy for cartilage harvest will be done as part of the normal ACI procedure, and the patient will be dosed. Post-treatment follow-up epoch will be at Day 2, Day 3, Week 1, Week 4 (i.e., time of ACI graft implantation), Week 12 and Week 28 for the End of Study (EoS) assessments.

At screening, after signing the informed consent, laboratory test for eligibility assessment **CCI** will be obtained. Patients may be randomized up to 7 days before treatment. After eligibility confirmation, starting from Day -7 till Day 1 patients can be randomized to receive either LNA043 (20 mg or 40mg) or matching placebo (2:1 randomization ratio). At Day 1, patients will undergo arthroscopic surgery for cartilage harvest, as per the standard ACI procedure, at the donor site in the intercondylar notch and will receive treatment at the end of the surgery. Patients will undergo safety and pharmacokinetic evaluations as detailed in the [Assessment Schedule](#). An overnight stay is needed to collect the last PK sample at 24 hours (Day 2) from the injection.

At Day 3 (+1), MRI assessment of the donor site and of the defect site will be performed as baseline.

At Week 1, patients will return to the hospital for regular medical check and safety evaluations as detailed in the [Assessment Schedule](#).

At Week 4 (Day 29 -3), MRI assessment of the donor site and of the defect site has to be performed on Day 29 or up to 3 days before. Surgery can be done on the same day of the 4 Week MRI, but MRI should be performed before surgery. .

Site should plan the open ACI graft implantation at Week 4 (Day 29 +/-5). However, in case the *in vitro* culture of the ACI graft takes longer than planned, or for any other unforeseeable reason related to surgical planning or to patient's needs, the second surgery can be delayed, after informing Sponsor. On the day of the open ACI graft implantation patients will return to the hospital and safety laboratory testing will be collected.

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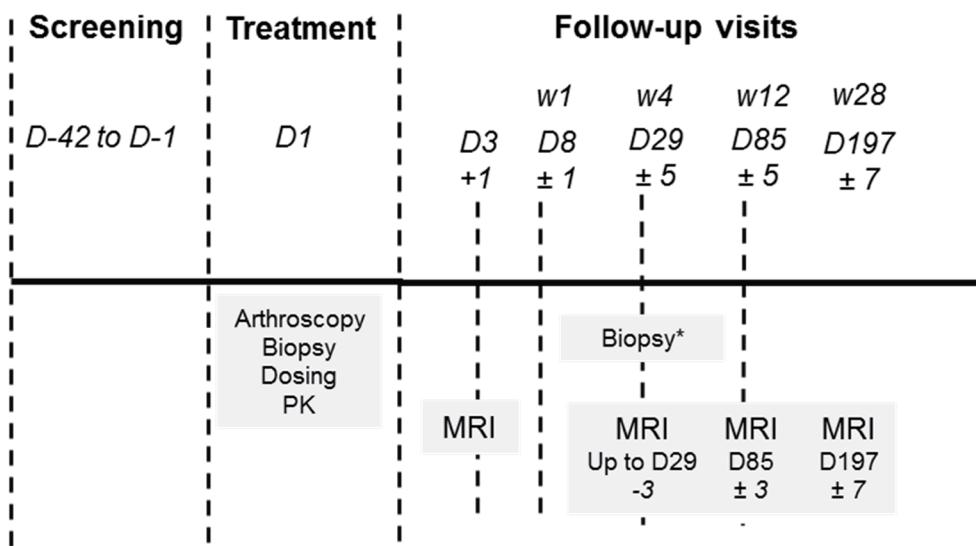
At Week 12 (Day 85 +/- 5) patients will return to the hospital for regular medical checks and safety evaluations as detailed in the [Assessment Schedule](#). The MRI assessment can be performed either the day of the visit or +/- 3 days from the visit as detailed in the [Assessment Schedule](#).

At Week 28 (Day 197 +/- 7), patients will return for an EoS visit. EoS visit assessments will include safety, **CCI** and other assessments as detailed in the [Assessment Schedule](#).

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All MRI assessments at Day 3, Week 4, Week 12 and Week 28 (EOS) will be performed at the specific site called investigational site for medical device (subsequent in the protocol referred to as imaging site, for simplicity).

**Figure 3-1 Study Design for Cohort 1 and Cohort 2**



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## 3.2 Rationale for study design

This study is designed to evaluate the safety, tolerability, pharmacokinetics and preliminary efficacy of two single doses of LNA043 (20 and 40 mg) administered by i.a. injection in regenerating the articular cartilage of the knee by assessing the quality and extent of repair tissue in a small, standardized acute cartilage defect over a 28 week period. The combination of the exploratory 7T MRI and of the ICRS II histologic score ([Mainil-Varlet et al 2010](#)) will ensure optimal characterization of the repair tissue at the donor sites. The 7T MRI was chosen because, by its high field, it is the only MRI able to detect sodium in tissues, that will allow to measure the GAG content by a sensitive method ([Bangerter et al 2016](#)).

Administration of LNA043 in this clinical scenario has been chosen for two main reasons.

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This may facilitate proof of concept while (i) minimizing the number of patients involved, because of the standardization of the donor sites; (ii) reducing the typically long observation time to detect cartilage tissue regeneration, because of the very small size of the donor sites; (iii)

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Second, no additional discomfort to the patients will be created by the planned assessments, because (i) they normally undergo two surgeries according to the standard ACI protocol; (ii) MRI is a non-invasive imaging method; (iii) a biopsy of donor sites is not associated with additional morbidity ([McCarthy et al 2016](#)); (iv)

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Restrictive inclusion criteria (e.g., BMI<30, age range 18-50 years) and non clinically-relevant lesions (very small, freshly generated, non weight-bearing areas) have been selected in order to ensure homogeneity in a small patient sample. Regeneration of hyaline cartilage in this particular scenario is considered translational, as the underlying processes are comparable to those occurring in clinically-relevant lesions. In subsequent studies, inclusion

criteria will be expanded (e.g., BMI <35, age range 18-55 years) and only clinically-relevant cartilage lesions will be targeted (e.g., weight-bearing areas, larger size, non freshly generated).

