NOVARTIS

Biostatistics & Statistical Programming /
Novartis Institutes for BioMedical Research

LNA043

CLNA043X2202 / NCT03275064

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

## Statistical Analysis Plan (SAP)

Author(s): Personal Protected Data

Document type: SAP Documentation – NIBR

Document status: Final Addendum v01

Release date: 05-Dec-2022

Number of pages: 21

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# 1 Introduction

## 1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial ***"CLNA043X2202"***.

The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

## 1.2 Study reference documentation

Final study protocol amendment (v07) is available at the time of finalization of Statistical Analysis Plan.

## 1.3 Study objectives

### 1.3.1. Primary objective(s)

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

### 1.3.2. Secondary objective(s)

| ***Secondary objective(s)*** | ***Endpoints related to secondary objective(s)*** |
|---|---|
| • To assess the extent of the repair cartilage tissue following multiple i.a. injections of LNA043 | • Change in volume of cartilage defect filling evaluated with MRI at Week 16 and 28 (Part A) |

| | |
|---|---|
| | • Articular cartilage bi-layer collagen organization evaluated with T2 relaxation times measured in superficial and deep layers by T2 mapping Magnetic Resonance Imaging (MRI) at Week 28 and 52 (Part B) |
| • To evaluate systemic and local PK of LNA043 following multiple i.a. injections of LNA043 | • Serum and synovial fluid PK profile of LNA043 and ANGPTL3 |
| • To assess the potential immunogenicity of LNA043 | • Presence and characterisation of anti-LNA043 antibodies in serum at Day 1, Day 15, Day 50, Day 106 and Day 190 (Part A) and Day 1, Day 29, Day 57, Day 85, Day 113, Day 197 and Day 365 (Part B) |

## 1.4 Study design and treatment

This is a two-part non-confirmatory, randomized, placebo-controlled, patient and investigator blinded study, multiple doses in patients with a partial thickness cartilage lesion of the knee (Part A) and in patients with knee osteoarthritis (Part B). In total 135 patients are expected to be randomized into the study.

### 1.4.1 Part A

Approximately 60 patients with partial thickness cartilage lesion of the knee, with knee regions: defect tissue, weight bearing and non-weight bearing, will be enrolled in Part A and randomization will be stratified by type of lesion, either femoral condyle or patella. At least 48 patients are expected to complete the study (20% drop out rate). Additional patients may be enrolled if the dropout rate exceeds 20%. Participants will be treated at four treatment visits.

Patients will be assigned to one of the following “two (2)” treatment arms in a ratio of “3:1, A: B”.

Study treatments are defined as:

- A: single i.a. injection of 20mg (3mL) LNA043, once-weekly injections CCI
- B: single i.a. injection of placebo (3mL) to 20mg LNA043, once-weekly injections

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### 1.4.2 Part B

Approximately 75 patients will be enrolled in Part B and randomized. This is a non-confirmatory, randomized, placebo-controlled, patient and investigator blinded study in patients with Kellgren & Lawrence (K&L) with grade 2 or 3 with osteoarthritis (OA). At least 69 patients are expected to complete the study (10% drop out rate). Additional patients may be enrolled if the dropout rate will exceed 10%. Participants will be treated at four treatment visits.

Patients will be assigned to one of the following “three (3)” treatment arms in a ratio of “1:1:1, A:B:C”.

Study treatments are defined as:

A: single i.a. injection of 20 mg (4mL) LNA043, every 4 weeks CCI

B: single i.a. injection of 40 mg (4mL) LNA043, every 4 weeks CCI

C: single i.a. injection of placebo (4mL) every 4 weeks CCI

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## 2 First interpretable results (FIR)

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## 3 Interim analyses

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# 4 Statistical methods: Analysis sets

For subjects for which the actual treatment received does not match the randomized treatment the treatment actually received will be used for the analysis.

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

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

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

The analysis sets and protocol deviation codes are related as follows:

**Table 4-1: Protocol deviation codes and analysis sets for Part A and Part B**

| Category<br>Deviation code | Text description of deviation | Data exclusion |
|---|---|---|
| **Subjects are excluded from PK analysis in case of these PDs:** | | Exclude subject from PK analysis set |
| INCL01 | Deviation from inclusion criterion 1 | Yes |
| TRT01 | Study treatment deviation, i.e. subject did not receive any study treatment or did not complete the full treatment (Part A)<br>Major study treatment deviation i.e.<br>subject did not receive the same dose throughout the study (Part B) | Yes |
| **Subjects are excluded from PD analysis in case of these PDs:** | | Exclude subject from PD analysis set |
| INCL01 | Deviation from inclusion criterion 1 | Yes |
| TRT01 | Study treatment deviation, i.e. subject did not receive any study treatment or did not complete the full treatment (Part A)<br>Major study treatment deviation i.e.<br>subject did not receive the same dose throughout the study (Part B) | Yes |

If updates to this table are needed, an amendment to the SAP needs to be implemented prior to DBL.

