



## Clinical trial results:

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

### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2020-003631-21    |
| Trial protocol           | DE CZ HU EE LT LV |
| Global end of trial date | 24 June 2024      |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 26 June 2025 |
| First version publication date | 26 June 2025 |

### Trial information

#### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | CLNA043A12203 |
|-----------------------|---------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT04814368 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Novartis Pharmaceuticals  |
| Sponsor organisation address | Novartis Campus, Basel, Switzerland,  |
| Public contact               | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com |

Notes:

### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |              |
|--|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 24 June 2024 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 24 June 2024 |
| Was the trial ended prematurely?                     | Yes          |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective is to assess the ability of LNA043 to regenerate articular cartilage tissue in patients with symptomatic knee osteoarthritis with inflammation, after injection of placebo or canakinumab intra articular and the co-primary objective is the ability of canakinumab to reduce pain and/or inflammation in patients with symptomatic knee osteoarthritis with inflammation.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 27 August 2021 |
| Long term follow-up planned                               | No             |
| Independent data monitoring committee (IDMC) involvement? | No             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Czechia: 1        |
| Country: Number of subjects enrolled | Estonia: 1        |
| Country: Number of subjects enrolled | Latvia: 1         |
| Country: Number of subjects enrolled | Poland: 1         |
| Country: Number of subjects enrolled | Hungary: 5        |
| Country: Number of subjects enrolled | United States: 14 |
| Worldwide total number of subjects   | 23                |
| EEA total number of subjects         | 9                 |

Notes:

### Subjects enrolled per age group

|   |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23 months)  | 0 |

|                           |    |
|---------------------------|----|
| Children (2-11 years)     | 0  |
| Adolescents (12-17 years) | 0  |
| Adults (18-64 years)      | 16 |
| From 65 to 84 years       | 7  |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Participants took part in 11 investigative sites in 6 countries.

### Pre-assignment

Screening details:

The study consisted of 4 screening visits (Screening 1-4), of which Screening 2 and 4 could be performed remotely.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Double blind                   |
| Roles blinded                | Subject, Investigator          |

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |                                |
|------------------|--------------------------------|
| <b>Arm title</b> | Placebo to ACZ885+LNA043 40 mg |
|------------------|--------------------------------|

Arm description:

Placebo to ACZ885 single dose intra-articular (i.a) followed by LNA043 40 mg administrated i.a every four weeks, three times.

|  |   |
|--|---|
| Arm type                               | Experimental  |
| Investigational medicinal product name | Placebo to ACZ885+LNA043                                  |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Solution for injection, Powder for solution for injection |
| Routes of administration               | Intraarticular use  |

Dosage and administration details:

Placebo to ACZ885 single dose i.a followed by LNA043 40 mg administrated i.a every four weeks, three times.

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | Placebo to ACZ885 |
|------------------|-------------------|

Arm description:

Placebo to ACZ885 single dose intra-articular.

|  |                        |
|--|------------------------|
| Arm type                               | Placebo                |
| Investigational medicinal product name | Placebo to ACZ885      |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intraarticular use     |

Dosage and administration details:

Placebo to ACZ885 single dose i.a.

|                  |                              |
|------------------|------------------------------|
| <b>Arm title</b> | ACZ885 600 mg + LNA043 40 mg |
|------------------|------------------------------|

Arm description:

ACZ885 600 mg single dose i.a. followed by LNA043 40 mg administrated i.a every four weeks, three times.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |   |
|--|---|
| Investigational medicinal product name | ACZ885+LNA043   |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Solution for injection, Powder for solution for injection |
| Routes of administration               | Intraarticular use  |

Dosage and administration details:

ACZ885 600 mg single dose i.a. followed by LNA043 40 mg administrated i.a every four weeks, three times.

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | ACZ885 600 mg |
|------------------|---------------|

Arm description:

ACZ885 600 mg single dose intra-articular.

|  |                        |
|--|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | ACZ885                 |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intraarticular use     |

Dosage and administration details:

ACZ885 600 mg single dose i.a.

| <b>Number of subjects in period 1</b> | Placebo to<br>ACZ885+LNA043 40<br>mg | Placebo to ACZ885 | ACZ885 600 mg +<br>LNA043 40 mg |
|---------------------------------------|--------------------------------------|-------------------|---------------------------------|
| Started                               | 3                                    | 9                 | 3                               |
| Completed                             | 2                                    | 4                 | 3                               |
| Not completed                         | 1                                    | 5                 | 0                               |
| Subject Decision                      | 1                                    | 2                 | -                               |
| Study Terminated by Sponsor           | -                                    | 3                 | -                               |

| <b>Number of subjects in period 1</b> | ACZ885 600 mg |
|---------------------------------------|---------------|
| Started                               | 8             |
| Completed                             | 6             |
| Not completed                         | 2             |
| Subject Decision                      | -             |
| Study Terminated by Sponsor           | 2             |