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The two cohorts design will allow investigating the safety, tolerability and preliminary efficacy of two doses (20 and 40 mg) of LNA043 in one study enrolling a small number of patients.

To reduce bias in the measurement and in the analysis of the imaging data, all the 7T MRI measurements will be performed at the specific imaging site, that is experienced and well equipped to perform imaging assessments planned in this study at the highest resolution available at the moment.

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**3.4 Rationale for choice of comparator**

No pharmacological therapy to promote cartilage healing has been approved so far. Therefore, the comparator will be placebo.

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

**3.5 Rationale for choice of background therapy**

No background pharmacological therapy is included in this study. However, all patients will undergo an ACI procedure for the repair of an articular cartilage defect to a knee joint. The rationale for the selection of this particular clinical scenario is clarified in [Section 3.2](#) (Rationale of study design)

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**3.7 Risks and benefits**

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The risk to patients in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, stopping rules and by exposure to only a single dose of LNA043.

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However, since these procedures will be performed during the planned surgeries, therefore under anesthesia and sterile conditions, no additional risks or discomfort for the patients is expected ([Harris et al 2011](#); [Salzler et al 2014](#)).

Women of child bearing potential will be informed that taking the investigational drug 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 requirement for the duration of the study. If there is any question that the subject will not reliably comply, they should not be entered in the study.

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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 triglyceride metabolism, will be monitored closely with the corresponding safety plan in place.

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

#### **3.7.1 Risks of imaging procedures**

The only imaging technique used in this study is the 7T MRI, which is an exploratory medical device. 7T MRI is a non-invasive radiology technique that has no x-ray radiation exposure. Up to now, no health risks of ultra-high field (7T) applications have been reported, and no additional contraindications beyond 3T MRI are required. As the switching gradients are the same as used for registered 3 Tesla or 1.5 Tesla MRI systems, no special safety management is needed for a 7T scanner. Only the presence of metal in the body would be a safety hazard (as with lower field MRI scanners); this can also affect the image quality. For more information, see exclusion criterion 11. However, as the specific absorption rate (SAR) is related to the radiofrequency (RF) electromagnetic field and this to the field strength of the MR system. Transmitted RF is safety-relevant for patients with non-ferromagnetic implants, because this can lead to hazardous heating due to local SAR increase. Thus, for these specific patients the radiologist at the imaging site will evaluate together with the patient the risk-benefit of performing the 7T MRI scan.

#### **3.7.2 Blood sample volumes**

A maximum of approximately 140 mL of blood is planned to be collected over a period of 33 weeks, from each subject as part of the study, independently of the cohort they are enrolled in. Additional samples for monitoring of any safety findings would be in addition to this. This is not considered to be a risk for this population.

Timings of blood sample collection are outlined in the Assessment Schedule, [Section 8.1](#).

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

See [Section 8.9](#) regarding the potential use of residual samples.

## 4 Population

The study population will be comprised of male and female patients with cartilage lesions of the knee scheduled for ACI surgery. A total of approximately 22 patients will be enrolled in the study and randomized. At least 18 patients, divided between the two Cohorts (12 completers in cohort 1 and 6 completers in Cohort 2), are expected to complete the study (considering a drop out rate of approximately 20%). If the dropout rate exceeds 20% additional patients will be enrolled.

Patient homogeneity in terms of age, smoking habit, and BMI will minimize inter-individual variability in tissue repair and will represent a substantial advantage for PoC) assessment.

The investigator must ensure that all subjects included in the study meet the eligibility criteria. No additional criteria should be applied by the investigator, in order that the study population will be representative of all eligible subjects. Patient selection is to be established by checking through all eligibility criteria at screening. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site.

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

### Patient

Patients undergoing autologous chondrocyte implantation.

#### 4.1 Inclusion criteria

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

1. Written informed consent must be obtained before any assessment is performed.
2. Patient is  $\geq 18$  and  $\leq 50$  years old at time of screening.
3. Patient has a body mass index (BMI)  $< 30 \text{ kg/m}^2$  at screening.
4. Patient has a localized articular cartilage defect of the knee and is scheduled for an ACI procedure.
5. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

#### 4.2 Exclusion criteria

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

1. Use of other investigational drugs within 5 half-lives of enrollment, or until the expected pharmacodynamic effect has returned to baseline, whichever is longer.
2. History of hypersensitivity to any of the study treatments or excipients or to drugs of similar chemical classes.
3. History or current diagnosis of ECG abnormalities indicating significant risk of safety for subjects 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

