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LNA043

CLNA043A12203 / NCT04814368

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

## Statistical Analysis Plan (SAP)

| | |
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| 12-Sep-2024 | Prior to DB lock | Amendment 1 | Early termination of the trial | Section 1, 2-5 to 2-11 and 4 |

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## List of abbreviations

| | |
|---|---|
| AE | Adverse Event |
| ADL | Function in Daily Living |
| AUC | Area Under the Curve |
| CRF | Case Report Form |
| CSR | Clinical Study Report |
| DCE | Dynamic Contrast Enhanced |
| DMS | Document Management System |
| dSPP | Development Safety Profiling Plan |
| ECG | Electrocardiogram |
| FAS | Full Analysis Set |
| IG | Immunogenicity |
| IA | Interim Analyses |
| KOOS | Knee injury and Osteoarthritis Outcome Score |
| LLOQ | Lower Limit of Quantification |
| MedDRA | Medical Dictionary for Drug Regulatory Affairs |
| MMRM | Mixed effect Model for Repeated Measures |
| MRI | Magnetic Resonance Imaging |
| NRS | Numeric Rating Scale |
| PD | Pharmacodynamics |
| OA | Osteoarthritis |
| PK | Pharmacokinetics |
| PoC | Proof-of-Concept |
| PPS | Per-Protocol Set |
| PRO | Patient-reported Outcomes |
| RAP | Reporting & Analysis Process |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis System |
| SOC | Standard of Care |
| TFLs | Tables, Figures, Listings |
| ULOQ | Upper Limit of Quantification |

# 1 Introduction

The Reporting and analysis plan (RAP) documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial "CLNA043A12203". The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

However the study had been terminated early because only 17% (23 of 138 patients) of the target population has been recruited after 30 months of screening activities, with very high screen failure rate CCI despite extensive mitigation activities. Study will be reported in a synoptic CSR including summary of primary and secondary endpoints, as well safety data. Only PK and Immunogenicity as part of exploratory objective will be reported. Considering the low number of participants enrolled, no inferential statistic will be reported.

## 1.1 Study design

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

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

**Figure 1-1 Study design**

## 1.2 Study objectives and endpoints

Study objectives and endpoints are listed in Table 1-1 below.

**Table 1-1 Objectives and related endpoints**

| Objective(s) | Endpoint(s) |
|---|---|
| **Primary objective(s)** | **Endpoint(s) for primary objective(s)** |
| • To assess the efficacy of q4wx3 i.a. injections of LNA043 vs. no injections of LNA043, in regenerating articular cartilage tissue (TA1 vs. TA2) | • Change in cartilage volume in the index region measured by MRI at Day 197 |
| • To assess the efficacy of a single i.a. injection of canakinumab vs. placebo in relieving OA pain (TA4 vs. TA2) | • Change in Knee injury and Osteoarthritis Outcome Score (KOOS) Pain subscale at Day 85 |
| **Secondary objective(s)** | **Endpoint(s) for secondary objective(s)** |
| • To assess the safety and tolerability of q4wx3 i.a. injections of LNA043, a single i.a. injection of canakinumab and a single injection of canakinumab followed by q4wx3 i.a. injections of LNA043 (TA1, TA3, TA4) relative to placebo to canakinumab/no LNA043 injections (TA2) | • Systemic and local Adverse Events (AEs)<br>Electrocardiograms (ECGs)<br>Vital signs<br>Hematology, blood chemistry and urinalysis |
| • To assess the potential immunogenicity of q4wx3 i.a. injections of LNA043 (TA1 and TA3) | • Anti-LNA043 antibodies in serum, at Day 15, 43, 85, 197 and 365 |
| • To assess endogenous ANGPTL3, and PK of LNA043, after q4wx3 i.a. injections of LNA043 and after a single i.a. injection of canakinumab followed by q4wx3 i.a. injections of LNA043 (TA1 and TA3) | • ANGPTL3 serum concentrations<br>ANGPTL3 synovial fluid concentrations<br>LNA043 PK profile in serum (Cmax, Tmax, AUC) |
| • To assess the efficacy of a single i.a. injection of canakinumab followed by q4wx3 i.a. injections of LNA043 vs. a single i.a. injection of canakinumab, in regenerating articular cartilage (TA3 vs. TA4) and vs. only q4wx3 ia. injections of LNA043 (TA3 vs. TA1) | • Change in cartilage volume and thickness of the index region measured by MRI at Day 197 and Day 365 |
| • To assess the efficacy of q4wx3 i.a. injections of LNA043 vs. no injections of LNA043, in regenerating articular cartilage (TA1 vs. TA2) | • Change in cartilage thickness of the index region measured by MRI at Day 197<br>Change in cartilage volume and thickness of the index region measured by MRI at Day 365 |