## Baseline characteristics

### Reporting groups

|   |                                |
|---|--------------------------------|
| Reporting group title   | Placebo to ACZ885+LNA043 40 mg |
| Reporting group description:<br>Placebo to ACZ885 single dose intra-articular (i.a) followed by LNA043 40 mg administrated i.a every four weeks, three times. |                                |
| Reporting group title   | Placebo to ACZ885              |
| Reporting group description:<br>Placebo to ACZ885 single dose intra-articular.  |                                |
| Reporting group title   | ACZ885 600 mg + LNA043 40 mg   |
| Reporting group description:<br>ACZ885 600 mg single dose i.a. followed by LNA043 40 mg administrated i.a every four weeks, three times.                      |                                |
| Reporting group title   | ACZ885 600 mg                  |
| Reporting group description:<br>ACZ885 600 mg single dose intra-articular.  |                                |

| Reporting group values                                | Placebo to<br>ACZ885+LNA043 40<br>mg | Placebo to ACZ885 | ACZ885 600 mg +<br>LNA043 40 mg |
|---|--------------------------------------|-------------------|---------------------------------|
| Number of subjects                                    | 3                                    | 9                 | 3                               |
| Age categorical<br>Units: Subjects                    |                                      |                   |                                 |
| In utero  | 0                                    | 0                 | 0                               |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                                    | 0                 | 0                               |
| Newborns (0-27 days)                                  | 0                                    | 0                 | 0                               |
| Infants and toddlers (28 days-23<br>months)           | 0                                    | 0                 | 0                               |
| Children (2-11 years)                                 | 0                                    | 0                 | 0                               |
| Adolescents (12-17 years)                             | 0                                    | 0                 | 0                               |
| Adults (18-64 years)                                  | 2                                    | 7                 | 2                               |
| From 65-84 years                                      | 1                                    | 2                 | 1                               |
| 85 years and over                                     | 0                                    | 0                 | 0                               |
| Age Continuous<br>Units: years                        |                                      |                   |                                 |
| arithmetic mean                                       | 66.3                                 | 61.1              | 59.3                            |
| standard deviation                                    | ± 10.97                              | ± 5.90            | ± 7.02                          |
| Sex: Female, Male<br>Units: participants              |                                      |                   |                                 |
| Female  | 1                                    | 7                 | 1                               |
| Male  | 2                                    | 2                 | 2                               |
| Race/Ethnicity, Customized<br>Units: Subjects         |                                      |                   |                                 |
| Black or African American                             | 0                                    | 0                 | 0                               |
| Native Hawaiian or other                              | 0                                    | 0                 | 0                               |
| White   | 3                                    | 9                 | 3                               |

| Reporting group values | ACZ885 600 mg | Total |  |
|------------------------|---------------|-------|--|
| Number of subjects     | 8             | 23    |  |

|   |        |    |  |
|---|--------|----|--|
| Age categorical<br>Units: Subjects                    |        |    |  |
| In utero  | 0      | 0  |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0      | 0  |  |
| Newborns (0-27 days)                                  | 0      | 0  |  |
| Infants and toddlers (28 days-23 months)              | 0      | 0  |  |
| Children (2-11 years)                                 | 0      | 0  |  |
| Adolescents (12-17 years)                             | 0      | 0  |  |
| Adults (18-64 years)                                  | 5      | 16 |  |
| From 65-84 years                                      | 3      | 7  |  |
| 85 years and over                                     | 0      | 0  |  |
| Age Continuous<br>Units: years                        |        |    |  |
| arithmetic mean                                       | 61.8   |    |  |
| standard deviation                                    | ± 8.55 | -  |  |
| Sex: Female, Male<br>Units: participants              |        |    |  |
| Female  | 7      | 16 |  |
| Male  | 1      | 7  |  |
| Race/Ethnicity, Customized<br>Units: Subjects         |        |    |  |
| Black or African American                             | 1      | 1  |  |
| Native Hawaiian or other                              | 1      | 1  |  |
| White   | 6      | 21 |  |

## End points

### End points reporting groups

|   |                                |
|---|--------------------------------|
| Reporting group title   | Placebo to ACZ885+LNA043 40 mg |
| Reporting group description:<br>Placebo to ACZ885 single dose intra-articular (i.a) followed by LNA043 40 mg administrated i.a every four weeks, three times. |                                |
| Reporting group title   | Placebo to ACZ885              |
| Reporting group description:<br>Placebo to ACZ885 single dose intra-articular.  |                                |
| Reporting group title   | ACZ885 600 mg + LNA043 40 mg   |
| Reporting group description:<br>ACZ885 600 mg single dose i.a. followed by LNA043 40 mg administrated i.a every four weeks, three times.                      |                                |
| Reporting group title   | ACZ885 600 mg                  |
| Reporting group description:<br>ACZ885 600 mg single dose intra-articular.  |                                |