4. Patient has radiologically apparent degenerative joint disease in the target knee as determined by Kellgren and Lawrence grade  $\geq 2$  based on X-ray evaluation performed within 6 months from screening
5. Patient has an unstable knee joint or insufficiently reconstructed ligaments based on medical history and physical examination by the investigator.
6. Patient scheduled for a concomitant articular surgical procedure (e.g., anterior cruciate ligament reconstruction) other than debridement or partial meniscectomy
7. Patient has malalignment (valgus- or varus-deformity) in the target knee  $\geq 5^\circ$  based on X-ray evaluation performed within 6 months from screening. In suspected cases, the mechanical axis must be established radiographically through complete leg imaging during standing and in postero-anterior projection.
8. Patient has a known autoimmune disease, inflammatory arthropathy (including but not limited to rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, CPPD, gout), active acute or chronic infection of the joint, recent Lyme disease to the knee, systemic cartilage disorder, or a known systemic connective tissue disease.
9. History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result.
10. Patient has had surgical treatment of the target knee using autologous osteochondral transplantation/mosaicplasty within 12 months prior to screening (Note: prior diagnostic arthroscopy with debridement and lavage, meniscal surgery, microfracture, anterior cruciate ligament reconstruction, and extra-articular surgery e.g., high-tibial osteotomy are acceptable).
11. Patient is unable to undergo magnetic resonance imaging (MRI) or presents absolute contraindications to MRI (e.g., metallic implants, metallic foreign bodies, pacemaker, defibrillator).
12. Patient taking medications prohibited by the protocol: corticosteroids by any route (except topical) from 4 weeks prior to screening; nonsteroidal anti-inflammatories or aspirin greater than 100 mg per day by any route except topical within 2 weeks prior to screening; paracetamol greater than 3000 mg per day within 2 weeks prior to screening; glucosamine or chondroitin sulfate within 2 weeks prior to screening; any local treatment i.a. into the knee within 3 months from screening.
13. Chronic infection with Hepatitis B (HBV) or Hepatitis C (HCV). A positive HBV surface antigen (HBsAg) test, or if standard local practice, a positive HBV core antigen test, excludes a subject. Subjects with a positive HCV antibody test should have HCV RNA levels measured. Subjects with positive (detectable) HCV RNA should be excluded.
14. The patient has at the site of surgery an active systemic or local microbial infection, eczematization or inflammable skin alterations.
15. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in-situ* cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
16. Pregnant or nursing (lactating) women.

17. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 15 days after stopping of investigational drug. Highly effective contraception methods include:

- Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

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

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

18. History of drug abuse or unhealthy alcohol use within the 12 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays conducted during screening. Unhealthy alcohol use is defined as a history of, or current alcohol misuse/abuse, defined as "Five or more drinks on the same occasion on each of 5 or more days in the past 30 days."
19. Regular smokers (use of tobacco/nicotine products in the previous 3 months > 5 cigarettes/day). Urine cotinine levels will be measured during screening for all subjects. Regular smokers will be defined as any subject who reports tobacco use of > 5 cigarettes/day and/or who has a urine cotinine  $\geq$  500 ng/mL.
20. History of multiple and recurring allergies or allergy to the investigational compound/compound class being used in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

## 5      **Restrictions for Study Subjects**

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

## 5.1 Contraception requirements

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

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

## 5.2 Prohibited treatment

Use of the treatments displayed in the table below is NOT allowed in the reported timeframe.

**Table 5-1 Prohibited medication**

Medication	Prohibited period	Action to be taken
Local i.a. treatment into the knee, including but not restricted to viscosupplementation and corticosteroids (impact on tissue repair/confounding of efficacy)	12 weeks prior to screening through end of study	Must be recorded on the Concomitant medications/ Significant non-drug therapies section of the CRF.
Corticosteroid use by any route except topical (impact on tissue repair)	4 weeks prior to screening through end of study	Must be recorded on the Concomitant medications/ Significant non-drug therapies section of the CRF.
Nonsteroidal anti-inflammatories, aspirin greater than 100 mg/day by any route except topical (impact on cartilage tissue repair). See <a href="#">Section 6.10</a> (Rescue Medication) for exceptions.	2 weeks prior to screening through end of study	Must be recorded on the Concomitant medications/ Significant non-drug therapies section of the CRF.
Paracetamol greater than 3000 mg per day (confounding of liver function). See <a href="#">Section 6.10</a> (Rescue Medication) for exceptions.	From screening through end of study	Must be recorded on the Concomitant medications/ Significant non-drug therapies section of the CRF.
Oral glucosamine, chondroitin sulfate, or any nutraceutical with potential activity on cartilage repair (confounding of efficacy)	2 weeks prior to screening through end of study	Must be recorded on the Concomitant medications/ Significant non-drug therapies section of the CRF.

## 5.3 Dietary restrictions and smoking

No cigarettes/use of nicotine products for 72 hours before dosing until after Study Completion evaluation.

## 5.4 Other restrictions

Patient will have to strictly follow the rehabilitation regimen prescribed by the Investigator according to the local protocol.

## 6 Treatment

### 6.1 Study treatment

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

#### 6.1.1 Investigational treatment and control drugs

**Table 6-1 Overview of study medication**

Study drug name	Formulation	Unit dose		Provided by
			Packaging	
LNA043	Lyophilisate in Vial (LYO)	10 mg	Open Label Bulk Supply	Novartis
Placebo	Lyophilisate in Vial (LYO)	0 mg	Open Label Bulk Supply	Novartis

##### 6.1.1.1 Bio-batch retention samples

NA

##### 6.1.2 Additional study treatment

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

## 6.2 Treatment arms

Subjects will be assigned to one of the following Cohorts. Each Cohort has two (2) treatment arms in a ratio of 2:1 (LNA043:placebo).

Cohort 1, study treatments are defined as:

- A: single dose of 20 mg LNA043
- B: single dose of matching placebo to 20 mg LNA043

Cohort 2, study treatments are defined as:

- C: single dose of 40 mg LNA043
- D: single dose of matching placebo to 40 mg LNA043

### **6.3 Treatment assignment and randomization**

At the first dosing visit (Day 1) or 7 days before Day 1, after eligibility confirmation, subjects will be randomized via Novartis Interactive Response Technology (NIRT) to one of the two treatment arms of Cohort 1 or Cohort 2. The investigator or his/her delegate will log into the NIRT system after confirming that the patient fulfills all the inclusion/exclusion criteria. The NIRT will assign a treatment arm to the patient.

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

### **6.4 Treatment blinding**

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

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

#### **Site staff**

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

Unblinding a single subject at site for safety reasons (necessary for subject management) will occur via an emergency system in place at the site (see [Section 6.7](#) (Emergency breaking of assigned treatment code)).