| | |
|---|---|
| • To assess the efficacy of a single i.a. injection of canakinumab vs. placebo to canakinumab, on synovitis (TA4 vs. TA2) | • Change in synovitis level measured from Ktrans by Dynamic Contrast Enhanced MRI (DCE-MRI) at Day 85 |
| • To assess the efficacy of a single i.a. injection of canakinumab vs. placebo to canakinumab, in relieving OA pain and improving function over time (TA4 vs. TA2) | • Change in numeric rating scale (NRS) Pain at Day 15, 29, 43, 57, 71, 85, 197, 365<br>Change in KOOS Pain and Function in daily living (ADL) subscales at Day 15, 29, 43, 57, 71, 85, 197, 365 |
| • To assess the efficacy of a single i.a. injection of canakinumab followed by q4wx3 i.a. injections of LNA043 vs. a single i.a. injection of canakinumab only, in relieving OA pain and improving function over time (TA3 vs. TA4) | • Change in numeric rating scale (NRS) Pain at Day 15, 29, 43, 57, 71, 85, 197, 365<br>Change in KOOS Pain and Function in daily living (ADL) subscales at Day 15, 29, 43, 57, 71, 85, 197, 365 |
| • To assess the efficacy of a single i.a. injection of canakinumab followed by q4wx3 i.a. injections of LNA043 vs. q4wx3 i.a. injections of LNA043 after i.a. injection of placebo in relieving OA pain and improving function over time (TA3 vs. TA1) | • Change in numeric rating scale (NRS) Pain at Day 15, 29, 43, 57, 71, 85, 197, 365<br>Change in KOOS Pain and Function in daily living (ADL) subscales at Day 15, 29, 43, 57, 71, 85, 197, 365 |

| **Exploratory objective(s)** | **Endpoint(s) for exploratory objective(s)** |
|---|---|
| CCI | |


CCI

# 2 Statistical methods

## 2.1 Data analysis general information

The primary analysis of the effect of canakinumab on change in KOOS Pain subscale will be conducted after all participants have completed Day 85 (Week 12) or discontinued prior to Day 85 (Week 12). The primary analysis of the effect of LNA043 on change in cartilage volume will be conducted after all participants have completed Day 197 (Week 28) or discontinued prior to Day 197 (Week 28). The final analysis will be conducted on all participant data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

The analyses (including the interim analyses) will be performed in-house by Novartis, and will be carried out using SAS software, Version 9.4 or higher.

### 2.1.1 General definitions

Baseline is defined as the assessments collected pre-dose on Day 1, except for MRI for which baseline data will be collected at Screening 2.

## 2.2 Analysis sets

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

The full analysis set (FAS) will include all participants that received any study drug.

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

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

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

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

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

## 2.3 Patient disposition, demographics and other baseline characteristics

### 2.3.1 Patient disposition

Patient disposition will be summarized descriptively by treatment arm for the FAS.

### 2.3.2 Demographics and other baseline characteristics

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

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

Relevant medical histories and current medical conditions at baseline will be listed by system organ class and preferred term.