### Primary: Change in cartilage volume in the index region measured by MRI at Day 197 (Placebo to ACZ885+LNA043 versus Placebo to ACZ885)

|  |   |
|--|---|
| End point title  | Change in cartilage volume in the index region measured by MRI at Day 197 (Placebo to ACZ885+LNA043 versus Placebo to ACZ885) <sup>[1][2]</sup> |
| End point description:<br>Magnetic resonance images (MRI) were obtained from the target knee to visualize and quantify changes in volume of cartilage in the index region. The index region was defined as the union of the femoral medial anterior (FMA), central (FMC) and posterior (FMP) cartilage subregions in the knee. |   |
| End point type   | Primary   |
| End point timeframe:<br>Baseline, Day 197  |   |

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: only analyzed descriptively.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The end point is specific for the arms presented.

| End point values                     | Placebo to ACZ885+LNA043 40 mg | Placebo to ACZ885      |  |  |
|--------------------------------------|--------------------------------|------------------------|--|--|
| Subject group type                   | Reporting group                | Reporting group        |  |  |
| Number of subjects analysed          | 2                              | 5                      |  |  |
| Units: $\mu\text{L}$                 |                                |                        |  |  |
| arithmetic mean (standard deviation) | 108.33 ( $\pm$ 226.451)        | -26.13 ( $\pm$ 65.204) |  |  |

## Statistical analyses



No statistical analyses for this end point

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**Primary: Change in Knee injury and Osteoarthritis Outcome Score (KOOS) Pain subscale (ACZ885 versus Placebo to ACZ885)**

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|                 |   |
|-----------------|---|
| End point title | Change in Knee injury and Osteoarthritis Outcome Score (KOOS) Pain subscale (ACZ885 versus Placebo to ACZ885) <sup>[3][4]</sup> |
|-----------------|---|

End point description:

The KOOS questionnaire is a commonly used instrument to assess the patient's perception about their knee and associated problems. The original KOOS consists of 5 subscales. One of those is the KOOS pain consisting of 9 questions with a recall of 7 days. Each question has 5 standardized answer options with a score from 0 to 4. A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline, Day 85

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: only analyzed descriptively.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The end point is specific for the arms presented.

| End point values                     | Placebo to ACZ885 | ACZ885 600 mg   |  |  |
|--------------------------------------|-------------------|-----------------|--|--|
| Subject group type                   | Reporting group   | Reporting group |  |  |
| Number of subjects analysed          | 7                 | 8               |  |  |
| Units: score on scale                |                   |                 |  |  |
| arithmetic mean (standard deviation) | 13.9 (± 13.89)    | 22.2 (± 20.09)  |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Number of participants with anti-LNA043 antibodies (Placebo to ACZ885+LNA043 versus ACZ885 + LNA043)**

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|                 |   |
|-----------------|---|
| End point title | Number of participants with anti-LNA043 antibodies (Placebo to ACZ885+LNA043 versus ACZ885 + LNA043) <sup>[5]</sup> |
|-----------------|---|

End point description:

To evaluate the immunogenicity of LNA043 via validated ligand-binding assay of potential anti-LNA043 antibodies.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From pre-dose up to Day 365

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: PK Endpoint not analyzed for participants on placebo

|                             |                                |                              |  |  |
|-----------------------------|--------------------------------|------------------------------|--|--|
| <b>End point values</b>     | Placebo to ACZ885+LNA043 40 mg | ACZ885 600 mg + LNA043 40 mg |  |  |
| Subject group type          | Reporting group                | Reporting group              |  |  |
| Number of subjects analysed | 3                              | 3                            |  |  |
| Units: Participants         | 0                              | 0                            |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Maximum serum concentration (Cmax) of LNA043 (Placebo to ACZ885+LNA043 versus ACZ885+LNA043)

|                 |   |
|-----------------|---|
| End point title | Maximum serum concentration (Cmax) of LNA043 (Placebo to ACZ885+LNA043 versus ACZ885+LNA043) <sup>[6]</sup> |
|-----------------|---|

End point description:

Cmax is defined as the maximum (peak) observed concentration following a dose. LNA043 serum concentrations were determined using the actual recorded sampling times and non-compartmental method with Phoenix WinNonlin (Version 8 or higher). LNA043 was determined by a validated immuno-capture and LC-MS/MS method; the anticipated LLOQ is 10 ng/mL in serum. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 15: pre-dose, 20, 60, 120 and 240 minutes, and 8 and 24 hours post LNA043 first injection on Day 15