#### **Investigational site for medical device staff**

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

#### **Sponsor staff**

The following unblinded sponsor roles are required for this study:

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

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 unless otherwise allowed.

The study statistician will be able to access the randomization list for interim analyses and is allowed to share unblinded information with the rest of the clinical team as appropriate for internal decision purposes, as outlined below. For example, unblinded summaries and unblinded individual data can be shared with the team for interim analyses.

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

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

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

Following final database lock all roles may be considered unblinded.

**Table 6-2      Blinding levels for the investigational drug**

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

B Remains blinded

B\* Blinded at individual level

NA Not applicable

UI Allowed to be unblinded on individual patient level

## **6.5 Treating the subject**

LNA043 or placebo will be administered to the subject via i.a injection at the end of the arthroscopy performed for cartilage harvest. See the Site Operations Manual for further details.

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

## **6.6 Permitted dose adjustments and interruptions of study treatment**

Study treatment dose adjustments and/or interruptions are not permitted.

## **6.7 Emergency breaking of assigned treatment code**

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

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

Refer also to Site Operations Manual for further details.

## **6.8 Treatment exposure and compliance**

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

## **6.9 Recommended treatment of adverse events**

Treatment of adverse events should be in line with the Investigational site procedures. Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

## **6.10      Rescue medication**

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

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

## **6.11      Concomitant treatment**

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

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

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

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

# **7            Study completion and discontinuation**

## **7.1          Study completion and post-study treatment**

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

Study completion is defined as when the last subject completes their Study Completion 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.

All subjects should have a safety follow-up call conducted 30 days after the last visit. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in [Section 9.3.2](#) and the Site Operations Manual. Documentation of attempts to contact the subject should be recorded in the source documentation.

## **7.2          Discontinuation of study treatment**

Since this is a single dose study, discontinuation of study treatment is not applicable. In addition, due to the single dose nature of the study, no individual treatment stopping rules are provided. Patients may voluntarily discontinue from the study for any reason at any time.

### **7.3 Withdrawal of informed consent**

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

Does not want to participate in the study anymore, and

Does not allow further collection of personal data

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

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

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

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

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

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

### **7.4 Lost to follow-up**

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

### **7.5 Study Stopping rules**

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

- One (1) or more patients presenting with a SAE that is related to LNA043.
- One (1) or more patients presenting with a SADE related to the 7T MRI.
- One (1) or more patients presenting with a serious local complication, defined as more severe or longer lasting than normally expected in patients undergoing arthroscopic knee surgery, as judged by the Investigator and the Sponsor.
- More than one (1) patient with acute allergic reaction of Grade 3 severity or greater according to the NCI-CTCAE/v4.03 Criteria within the first 5 treated subjects in the study or an incidence of >20% thereafter.
- Two (2) or more patients experience acute exacerbation of the articular cartilage defect, which is considered related to LNA043.

## **7.6 Early study termination by the sponsor**

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. Should this be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests.

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

## 8 Procedures and assessments

### 8.1 Assessment Schedule

**Table 8-1 Assessment Schedule for Cohort 1 and Cohort 2**

Epoch	Screening	Treatment			Post-Treatment Follow-Up					
		Treatment			Day 2	Day 3	Week 1	Week 4	Week 12	EOS (Week 28)
Visit Name	Screening	101			201	202	203	204	205	299 <sup>2</sup>
Visit Numbers <sup>1</sup>	1	101			201	202	203	204	205	299 <sup>2</sup>
Study Day(s)	-42 to -1	1			2	3 +1	8 ±1	29 ±5	85 ±5	197 ±7
Time (post-dose)	-	0h <sup>3</sup>	120m ±15	240m ±30	8h ±1	24h ±1	-	-	-	-
Informed consent	X									
Inclusion / Exclusion criteria	X									
<b>Corporate Confidential Information</b>										
Demography	X									
Medical history/current medical conditions	X									
Concomitant medications								X		
Alcohol Test, Drug Screen, and Cotinine Test	X									
Pregnancy test	X <sup>4</sup>	X <sup>5</sup>						X <sup>5</sup>	X <sup>5</sup>	X <sup>4</sup>
HIV screen	X									
Hepatitis screen	X									
Physical Examination	X	X					X	X	X	X
Blood Pressure	X	X	X				X	X	X	X
Pulse rate	X	X	X				X	X	X	X
Electrocardiogram (ECG)	X	X	X				X			X
Body Height	X									
Body Temperature	X	X					X	X	X	X



- <sup>1</sup> Visit structure given for internal programming purpose only
- <sup>2</sup> EOS visit assessments should be performed also in case of premature patient discontinuation for any reason (except in case of consent withdrawal)
- <sup>3</sup> Pre-dose sample can be taken within 2 hours prior of injection (0 h)
- <sup>4</sup> Serum pregnancy test
- <sup>5</sup> Urine pregnancy test
- <sup>6</sup> Randomization can be performed up to 7 days before study drug administration (Day 1), only after eligibility confirmation (details on NIRT randomization in the SOM)
- <sup>7</sup> Overnight fast of at least 10 hours before blood sampling
- <sup>8</sup> Blood collection for PK of both LNA043 and ANGPTL3

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- <sup>14</sup> This is used as baseline MRI
- <sup>15</sup> MRI can be performed either the same day of surgery, in this case MRI has to be performed before it, or up to three days before Day 29 .
- <sup>16</sup> MRI assessment can be performed either the same day of the visit or  $\pm 3$  days from the visit
- <sup>17</sup> MRI assessment can be performed either the same day of visit or  $\pm 7$  days from the visit
- <sup>18</sup> X-rays will be performed at screening in case the patient doesn't have previous examinations
- <sup>19</sup> Drug will be administered at the end of the surgery
- <sup>20</sup> To check if there is SAE 30 days post EOS.