Additional analyses may be considered in relation to the quality and interpretability of the MRI assessments for cartilage volume and thickness. Flags (ANL0XFLs) based on the comments related to insufficient image quality (e.g., “low”) will be derived in order to define these sets. The derivation logic for these will be described in the Programming Data Specifications (PDS).

# 5 Statistical methods for Pharmacokinetic (PK) parameters

All subjects within the PK analysis set will be included in the PK data analysis.

## 5.1 Descriptive analyses

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

LNA043 and ANGPTL3 serum and synovial fluid concentration data will be listed by subject, and visit/sampling time point, separately for each study part. Descriptive summary statistics will be provided by treatment, study part and visit/sampling time point, including

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

The PK analysis will be done separately for part A and part B.

# 6 Statistical methods for Pharmacodynamic (PD) parameters

All subjects within the PD analysis set will be included in the efficacy PD data analysis, unless otherwise stated. For MRI related assessments, all subjects within the PD analysis set and subjects who completed Week 28 and/or Week 52, for Part B will be included.

## 6.1 Primary objective

The primary objective of this study related to efficacy is to assess the efficacy of multiple i.a. injections of LNA043 in regenerating the articular cartilage tissue.

### 6.1.1 Variables

The primary efficacy variables are:

- The change from baseline in **articular cartilage bi-layer collagen organization from T2 relaxation rates** in superficial and deep cartilage layers measurements, and overall, will be evaluated with MRI at baseline, Weeks 8, 16 and 28 from both lesions (femoral condyle and patella) for **Part A**.

  Baseline for bi-layer collagen organization is defined as Visit 1 (Day -35 to -5) from Part A.

- The change from baseline in **cartilage volume in the index region**, assessed based on MRI at Weeks 28 and 52 (**Part B**). The index region is defined as being a combination of 3 sub-regions, i.e. the femur medial anterior (FMA), femur medial central (FMC) and femur medial posterior (FMP).

  The **cartilage volume in index region** is defined as the summation of the three subcategories, i.e.:

Cartilage volume in index region (mm3) = FMA volume + FMC volume + FMP volume

Baseline for the cartilage volume is defined as Visit 1 (Day -35 to -5) from Part B.

- The change from baseline in **cartilage thickness in the index region**, assessed based on MRI at Weeks 28 and 52 (**Part B**). The index region is defined on the above bulletpoint.

  The **cartilage thickness in index region** is defined as the mean of the three subcategories, i.e.:

  Cartilage thickness in index region (micrometer) = (FMA thickness + FMC thickness + FMP thickness)/3

  Baseline for the cartilage thickness is defined as Visit 1 (Day -35 to -5) from Part B.

### 6.1.2 Descriptive analyses

The articular cartilage bi-layer collagen organization (Part A) will be listed by treatment group, patient, visit/time, cartilage layer (deep, superficial and overall) and lesion type (femoral condyles, patella) and region. Summary statistics will be provided for both layer (and overall), lesion type (and overall), regions and their difference by treatment group and visit/time.

Similarly, for the cartilage volume and cartilage thickness in the index region (Part B), will be listed separately by treatment group, patient and visit/time. Summary statistics will be provided by treatment group and visit/time.

For primary endpoints, summary statistics will include mean (arithmetic), SD, CV, median, minimum, maximum and graphical methods will be employed for each endpoint to show group and individual summary plots over time by treatment group, visit/time, layer (and overall), lesion type (and overall), and regions, if applicable depending on study Part. Lesion type and region is only applicable from Part A endpoints.

Additional summary statistics, boxplots and individual plots on raw data for cartilage volume in index region and in sub-regions of the knee cartilage, may be employed based on Population B, defined in Section 6, whereas boxplots and individual plots for change from baseline of cartilage volume may be employed based on Population Aa. Moreover, data based on Population B will be only summarized for cartilage thickness in the index region and in sub-regions of the knee cartilages

### 6.1.3 Statistical model, assumptions and hypotheses

#### 6.1.3.1 Part A

The primary efficacy variable for Part A, change from baseline in articular cartilage bi-layer collagen organization will be analyzed using a mixed effect model for repeated measures (MMRM) analysis of variance model for each layer (deep and superficial) separately and for both layers combined, and region; including all-time points to compare treatment groups at Weeks 16 and 28. The model will include baseline as a covariate, treatment, timepoint, treatment*timepoint and type of lesion as fixed effects and subject as a random effect.

A two-sided 90% confidence intervals for the treatment effect will be formed at Weeks 8, 16 and 28. Considering that the time course of response to LNA043 is not known, statistically significant differences (one-sided p-value of treatment superiority to placebo at 95% significance level) between active drug and placebo at either Week 16 or Week 28 will be considered as a positive result.

#### 6.1.3.2 Part B

The primary efficacy variable for Part B, change from baseline in cartilage volume in the index region will be analyzed using a mixed effect model for repeated measures (MMRM) analysis of variance model, including all-time points to compare treatment groups at Weeks 28 and 52. The model will include baseline as a covariate, treatment, timepoint, treatment*timepoint as fixed effects. An unstructured covariance will be assumed; if not possible, other appropriate covariance structures will be explored such as Autoregressive (AR(1)), Compound symmetry, etc.