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: PK Endpoint not analyzed for participants on placebo

|                                      |                                |                              |  |  |
|--------------------------------------|--------------------------------|------------------------------|--|--|
| <b>End point values</b>              | Placebo to ACZ885+LNA043 40 mg | ACZ885 600 mg + LNA043 40 mg |  |  |
| Subject group type                   | Reporting group                | Reporting group              |  |  |
| Number of subjects analysed          | 1                              | 1                            |  |  |
| Units: ng/mL                         |                                |                              |  |  |
| arithmetic mean (standard deviation) | 120 (± 999)                    | 149 (± 999)                  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Synovial fluid concentrations of ANGPTL3 (Placebo to ACZ885+LNA043 versus ACZ885+LNA043)

|                 |   |
|-----------------|---|
| End point title | Synovial fluid concentrations of ANGPTL3 (Placebo to ACZ885+LNA043 versus ACZ885+LNA043) <sup>[7]</sup> |
|-----------------|---|

End point description:

ANGPTL3 is a protein that is primarily involved in the lipid metabolism but has recently been shown to have chondrogenic and chondroprotective effects. ANGPTL3 was measured in synovial fluid. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated

as '999'.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Day 1, 15, 43 and 71 |           |

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: PK Endpoint not analyzed for participants on placebo

|                                      |                                |                              |  |  |
|--------------------------------------|--------------------------------|------------------------------|--|--|
| <b>End point values</b>              | Placebo to ACZ885+LNA043 40 mg | ACZ885 600 mg + LNA043 40 mg |  |  |
| Subject group type                   | Reporting group                | Reporting group              |  |  |
| Number of subjects analysed          | 1                              | 1                            |  |  |
| Units: ng/mL                         |                                |                              |  |  |
| arithmetic mean (standard deviation) | 999 (± 999)                    | 999 (± 999)                  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum serum concentration (C<sub>max</sub>) of ANGPTL3 (Placebo to ACZ885+LNA043 versus ACZ885+LNA043)

|                 |   |
|-----------------|---|
| End point title | Maximum serum concentration (C <sub>max</sub> ) of ANGPTL3 (Placebo to ACZ885+LNA043 versus ACZ885+LNA043) <sup>[8]</sup> |
|-----------------|---|

End point description:

ANGPTL3 is a protein that is primarily involved in the lipid metabolism but has recently been shown to have chondrogenic and chondroprotective effects.

C<sub>max</sub> is defined as the maximum (peak) observed concentration following a dose. ANGPTL3 serum concentrations were determined using the actual recorded sampling times and non-compartmental method with Phoenix WinNonlin (Version 8 or higher). ANGPTL3 was determined by a validated ligand binding assay; the anticipated LLOQ is 39.7 pmol/L in serum.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose Day 1 and 60 minutes after first injection of LNA043 on Day 15

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: PK Endpoint not analyzed for participants on placebo

|                                      |                                |                              |  |  |
|--------------------------------------|--------------------------------|------------------------------|--|--|
| <b>End point values</b>              | Placebo to ACZ885+LNA043 40 mg | ACZ885 600 mg + LNA043 40 mg |  |  |
| Subject group type                   | Reporting group                | Reporting group              |  |  |
| Number of subjects analysed          | 2                              | 3                            |  |  |
| Units: ng/mL                         |                                |                              |  |  |
| arithmetic mean (standard deviation) | 16.2 (± 2.47)                  | 24.1 (± 7.32)                |  |  |

## Statistical analyses

**Secondary: Time to reach maximum serum concentration (Tmax) of LNA043 (Placebo to ACZ885+LNA043 versus ACZ885+LNA043)**

|                 |   |
|-----------------|---|
| End point title | Time to reach maximum serum concentration (Tmax) of LNA043 (Placebo to ACZ885+LNA043 versus ACZ885+LNA043) <sup>[9]</sup> |
|-----------------|---|

## End point description:

Tmax is the time to reach maximum (peak) drug concentration after single-dose administration (time). LNA043 serum concentrations were determined using the actual recorded sampling times and non-compartmental method with Phoenix WinNonlin (Version 8 or higher). LNA043 was determined by a validated immuno-capture and LC-MS/MS method; the anticipated LLOQ is 10 ng/mL in serum. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

## End point timeframe:

Day 15: pre-dose, 20, 60, 120 and 240 minutes, and 8 and 24 hours post LNA043 first injection on Day 15

## Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: PK Endpoint not analyzed for participants on placebo

| End point values                     | Placebo to ACZ885+LNA043 40 mg | ACZ885 600 mg + LNA043 40 mg |  |  |
|--------------------------------------|--------------------------------|------------------------------|--|--|
| Subject group type                   | Reporting group                | Reporting group              |  |  |
| Number of subjects analysed          | 1                              | 1                            |  |  |
| Units: hour                          |                                |                              |  |  |
| arithmetic mean (standard deviation) | 2 (± 999)                      | 4.02 (± 999)                 |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Change in cartilage volume of the index region measured by MRI at Day 197 and Day 365 (ACZ885+LNA043 versus ACZ885, and ACZ885+LNA043 versus Placebo to ACZ885+LNA043)**

|                 |  |
|-----------------|--|
| End point title | Change in cartilage volume of the index region measured by MRI at Day 197 and Day 365 (ACZ885+LNA043 versus ACZ885, and ACZ885+LNA043 versus Placebo to ACZ885+LNA043) <sup>[10]</sup> |
|-----------------|--|