## **8.2 Informed consent procedures**

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

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

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

Ensure subjects are informed of the contraception requirements outlined in the [Section 4.2](#) (Exclusion criteria) and in [Section 5.1](#) (Contraception requirements).

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

## **8.3 Subject screening**

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

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

## **8.4 Subject demographics/other baseline characteristics**

Subject demographic and baseline characteristic data will be collected on all subjects. Relevant medical history/current medical conditions data will also be collected until signature of informed consent. Details are outlined in the Site Operations Manual.

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

#### **8.4.1 Hepatitis screen, HIV screen**

All subjects will be screened for HIV, Hepatitis B and C. See the Site Operations Manual for details.

#### **8.4.2 Alcohol test, Drug screen, Urine cotinine**

All subjects will be screened substances of abuse and cotinine. See the Site Operations Manual for details.

#### **8.4.3 X-ray**

Standing long leg view X-ray will be performed except for those who have had a valid X-ray done within 6 months of first dosing.

### **8.5 Efficacy / Pharmacodynamics**

#### **8.5.1 Knee imaging**

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.

Magnetic resonance images (MRI) will be obtained from the injured knee to visualize the cartilage tissue both at donor sites in the intercondylar notch and the defect site in the femoral, tibial or patellofemoral region. The imaging protocol was developed in order to quantify changes in GAG levels, collagen network, cartilage loss and, when visible, sub-chondral bone edema. Details inherent to the image acquisition and analysis can be found in the imaging protocol.

##### **8.5.1.1 Image collection**

All patients will be imaged at the specific imaging site using a 7T MRI scanner. For each MRI session, images will be acquired as described in the imaging protocol to assess cartilage macromolecular composition (i.e. GAG content and collagen fibril network), bone marrow edema and the extent of cartilage injury.

During the 7T MRI, patients are positioned in supine position with feet first in the 7T magnet as is usually done with knee MR examinations. For sodium examination, a double-tuned coil will be used to collect <sup>1</sup>H and <sup>23</sup>Na signals at 7T.

To obtain a similar position of the knee at the different time-points during the study, a custom-made positioning device will be used. This device allows immobilization of the leg from the knee downwards. In addition, a vacuum mattress is applied, which enables better fixation of the lower leg. The mattress stays in place during the coil change to ensure exact repositioning of the knee. This positioning is very comfortable for the patient and increases patient compliance.

During the change of coils, if needed, the patient remains in the supine position. Patient will need to raise his examined leg for a few seconds while the coils are changed. Total measurement time will be about 80 minutes.

For more details on 7T MRI procedures, please refer to the Imaging Protocol.

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## **8.6 Safety**

Safety assessments are specified below; methods for assessment and recording are specified in the Site Operations Manual, with the Assessment Schedule, [Section 8.1](#) detailing when each assessment is to be performed.

### **8.6.1 Physical examination**

See the Site Operations Manual for details.

### **8.6.2 Vital signs**

- Body temperature
- Blood pressure (BP)
- Pulse

### **8.6.3 Height and weight**

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

### **8.6.4 Laboratory evaluations**

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

#### **8.6.4.1 Hematology**

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

#### **8.6.4.2 Clinical chemistry**

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

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

#### **8.6.4.3 Urinalysis**

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

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

### **8.6.5 Electrocardiogram (ECG)**

PR interval, QRS duration, heart rate, RR, QT, QTc.

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

### **8.6.6 Pregnancy and assessment of fertility**

All pre-menopausal women who are not surgically sterile will have pregnancy testing. See the Assessment Schedule, [Section 8.1](#), for timing of the protocol required pregnancy testing; additional pregnancy testing may be performed to meet local requirements\*. A positive urine pregnancy test requires immediate interruption of study treatment until serum  $\beta$ -hCG is performed and found to be negative.

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

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## **8.7 Pharmacokinetics**

PK samples will be collected at the timepoints defined in the Assessment Schedule, [Section 8.1](#). Follow instructions outlined in the Site Operations Manual regarding sample collection, numbering, processing and shipment. See [Section 8.9](#) regarding the potential use of residual samples.

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

Pharmacokinetic (PK) samples will be obtained from all subjects at all dose levels.

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

The following pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.2 or higher): Cmax, Tmax, AUClast from the serum concentration-time data.

The linear trapezoidal rule will be used for AUC calculation.