## 2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

### 2.4.1 Study treatment / compliance

The Safety set will be used for the analyses below.

Dose administration will be listed by treatment arm, date and time.

### 2.4.2 Prior, concomitant and post therapies

Concomitant, rescue and prohibited medications, as well as significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment arm. A summary table displaying the frequency (n, %) of the use of Basic Pain Medications and Other Pain Medications per week till Day 85 (Week 12) will be provided.

## 2.5 Analysis supporting primary objectives

This study has two co-primary objectives.

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

The primary objective for LNA043 (TA1) is to assess its efficacy vs. no injection (TA2) in regenerating the articular cartilage in patients with symptomatic knee OA with inflammation.

### 2.5.1 Primary endpoint

The primary efficacy variable for canakinumab is the change from baseline in KOOS, pain subscale at Day 85 (Week 12). KOOS has a total of 42 items grouped in 5 subscales. Standardized answer options are given and each question gets a score from 0-4. A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale.

The primary efficacy variable for LNA043 is the change from baseline in cartilage volume in the index region at Day 197 (Week 28). The index region comprises three cartilage subfields: femur medial anterior, central and posterior. The cartilage volume in the index region is calculated as the sum of the three individual subfield volumes.

The PD analysis set will be used for the analyses below.

### 2.5.2 Statistical hypothesis, model, and method of analysis

The primary efficacy variable for canakinumab, change from baseline in KOOS pain subscale, will be summarized descriptively by treatment arm.

The primary efficacy variable for LNA043, change from baseline in cartilage volume in the index region, will be summarized descriptively by treatment arm.

Summary statistics will include mean, standard deviation, median, minimum, and maximum.

### 2.5.3 Handling of missing values/censoring/discontinuations

Missing data will not be imputed.

## 2.6 Analysis supporting secondary objectives

### 2.6.1 Secondary endpoints

The secondary efficacy objectives for LNA043 are as follows:

- To assess the efficacy of q4wx3 i.a. injections of LNA043 after i.a. injection of placebo (TA1) vs q4wx3 i.a. injections of LNA043 after i.a. injection of canakinumab (TA3) in regenerating the articular cartilage in participants with symptomatic knee OA with inflammation. The variables associated with this objective is change from baseline in cartilage volume and change from baseline in cartilage thickness in the index region at Days 197 (Week 28) and 365 (Week 52).
- To assess the efficacy of q4wx3 i.a. injections of LNA043 (TA3) vs no LNA043 injections (TA4) in regenerating the articular cartilage in participants with symptomatic knee OA with inflammation after both trial arms (i.e. TA3 and TA4) have been administered with an i.a. injection of canakinumab to relieve OA pain. The variables associated with this objective are change from baseline in cartilage volume and change from baseline in cartilage thickness in the index region at Days 197 (Week 28) and 365 (Week 52).
- To assess the efficacy of q4wx3 i.a. injections of LNA043 (TA1) vs no LNA043 injections (TA2) in mantaining or regenerating the articular cartilage in participants with symptomatic knee OA with inflammation. The variables associated with this objective are change from baseline in cartilage volume at Day 365 (Week 52) and change from baseline in cartilage thickness at Days 197 (Week 28) and 365 (Week 52) in the index region.
- To assess a single i.a. injection of canakinumab followed by q4wx3 i.a. injections of LNA043 vs. q4wx3 i.a. injections of LNA043 after i.a. injection of placebo (TA3 vs. TA1), in participants with symptomatic knee OA with inflammation in relieving OA pain. The variables associated with this objective is change from baseline in the numeric rating scale (NRS) pain and in KOOS pain subscale at Day 15, 29, 43, 57, 71, 85, 197, 365 (Weeks 2, 4, 6, 8, 10, 12, 28, 52).
- To assess a single i.a. injection of canakinumab followed by q4wx3 i.a. injections of LNA043 vs. q4wx3 i.a. injections of LNA043 after i.a. injection of placebo (TA3 vs.