## End point description:

Magnetic resonance images (MRI) were obtained from the target knee to visualize and quantify changes in volume of cartilage in the index region. The index region was defined as the union of the femoral medial anterior (FMA), central (FMC) and posterior (FMP) cartilage subregions in the knee.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

## End point timeframe:

Baseline, Day 197 and Day 365

## Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The end point is specific for the arms presented.

| End point values                     | Placebo to ACZ885+LNA043 40 mg | ACZ885 600 mg + LNA043 40 mg | ACZ885 600 mg       |  |
|--------------------------------------|--------------------------------|------------------------------|---------------------|--|
| Subject group type                   | Reporting group                | Reporting group              | Reporting group     |  |
| Number of subjects analysed          | 2                              | 3                            | 6                   |  |
| Units: µL                            |                                |                              |                     |  |
| arithmetic mean (standard deviation) |                                |                              |                     |  |
| Day 197                              | 108.33 (± 226.451)             | 307.90 (± 580.213)           | -82.33 (± 390.645)  |  |
| Day 365                              | 152.78 (± 135.128)             | 20.54 (± 557.708)            | -129.93 (± 544.793) |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Area under serum concentration-time curve from time zero to the last measurable concentration sampling time (AUClast) of LNA043 (Placebo to ACZ885+LNA043 versus ACZ885+LNA043)

|                 |   |
|-----------------|---|
| End point title | Area under serum concentration-time curve from time zero to the last measurable concentration sampling time (AUClast) of LNA043 (Placebo to ACZ885+LNA043 versus ACZ885+LNA043) <sup>[11]</sup> |
|-----------------|---|

End point description:

AUClast is the area under the serum concentration-time curve from time zero to the time of last quantifiable concentration (tlast) of LNA043. LNA043 serum concentrations were determined using the actual recorded sampling times and non-compartmental method with Phoenix WinNonlin (Version 8 or higher). LNA043 was determined by a validated immuno-capture and LC-MS/MS method; the anticipated LLOQ is 10 ng/mL in serum. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 15: pre-dose, 20, 60, 120 and 240 minutes, and 8 and 24 hours post LNA043 first injection on Day 15

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: PK Endpoint not analyzed for participants on placebo

| End point values                     | Placebo to ACZ885+LNA043 40 mg | ACZ885 600 mg + LNA043 40 mg |  |  |
|--------------------------------------|--------------------------------|------------------------------|--|--|
| Subject group type                   | Reporting group                | Reporting group              |  |  |
| Number of subjects analysed          | 1                              | 1                            |  |  |
| Units: h*ng/mL                       |                                |                              |  |  |
| arithmetic mean (standard deviation) | 800 (± 999)                    | 1880 (± 999)                 |  |  |

## Statistical analyses

No statistical analyses for this end point

**Secondary: Change in cartilage volume of the index region measured by MRI at Day 365 (Placebo to ACZ885+LNA043 versus Placebo to ACZ885)**

|                 |   |
|-----------------|---|
| End point title | Change in cartilage volume of the index region measured by MRI at Day 365 (Placebo to ACZ885+LNA043 versus Placebo to ACZ885) <sup>[12]</sup> |
|-----------------|---|

End point description:

Magnetic resonance images (MRI) were obtained from the target knee to visualize and quantify changes in volume of cartilage in the index region. The index region was defined as the union of the femoral medial anterior (FMA), central (FMC) and posterior (FMP) cartilage subregions in the knee.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Day 365

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The end point is specific for the arms presented.

|                                      |                                |                        |  |  |
|--------------------------------------|--------------------------------|------------------------|--|--|
| <b>End point values</b>              | Placebo to ACZ885+LNA043 40 mg | Placebo to ACZ885      |  |  |
| Subject group type                   | Reporting group                | Reporting group        |  |  |
| Number of subjects analysed          | 2                              | 3                      |  |  |
| Units: $\mu\text{L}$                 |                                |                        |  |  |
| arithmetic mean (standard deviation) | 152.78 ( $\pm$ 135.128)        | 20.54 ( $\pm$ 557.708) |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Change in cartilage thickness of the index region measured by MRI at Day 197 and Day 365 (Placebo to ACZ885+LNA043 versus Placebo to ACZ885)**

|                 |  |
|-----------------|--|
| End point title | Change in cartilage thickness of the index region measured by MRI at Day 197 and Day 365 (Placebo to ACZ885+LNA043 versus Placebo to ACZ885) <sup>[13]</sup> |
|-----------------|--|

End point description:

Magnetic resonance images (MRI) were obtained from the target knee to visualize and quantify changes in thickness of cartilage in the index region. The index region was defined as the union of the femoral medial anterior (FMA), central (FMC) and posterior (FMP) cartilage subregions in the knee.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Day 197 and 365