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## 9 Safety monitoring

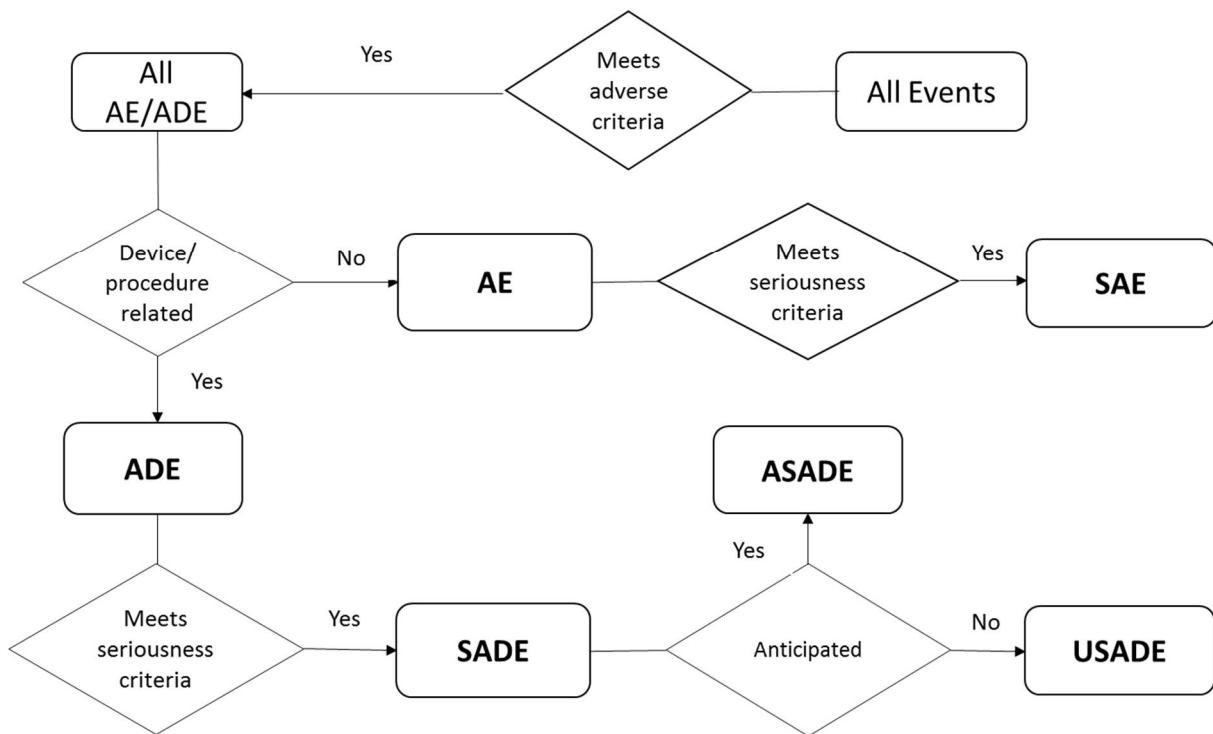
In this trial, safety monitoring will be done for

- (1) the 7T MRI exploratory device
- (2) the investigational drug LNA043 and its placebo

by reporting:

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

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

**Figure 9-1 Safety monitoring**

## 9.1 Adverse events and Adverse device effects

### 9.1.1 Adverse events

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

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an adverse event irrespective if a clinical event has occurred. See [Section 9.6](#) for an overview of the reporting requirements.

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

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

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

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

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

1. the Common Toxicity Criteria (CTC) AE grade (version 4.03)

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

- 1 = mild,
- 2 = moderate,
- 3 = severe
- 4 = life threatening\* (see [Section 9.3.1](#) for definition of a serious adverse event (SAE))

\*Note: There may be cases where a CTCAE with a grade of 4 (life-threatening) may not necessarily be an SAE (e.g. certain laboratory abnormalities in the absence of meeting other seriousness criteria).

- CTC-AE grade 5 (death) is not used, but is collected as a seriousness criteria and also collected in other CRFs (e.g. Study Completion, Death/Survival).

2. its relationship to the study treatment

- Yes or No

3. its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.

4. whether it constitutes a SAE (see [Section 9.3.1](#) for definition of SAE) and which seriousness criteria have been met

5. Action taken regarding investigational treatment.

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

- no action taken (e.g. further observation only)
- investigational treatment dosage increased/reduced
- investigational treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- hospitalization/prolonged hospitalization (see [Section 9.3.1](#) for definition of SAE)

6. its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

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

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

## **9.2 Adverse device effects**

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

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

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

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

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

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

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

## 9.3 Serious adverse events and serious adverse device effects

### 9.3.1 Definition of SAE

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

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

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

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

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

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

All AEs (serious and non-serious) are captured on the CRF; SAEs also require individual reporting to Novartis Chief Medical Office & Patient Safety (CMO&PS) as per [Section 9.3.2](#).

### **9.3.2 SAE reporting**

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit must be reported to Novartis within 24 hours of learning of its occurrence as described below. Any SAEs experienced after this period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

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

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a CMO&PS 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.

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

### **9.3.3 Serious Adverse Device Effect**

#### **9.3.3.1 Definition of SADE**

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

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

#### **9.3.3.2 SADE reporting**

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

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

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

**1) Not related:** relationship to the device or procedures can be excluded when:

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

- harms to the subject are not clearly due to use error;

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

2) **Unlikely**: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

3) **Possible**: the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.

4) **Probable**: the relationship with the use of the investigational device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.

5) **Causal relationship**: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;

- the event has a temporal relationship with investigational device use/application or procedures;

- the event involves a body-site or organ that
  - the investigational device or procedures are applied to;
  - the investigational device or procedures have an effect on;

- the serious event follows a known response pattern to the medical device (if the response pattern is previously known);

- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact the serious event (when clinically feasible);

- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;

- harm to the subject is due to error in use;

- the event depends on a false result given by the investigational device used for diagnosis, when applicable;

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

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

provided using a new paper form stating that this is a follow-up to a previously reported SADE.

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

Events to be reported include:

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

If the SADE is not previously documented and it is thought to be related to the study intervention a Patient Safety associate urgently may require further information from the Investigator of the specific imaging site for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all Investigators involved in any study with the same study intervention that this SADE has been reported. Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified previously, then it is defined as an unanticipated serious adverse device effect. Unanticipated serious adverse device effect (USADE) 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.

## **9.4 Liver safety monitoring**

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

Please refer to [Table 15-1-Appendix 1](#) for complete definitions of liver events.

### **Follow-up of liver events**

Every liver event defined in [Table 15-1-Appendix 1](#) should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in [Table 15-2-Appendix 1](#).

- Repeating liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and  $\gamma$ GT) to confirm elevation within 48-72 hours. These liver chemistry repeats should always be performed using the central laboratory, with the results provided via the standard electronic transfer. If results will not be available from the central laboratory within 24 hours, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results reported on the unscheduled local laboratory CRF.
- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to [Section 7.2](#) (Discontinuation of study treatment), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include:
  - Repeating liver chemistry tests two or three times weekly. Testing should include ALT, AST, ALP, PT/INR, and  $\gamma$ GT. If total bilirubin is elevated  $> 2 \times$  ULN, fractionation into direct and indirect bilirubin is required. To rule out muscular origin of transaminase elevations, CPK should be measured along with liver chemistry tests. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic. Retesting should be continued up to resolution.
  - Obtaining a more detailed history of symptoms and prior or concurrent diseases.
  - Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
  - Exclusion of underlying liver disease, as specified in [Table 15-3](#).
  - Imaging such as abdominal US, CT or MRI, as appropriate
  - Obtaining a history of exposure to environmental chemical agents.
  - Considering gastroenterology or hepatology consultations.