TA1), in participants with symptomatic knee OA with inflammation in improving functions of daily living over time. The variable associated with this objective is change from baseline in KOOS function daily living subscale at Day 15, 29, 43, 57, 71, 85, 197, 365 (Weeks 2, 4, 6, 8, 10, 12, 28, 52).

The secondary efficacy objectives for canakinumab are as follows:

- To assess the efficacy of canakinumab (TA4) vs placebo (TA2) on synovitis in participants with symptomatic knee OA with inflammation at Day 85 (Week 12). The variable associated with this objective is change from baseline in synovitis level measured from Ktrans by DCE-MRI at Day 85 (Week 12).
- To assess the efficacy of canakinumab (TA4) vs placebo (TA2) in participants with symptomatic knee OA with inflammation in relieving OA pain. The variables associated with this objective is change from baseline in the numeric rating scale (NRS) pain and in KOOS pain subscale at Day 15, 29, 43, 57, 71, 85, 197, 365 (Weeks 2, 4, 6, 8, 10, 12, 28, 52).
- To assess the efficacy of canakinumab (TA4) vs placebo (TA2) in participants with symptomatic knee OA with inflammation in improving functions of daily living over time. The variable associated with this objective is change from baseline in KOOS function daily living subscale at Day 15, 29, 43, 57, 71, 85, 197, 365 (Weeks 2, 4, 6, 8, 10, 12, 28, 52).
- To assess the efficacy of a single i.a. injection of canakinumab followed by q4wx3 i.a. injections of LNA043 vs. a single i.a. injection of canakinumab only (TA3 vs. TA4), in participants with symptomatic knee OA with inflammation in relieving OA pain. The variables associated with this objective is change from baseline in the numeric rating scale (NRS) pain and in KOOS pain subscale at Day 15, 29, 43, 57, 71, 85, 197, 365 (Weeks 2, 4, 6, 8, 10, 12, 28, 52).
- To assess the efficacy of a single i.a. injection of canakinumab followed by q4wx3 i.a. injections of LNA043 vs. a single i.a. injection of canakinumab only (TA3 vs. TA4), in participants with symptomatic knee OA with inflammation in improving functions of daily living over time. The variable associated with this objective is change from baseline in KOOS function daily living subscale at Day 15, 29, 43, 57, 71, 85, 197, 365 (Weeks 2, 4, 6, 8, 10, 12, 28, 52).

### 2.6.2 Statistical hypothesis, model, and method of analysis

The variables described in Section 2.6.1 will also be summarized descriptively by treatment arm similarly to the primary endpoints.

### 2.6.3 Handling of missing values/censoring/discontinuations

Missing data will not be imputed.

## 2.7 Safety analyses

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

### 2.7.1 Adverse events (AEs)

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

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

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

Separate summaries will be provided for death and serious adverse events.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than 5% and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

An adverse event starting in one period and continuing into the next period is counted only in the onset period. A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

### 2.7.2 Deaths

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

### 2.7.3 Laboratory data

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

Summary statistics will be provided by treatment and visit/time.

### 2.7.4 Other safety data

#### 2.7.4.1 ECG and cardiac imaging data

All single 12-lead ECG data (included but not limited to PR, QRS, QT, QTcF and RR intervals) will be listed by treatment group, participant and visit/time, abnormalities will be flagged.

Notable criteria are as follows:

- new QT/QTc >450 to <=480 ms
- new QT/QTc >480 to <=500 ms
- new QT/QTc >500 ms
- QT/QTc increase >30 to <=60 ms from baseline
- QT/QTc increase >60 ms from baseline
- HR decrease from baseline >25% and HR <50 bpm
- HR increase from baseline >25% and HR >100 bpm
- new PR >200 ms
- PR increase from baseline >25% and PR >200 ms
- new QRS ><110 or 120> ms.
- QRS increase from baseline >25% and QRS ><110 or 120> ms

Summary statistics will be provided by treatment and visit/time.