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The end point is specific for the arms presented.

| End point values                     | Placebo to ACZ885+LNA043 40 mg | Placebo to ACZ885 |  |  |
|--------------------------------------|--------------------------------|-------------------|--|--|
| Subject group type                   | Reporting group                | Reporting group   |  |  |
| Number of subjects analysed          | 2                              | 3                 |  |  |
| Units: mm                            |                                |                   |  |  |
| arithmetic mean (standard deviation) |                                |                   |  |  |
| Day 197                              | 0.07 (± 0.083)                 | 0.06 (± 0.112)    |  |  |
| Day 365                              | -0.03 (± 0.046)                | 0.11 (± 0.072)    |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in cartilage thickness of the index region measured by MRI at Day 197 and Day 365 (ACZ885+LNA043 versus ACZ885, and ACZ885+LNA043 versus Placebo to ACZ885+LNA043)

|                 |   |
|-----------------|---|
| End point title | Change in cartilage thickness of the index region measured by MRI at Day 197 and Day 365 (ACZ885+LNA043 versus ACZ885, and ACZ885+LNA043 versus Placebo to ACZ885+LNA043) <sup>[14]</sup> |
|-----------------|---|

End point description:

Magnetic resonance images (MRI) were obtained from the target knee to visualize and quantify changes in thickness of cartilage in the index region. The index region was defined as the union of the femoral medial anterior (FMA), central (FMC) and posterior (FMP) cartilage subregions in the knee. The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Day 197 and 365

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The end point is specific for the arms presented.

| End point values                     | Placebo to ACZ885+LNA043 40 mg | ACZ885 600 mg + LNA043 40 mg | ACZ885 600 mg   |  |
|--------------------------------------|--------------------------------|------------------------------|-----------------|--|
| Subject group type                   | Reporting group                | Reporting group              | Reporting group |  |
| Number of subjects analysed          | 2                              | 3                            | 7               |  |
| Units: mm                            |                                |                              |                 |  |
| arithmetic mean (standard deviation) |                                |                              |                 |  |
| Day 197 (n=2,3,7)                    | 0.07 (± 0.083)                 | 0.13 (± 0.212)               | -0.02 (± 0.121) |  |
| Day 365 (n=2,3,6)                    | -0.03 (± 0.046)                | 0.04 (± 0.168)               | -0.05 (± 0.152) |  |

## Statistical analyses

**Secondary: Change in numeric rating scale (NRS) over time (ACZ885 versus Placebo to ACZ885)**

|                 |  |
|-----------------|--|
| End point title | Change in numeric rating scale (NRS) over time (ACZ885 versus Placebo to ACZ885) <sup>[15]</sup> |
|-----------------|--|

## End point description:

The Numerical Rating Scale (NRS) Pain is a subjective assessment in which individuals rate their pain on an eleven-point numerical scale. The scale ranges from 0 (no pain) to 10 (worst possible pain). The NRS Pain instrument had a recall period of 24 hours and the participants were asked to rate the pain intensity at its worst. The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

## End point timeframe:

Baseline, Day 15, 29, 43, 57, 71, 85

## Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The end point is specific for the arms presented.

| End point values                     | Placebo to ACZ885 | ACZ885 600 mg   |  |  |
|--------------------------------------|-------------------|-----------------|--|--|
| Subject group type                   | Reporting group   | Reporting group |  |  |
| Number of subjects analysed          | 8                 | 7               |  |  |
| Units: score on scale                |                   |                 |  |  |
| arithmetic mean (standard deviation) |                   |                 |  |  |
| Day 15 (n=8,7)                       | -1.5 (± 2.33)     | -2.1 (± 2.27)   |  |  |
| Day 29 (n=8,7)                       | -2.5 (± 2.73)     | -3.1 (± 1.95)   |  |  |
| Day 43 (n=8,7)                       | -1.8 (± 2.25)     | -2.4 (± 2.15)   |  |  |
| Day 57 (n=8,6)                       | -2.1 (± 2.80)     | -3.5 (± 2.35)   |  |  |
| Day 71 (n=7,7)                       | -2.1 (± 1.95)     | -3.1 (± 2.19)   |  |  |
| Day 85 (n=7,7)                       | -1.7 (± 2.29)     | -2.7 (± 2.06)   |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Change in synovitis level measured from Ktrans by Dynamic Contrast Enhanced MRI (DCE-MRI) (ACZ885 versus Placebo to ACZ885)**

|                 |   |
|-----------------|---|
| End point title | Change in synovitis level measured from Ktrans by Dynamic Contrast Enhanced MRI (DCE-MRI) (ACZ885 versus Placebo to ACZ885) <sup>[16]</sup> |
|-----------------|---|