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

## **9.5 Renal safety monitoring**

Renal events are defined as one of the following:

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

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

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

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

## 9.6 Reporting Medication errors including misuse/abuse

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

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

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

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

All instances of misuse or abuse must be documented in the adverse event (AE) CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to Novartis CMO&PS. As such, instances of misuse or abuse are also to be reported using the SAE form/CRF. [Table 9-1](#) summarizes the reporting requirements.

**Table 9-1 Summary of reporting requirements for medication errors**

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

For more information on AE and SAE definition and reporting requirements, please see [Section 9.1.1](#) and [Section 9.3.1](#), respectively.

## **9.7      Pregnancy reporting**

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

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

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

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

## **9.8      Prospective suicidality assessment**

Not applicable.

## **9.9      Early phase safety monitoring**

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

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

# **10      Data review and database management**

## **10.1    Site monitoring**

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

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

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

## **10.2 Data collection**

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

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

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

## **10.3 Database management and quality control**

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

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

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

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

The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the COAR Analytics NIBR Franchise Head and the relevant NIBR TA Head.

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### **10.4 Data Monitoring Committee**

Not required.

### **10.5 Adjudication Committee**

Not required

## **11 Data analysis**

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

### **11.1 Analysis sets**

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

The safety analysis set will include all patients who received any study drug.

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

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

## **11.2 Subject demographics and other baseline characteristics**

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

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

## **11.3 Treatments**

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

## **11.4 Analysis of the primary variable(s)**

The primary aim of this study is to determine safety, tolerability, the percent cartilage GAG content change and bi-layer collagen organization based on 7T high-field MRI at week 4.

### **11.4.1 Variable(s)**

MRI-based measurements of GAG content will be available at baseline and week 4 from both donor sites and a nearby "healthy" cartilage region (as a reference tissue). Regarding the collagen network organization, the difference in T2 relaxation time between the superficial layer and deep layer of cartilage will be determined similarly to the GAG content assessment (i.e., same cartilage regions and time-points).

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

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

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

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

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

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### **11.4.3 Handling of missing values/censoring/discontinuations**

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

Subjects with missing PK parameters (e.g. Cmax, AUClast, AUCinf) in some but not all periods will be included in a mixed model analysis assuming missing at random.

### **11.4.4 Summary statistics of safety**

#### **11.4.4.1 Vital signs**

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

#### **11.4.4.2 ECG evaluations**

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

#### **11.4.4.3 Clinical laboratory evaluations**

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

#### **11.4.4.4 Adverse events**

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

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

#### **11.4.5 Sensitivity analyses**

Not applicable.

#### **11.5 Analysis of secondary variable(s)**

Secondary variables include ICRS scoring at Week 4, % donor sites filling at Weeks 4, 12 and 28, GAG content at Weeks 12 and 28, PK and immunogenicity. All secondary variables will be summarized descriptively and analyses similar to the primary analysis will be performed.

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**11.8 Power for analysis of key secondary variables**

Not Applicable.

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## **12 Ethical considerations**

### **12.1 Regulatory and ethical compliance**

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

### **12.2 Responsibilities of the investigator and IRB/IEC**

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

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

### **12.3 Publication of study protocol and results**

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

## **13 Protocol adherence**

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

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

### **13.1 Protocol Amendments**

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

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

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

## 14 References

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

**Table 15-1 Liver Event Definitions**

Definition	Thresholds
Potential Hy's law cases	<ul style="list-style-type: none"> <li>ALT or AST <math>&gt; 3 \times \text{ULN}</math> and TBL <math>&gt; 2 \times \text{ULN}</math> without initial increase in ALP to <math>&gt; 2 \times \text{ULN}</math></li> </ul>
ALT or AST elevation with coagulopathy	<ul style="list-style-type: none"> <li>ALT or AST <math>&gt; 3 \times \text{ULN}</math> and INR <math>&gt; 1.5</math> (in the absence of anticoagulation)</li> </ul>
ALT or AST elevation accompanied by symptoms	<ul style="list-style-type: none"> <li>ALT or AST <math>&gt; 3 \times \text{ULN}</math> accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash, or eosinophilia</li> </ul>
Isolated ALT or AST elevation	<ul style="list-style-type: none"> <li>ALT or AST <math>&gt; 8 \times \text{ULN}</math></li> <li><math>5 \times \text{ULN} &lt; \text{ALT/AST} &lt; 8 \times \text{ULN}</math></li> <li><math>3 \times \text{ULN} &lt; \text{ALT/AST} &lt; 5 \times \text{ULN}</math></li> </ul>
Isolated ALP elevation	<ul style="list-style-type: none"> <li>ALP <math>&gt; 2 \times \text{ULN}</math> (in the absence of known bone pathology)</li> </ul>
Others	<ul style="list-style-type: none"> <li>Any clinical event of jaundice (or equivalent term)</li> <li>Any adverse event potentially indicative of liver toxicity</li> </ul>