The change from baseline in cartilage thickness in the index region will be similarly analyzed using the MMRM described above for the change from baseline in cartilage volume in the index region.

A two-sided 90% confidence intervals for the treatment effect will be formed at Weeks 28 and 52. Considering that the time course of response to LNA043 is not known, statistically significant differences (one-sided p-value of treatment superiority to placebo at 95% significance level) between active drug (either LNA043 dose) and placebo at either Week 28 or Week 52 will be considered as a positive result. No multiplicity adjustment will be considered. If deemed appropriate, the endpoint measure data will be transformed to facilitate analysis.

Same analyses (table and figures) for the MMRM models of change from baseline in cartilage volume in the index region as well as for the change from baseline in the cartilage thickness in the index region may be implemented based on the Population A, defined in Section 6.

### 6.1.4 Supportive analysis

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## 6.2 Secondary objectives

### 6.2.1 Variables

The secondary variables are:

- Change from baseline in **volume of cartilage defect filling** (mm3) assessed based on MRI at Weeks 8, Weeks 16 and 28 (**Part A**).

  Baseline for volume of cartilage defect filling (mm3) is defined as Visit 1 (Days -35 to -5).

- Change from baseline in articular cartilage bi-layer collagen organization, evaluated with T2 relaxation times measured in superficial and deep layers of the index region by T2 mapping MRI at Week 28 and 52 (**Part B**).

  The **cartilage T2 in index region** is defined as the mean of the three subcategories, i.e.:

  Cartilage mean T2 in index region (ms) = (FMA T2 + FMC T2 + FMP T2)/3.

  Baseline for bi-layer collagen organization is defined as Visit 1 (Day -35 to -5).

### 6.2.2 Descriptive analyses

The volume of cartilage defect filling variable (Part A) will be listed by treatment group, patient, visit/time, region and lesion type. Summary statistics will be provided by treatment group, visit/time and lesion type (femoral condyle, patella and overall).

The articular cartilage bi-layer collagen organization (Part B) will be listed by treatment group, patient, visit/time, cartilage layer (deep, middle, superficial and overall). Summary statistics will be provided for all layers (and overall) and their difference by treatment group and visit/time.

For both secondary endpoints, summary statistics will include mean (arithmetic), SD, CV, median, minimum, maximum and graphical methods will be employed for each endpoint, to show group and individual summary plots over time by treatment, lesion type (and overall) and layer (and overall), if applicable depending on study Part. Lesion type is only applicable from Part A endpoint.

Other secondary efficacy variables will be summarized graphically and in summary tables.

### 6.2.3 Statistical model, assumptions and hypotheses

#### 6.2.3.1 Part A

Change from baseline in volume of cartilage defect filling (mm3) will be analyzed at Weeks 16 and 28 using similar MMRM and confidence intervals for the treatment effect as described in Section 6.1.3.1. A single MMRM model will be used, since there are no layers for this secondary endpoint.

#### 6.2.3.2 Part B

Change from baseline in articular cartilage bi-layer collagen organization, assessed based on MRI, will be analyzed at Weeks 28 and 52, using a similar MMRM and confidence intervals for the treatment effect as described in Section 6.1.3.2, where layer categories are deep, middle and superficial.

## 6.3 Exploratory objectives

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# 7 Statistical methods for safety and tolerability data

All subjects within the safety analysis set will be included in the safety data analysis.

## 7.1 Variables

Adverse events, vital signs (blood pressure, pulse rate, body temperature), ECG intervals, clinical laboratory measurements, immunogenicity, hematology, blood chemistry as well as subject demographics, baseline characteristics, and treatment information,with primary of interest the systemic and local Adverse Events, ECGs, vital signs, hematology, blood chemistry and urinalysis.

## 7.2 Descriptive analyses

All safety variables will be summarized descriptively by treatment group for Part A and Part B, separately.

### 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.

### Treatment

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

### Vital signs

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

### ECG evaluations

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

### Clinical laboratory evaluations

All laboratory data will be listed by treatment group, subject, and visit/time and if normal ranges are available abnormalities will be flagged. A separate listing is provided presenting all parameters in a subject with any abnormal values. Summary statistics will be provided by treatment and visit/time.

### Adverse events

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

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

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

The treatment emergent adverse events (TEAEs) are also included i.e. the adverse events started at or after the date of first administration of study treatment to 30 days after the date of the last administration of study treatment.

### Immunogenicity

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

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# 9 Considerations due to COVID-19

Due to the COVID-19 pandemic, it was not possible to perform some procedures as per protocol. All deviations due to COVID-19 will be listed separately to other deviations and may be also tabulated.

Observations that were impacted due to COVID-19, may be excluded from the primary analyses and separately explored to identify if there is an impact of them on the analyses.

# 10 Reference list

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