## End point description:

Magnetic resonance images (MRI) were obtained from the target knee with dynamic contrast enhancement (DCE) to visualize and quantify changes in k-trans as a marker of the activity of synovial inflammation. During the DCE-MRI acquisition, while the contrast agent is preferentially taken up at sites with an increased perfusion due to the formation of new vessels with high porosity (such as the inflamed synovial membrane), a temporal variation of the MRI signal intensity occurs. When the contrast distributes through the intravascular and extravascular spaces, the MR signal intensity in the image volume elements (voxels) of the target tissue changes over time, generating so-called signal intensity (SI) curves. These curves can then be analyzed to derive parameters related to tissue perfusion. The parameter of primary interest was the volume transfer rate of the gadolinium-based contrast agent (GBCA) from the blood plasma in synovium, commonly referred to as Ktrans.



|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Baseline, Day 85   |           |
| Notes:   |           |
| [16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. |           |
| Justification: The end point is specific for the arms presented.   |           |

| End point values                     | Placebo to ACZ885   | ACZ885 600 mg       |  |  |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed          | 6                   | 7                   |  |  |
| Units: min <sup>-1</sup>             |                     |                     |  |  |
| arithmetic mean (standard deviation) | -0.0009 (± 0.01185) | -0.0051 (± 0.00702) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in numeric rating scale (NRS) over time (ACZ885+LNA043 versus ACZ885, and ACZ885+LNA043 versus Placebo to ACZ885+LNA043)

|                 |   |
|-----------------|---|
| End point title | Change in numeric rating scale (NRS) over time (ACZ885+LNA043 versus ACZ885, and ACZ885+LNA043 versus Placebo to ACZ885+LNA043) <sup>[17]</sup> |
|-----------------|---|

End point description:

The Numerical Rating Scale (NRS) Pain is a subjective assessment in which individuals rate their pain on an eleven-point numerical scale. The scale ranges from 0 (no pain) to 10 (worst possible pain). The NRS Pain instrument had a recall period of 24 hours and the participants were asked to rate the pain intensity at its worst. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'. The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| Baseline, Day 15, 29, 43, 57, 71, 85, 197 and 365  |           |
| Notes:   |           |
| [17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. |           |
| Justification: The end point is specific for the arms presented.   |           |

| End point values                     | Placebo to ACZ885+LNA043 40 mg | ACZ885 600 mg + LNA043 40 mg | ACZ885 600 mg   |  |
|--------------------------------------|--------------------------------|------------------------------|-----------------|--|
| Subject group type                   | Reporting group                | Reporting group              | Reporting group |  |
| Number of subjects analysed          | 2                              | 3                            | 7               |  |
| Units: score on scale                |                                |                              |                 |  |
| arithmetic mean (standard deviation) |                                |                              |                 |  |
| Day 15 (n=1,3,7)                     | -3.0 (± 999)                   | -0.7 (± 1.15)                | -2.1 (± 2.27)   |  |
| Day 29 (n=1,3,7)                     | -3.0 (± 999)                   | -1.0 (± 1.00)                | -3.1 (± 1.95)   |  |
| Day 43 (n=2,3,7)                     | -4.5 (± 2.12)                  | -0.7 (± 0.58)                | -2.4 (± 2.15)   |  |
| Day 57 (n=1,3,6)                     | -4.0 (± 999)                   | -2.0 (± 0.00)                | -3.5 (± 2.35)   |  |

|                   |               |               |               |  |
|-------------------|---------------|---------------|---------------|--|
| Day 71 (n=1,3,7)  | -4.0 (± 999)  | -2.0 (± 1.00) | -3.1 (± 2.19) |  |
| Day 85 (n=2,3,7)  | -5.5 (± 0.71) | -3.3 (± 0.58) | -2.7 (± 2.06) |  |
| Day 197 (n=1,3,6) | -6.0 (± 999)  | -3.3 (± 2.08) | -2.8 (± 2.64) |  |
| Day 365 (n=1,3,4) | -3.0 (± 999)  | -4.3 (± 2.31) | -3.0 (± 3.83) |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in Knee Injury and Osteoarthritis Outcome Score (KOOS) Pain subscale over time (ACZ885 versus Placebo to ACZ885)

|                 |   |
|-----------------|---|
| End point title | Change in Knee Injury and Osteoarthritis Outcome Score (KOOS) Pain subscale over time (ACZ885 versus Placebo to ACZ885) <sup>[18]</sup> |
|-----------------|---|

End point description:

The KOOS questionnaire is a commonly used instrument to assess the patient's perception about their knee and associated problems. The original KOOS consists of 5 subscales. One of those is the KOOS pain consisting of 9 questions with a recall of 7 days. Each question has 5 standardized answer options with a score from 0 to 4. A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale. The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Day 15, 29, 43, 57, 71, 85

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The end point is specific for the arms presented.