**Table 15-2 Actions required for Liver Events**

Criteria	Actions required
Potential Hy's Law case	
ALT or AST elevation with coagulopathy	<ul style="list-style-type: none"> <li>Discontinue the study treatment immediately</li> </ul>
ALT or AST elevation accompanied by symptoms	<ul style="list-style-type: none"> <li>Hospitalize, if clinically appropriate</li> <li>Establish causality</li> </ul>
Isolated ALT or AST elevation $> 8 \times \text{ULN}$	<ul style="list-style-type: none"> <li>Complete CRFs per liver event guidance</li> </ul>
Jaundice	
Isolated ALT or AST elevation $> 5$ to $\leq 8 \times \text{ULN}$	<ul style="list-style-type: none"> <li>If confirmed, consider interruption or discontinuation of study drug</li> <li>If elevation persists for more than 2 weeks, discontinue the study drug</li> <li>Establish causality</li> <li>Complete CRFs per liver event guidance</li> </ul>
Isolated ALT or AST elevation $> 3$ to $\leq 5 \times \text{ULN}$ (patient is asymptomatic)	<ul style="list-style-type: none"> <li>Monitor liver chemistry tests two or three times weekly</li> </ul>
Isolated ALP elevation	<ul style="list-style-type: none"> <li>Repeat liver chemistry tests within 48-72 hours</li> <li>If elevation is confirmed, measure fractionated ALP; if <math>&gt;50\%</math> is of liver origin, establish hepatic causality</li> <li>Complete CRFs per liver event guidance</li> </ul>
Any AE potentially indicative of liver toxicity	<ul style="list-style-type: none"> <li>Consider study treatment interruption or discontinuation</li> <li>Hospitalize if clinically appropriate</li> <li>Complete CRFs per liver event guidance</li> </ul>

**Table 15-3      Exclusion of underlying liver disease**

<b>Disease</b>	<b>Assessment</b>
Hepatitis A, B, C, E	<ul style="list-style-type: none"><li>• IgM anti-HAV; HBSAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM &amp; IgG anti-HEV, HEV RNA</li></ul>
CMV, HSV, EBV infection	<ul style="list-style-type: none"><li>• IgM &amp; IgG anti-CMV, IgM &amp; IgG anti-HSV; IgM &amp; IgG anti-EBV</li></ul>
Autoimmune hepatitis	<ul style="list-style-type: none"><li>• ANA &amp; ASMA titers, total IgM, IgG, IgE, IgA</li></ul>
Alcoholic hepatitis	<ul style="list-style-type: none"><li>• Ethanol history, gGT, MCV, CD-transferrin</li></ul>
Nonalcoholic steatohepatitis	<ul style="list-style-type: none"><li>• Ultrasound or MRI</li></ul>
Hypoxic/ischemic hepatopathy	<ul style="list-style-type: none"><li>• Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.</li></ul>
Biliary tract disease	<ul style="list-style-type: none"><li>• Ultrasound or MRI, ERCP as appropriate.</li></ul>
Wilson disease	<ul style="list-style-type: none"><li>• Ceruloplasmin</li></ul>
Hemochromatosis	<ul style="list-style-type: none"><li>• Ferritin, transferrin</li></ul>
Alpha-1-antitrypsin deficiency	<ul style="list-style-type: none"><li>• Alpha-1-antitrypsin</li></ul>

## 16 Appendix 2: Specific Renal Alert Criteria and Actions

**Table 16-1 Specific Renal Alert Criteria and Actions**

Criteria	Action required
Serum creatinine (sCr) increase 25 – 49% compared to baseline	<ul style="list-style-type: none"><li>Consider causes and possible interventions</li><li>Follow up within 2-5 days</li></ul>
Serum creatinine increase $\geq$ 50%	<ul style="list-style-type: none"><li>Consider causes and possible interventions</li><li>Repeat assessment within 24-48h if possible</li><li>Consider drug interruption or discontinuation unless other causes are diagnosed and corrected</li><li>Consider hospitalization and specialized treatment</li></ul>
Protein-creatinine or albumin-creatinine ratio increase $\geq$ 2-fold or new onset dipstick proteinuria $\geq$ 1+ or Albumin-creatinine ratio (ACR) $\geq$ 30 mg/g or $\geq$ 3 mg/mmol; or Protein-creatinine ratio (PCR) $\geq$ 150 mg/g or $>15$ mg/mmol	<ul style="list-style-type: none"><li>Consider causes and possible interventions</li><li>Assess serum albumin &amp; serum protein</li><li>Repeat assessment to confirm</li><li>Consider drug interruption or discontinuation unless other causes are diagnosed and corrected</li></ul>
New onset glucosuria on urine dipstick (unless related to concomitant treatment, diabetes)	<u>Assess &amp; document:</u> <ul style="list-style-type: none"><li>Blood glucose (fasting)</li><li>Serum creatinine</li><li>Urine albumin-creatinine ratio</li></ul>
New hematuria on dipstick	<u>Assess &amp; document:</u> <ul style="list-style-type: none"><li>Urine sediment microscopy</li><li>Assess sCr and urine albumin-creatinine ratio</li><li>Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation</li><li>Consider bleeding disorder</li></ul>

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

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

- Blood pressure assessment (after 5 min rest, with an appropriate cuff size)
- Signs and symptoms such as fever, headache, shortness of breath, back or abdominal pain, dysuria, hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other potential causes of renal dysfunction, e.g., dehydration, hemorrhage, tumor lysis

**Table 16-2 Follow-up of renal events**

Action	Follow up
Assess*, document and record in the Case Report Form (CRF) or via electronic data load. Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc) in the CRF.	<ul style="list-style-type: none"><li>• Urine dipstick and sediment microscopy</li><li>• Blood pressure and body weight</li><li>• Serum creatinine, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid</li><li>• Urine output</li></ul> <p>• Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline)</p> <p>or</p> <p>• Event stabilization: sCr level with <math>\pm 10\%</math> variability over last 6 months or protein-creatinine ratio stabilization at a new level with <math>\pm 50\%</math> variability over last 6 months.</p>
Monitor subject regularly (frequency at investigator's discretion) until:	

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