#### 2.7.4.2 Vital signs

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

Notable criteria (High/Low) are as follows:

- Systolic blood pressure [mmHg]: >139/<90 mmHg
- Diastolic blood pressure [mmHg]: >89/<50 mmHg
- Heart rate [bpm]: >90/<40 bpm
- Weight [kg]: >120/<50 kg
- Temperature [°C]: >37.6/<35 °C"

Summary statistics will be provided by treatment and visit/time.

## 2.8 Pharmacokinetic endpoints

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

LNA043, ANGPTL3, and CCI [redacted] serum and synovial fluid (only ANGPTL3) concentration data will be listed by treatment, participant, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero. Samples collected outside the protocol defined collection time window will be listed but not included in summary statistics.

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

Graphical methods will be employed to show mean and individual concentration-time profile.

Pharmacokinetic parameters Cmax, Tmax and AUClast will be calculated for LNA043 at Day 15 (Week 2) in patients with sufficient data and will be listed by treatment and participant. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is Tmax where median, minimum, and maximum will be presented.

Pharmacokinetic parameters Cmax, Cav and Cmin will be calculated for ANGPTL3 and will be listed by treatment and participant. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum.

The linear trapezoidal rule will be used for AUC calculation.

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

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

Subjects receiving less than 80% of dose will be excluded from summary statistics.

**Table 2-1 Non-compartmental pharmacokinetic parameters**

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

## 2.9 Immunogenicity

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

## 2.10 CCI

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## 2.11 Interim analysis

No interim analysis was done due to early termination of the study.

# 3 Sample size calculation

For LNA043, we expect to detect a difference of 100 $mm^3$ in change from baseline in cartilage volume in the index region. CCI [redacted], a total of 23 evaluable participants per arm will provide more than 80% power, with a 1-sided alpha of 0.05, to detect 100 $mm^3$ difference between LNA043 and no injection at Day 197 (Week 28).

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

# 4 Change to protocol specified analyses

The study had been terminated early because only 17% (23 of 138 patients) of the target population has been recruited after 30 months of screening activities, with very high screen failure rate CCI [redacted] despite extensive mitigation activities. Study will be reported in a synoptic CSR including summary of primary and secondary endpoints, as well safety data. Only PK and Immunogenicity as part of exploratory objective will be reported. Considering the low number of participants enrolled, no inferential statistic will be reported.

# 5 Consideration due to COVID-19

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

Observations that were impacted due to COVID-19, may be excluded from the primary analyses, for example including (but not limited to) observations taken at participant's house instead of site, and separately explored to identify if there is an impact of them on the analyses.

# 6 Appendix

### Rule of exclusion criteria of analysis sets

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

Table 1 Protocol deviations that cause subjects to be excluded

| ***Deviation ID*** | ***Description of Deviation*** | ***Exclusion in Analyses*** |
|---|---|---|
| INCL01 | No informed consent form is signed prior to study assessments performed | Excluded from all analysis sets |
| INCL07 | Primary source of pain throughout the body is not due to OA in the target knee, and no Widespread Pain Index (WPI) score of ≤4 | Excluded from secondary PD analysis set |
| EXCL07 | Any diagnosis of inflammatory arthritis or connective tissue disease or other systemic condition that might confound assessment of OA | Excluded from PD analysis set |
| EXCL08 | Presence of: septic arthritis, reactive arthritis, recurrent clinical episodes of pseudogout or articular fracture or other local conditions | Exclude from PD analysis set |

# 7 References

The 2012 User's Guide to: Knee injury and Osteoarthritis Outcome Score KOOS (2012). Website: www.KOOS.nu.

Independent Review Charter for X-Ray, MRI and DCE-MRI (2021).