| End point values                     | Placebo to ACZ885 | ACZ885 600 mg   |  |  |
|--------------------------------------|-------------------|-----------------|--|--|
| Subject group type                   | Reporting group   | Reporting group |  |  |
| Number of subjects analysed          | 8                 | 8               |  |  |
| Units: score on scale                |                   |                 |  |  |
| arithmetic mean (standard deviation) |                   |                 |  |  |
| Day 15 (n=8,8)                       | 12.8 (± 21.72)    | 20.1 (± 20.40)  |  |  |
| Day 29 (n=8,8)                       | 16.3 (± 17.60)    | 24.0 (± 20.52)  |  |  |
| Day 43 (n=8,8)                       | 11.8 (± 12.31)    | 21.9 (± 21.28)  |  |  |
| Day 57 (n=8,8)                       | 13.9 (± 18.96)    | 28.1 (± 19.38)  |  |  |
| Day 71 (n=7,8)                       | 14.3 (± 15.75)    | 26.4 (± 20.03)  |  |  |
| Day 85 (n=7,8)                       | 25.0 (± 3.93)     | 22.2 (± 20.09)  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in Knee Injury and Osteoarthritis Outcome Score (KOOS) Pain subscale over time (ACZ885+LNA043 versus ACZ885, and ACZ885+LNA043 versus Placebo to ACZ885+LNA043)

|                 |  |
|-----------------|--|
| End point title | Change in Knee Injury and Osteoarthritis Outcome Score (KOOS) Pain subscale over time (ACZ885+LNA043 versus ACZ885, and ACZ885+LNA043 versus Placebo to ACZ885+LNA043) <sup>[19]</sup> |
|-----------------|--|

End point description:

The KOOS questionnaire is a commonly used instrument to assess the patient's perception about their knee and associated problems. The original KOOS consists of 5 subscales. One of those is the KOOS pain consisting of 9 questions with a recall of 7days. Each question has 5 standardized answer options with a score from 0 to 4. A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale. The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Day 15, 29, 43, 57, 71, 85, 197 and 365

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The end point is specific for the arms presented.

| End point values                     | Placebo to ACZ885+LNA043 40 mg | ACZ885 600 mg + LNA043 40 mg | ACZ885 600 mg   |  |
|--------------------------------------|--------------------------------|------------------------------|-----------------|--|
| Subject group type                   | Reporting group                | Reporting group              | Reporting group |  |
| Number of subjects analysed          | 2                              | 3                            | 8               |  |
| Units: score on scale                |                                |                              |                 |  |
| arithmetic mean (standard deviation) |                                |                              |                 |  |
| Day 15 (n=2,3,8)                     | 25.0 (± 27.50)                 | 3.7 (± 18.91)                | 20.1 (± 20.40)  |  |
| Day 29 (n=2,3,8)                     | 36.1 (± 19.64)                 | 15.7 (± 9.76)                | 24.0 (± 20.52)  |  |
| Day 43 (n=2,3,8)                     | 25.0 (± 15.71)                 | 15.7 (± 16.74)               | 21.9 (± 21.28)  |  |
| Day 57 (n=2,3,8)                     | 25.0 (± 7.86)                  | 17.6 (± 5.78)                | 28.1 (± 19.38)  |  |
| Day 71 (n=2,3,8)                     | 29.2 (± 5.89)                  | 16.7 (± 2.78)                | 26.4 (± 20.03)  |  |
| Day 85 (n=2,3,8)                     | 25.0 (± 3.93)                  | 22.2 (± 14.70)               | 22.2 (± 20.09)  |  |
| Day 197 (n=2,3,8)                    | 37.5 (± 9.82)                  | 38.0 (± 12.83)               | 25.0 (± 21.87)  |  |
| Day 365 (n=2,3,6)                    | 31.9 (± 17.68)                 | 45.4 (± 10.52)               | 31.5 (± 26.33)  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in Knee Injury and Osteoarthritis Outcome Score (KOOS) Function in daily living (ADL) subscale over time (ACZ885 versus Placebo to ACZ885)

|                 |   |
|-----------------|---|
| End point title | Change in Knee Injury and Osteoarthritis Outcome Score (KOOS) Function in daily living (ADL) subscale over time (ACZ885 versus Placebo to ACZ885) <sup>[20]</sup> |
|-----------------|---|

End point description:

The KOOS questionnaire is a commonly used instrument to assess the patient's perception about their knee and associated problems. The original KOOS consists of 5 subscales. One of those is the KOOS Function in Daily Living (ADL) subscale consisting of 17 questions with a recall of 7days. Each question has 5 standardized answer options with a score from 0 to 4. A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale. The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Day 15, 29, 43, 57, 71, 85

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The end point is specific for the arms presented.

| End point values                     | Placebo to ACZ885 | ACZ885 600 mg   |  |  |
|--------------------------------------|-------------------|-----------------|--|--|
| Subject group type                   | Reporting group   | Reporting group |  |  |
| Number of subjects analysed          | 8                 | 8               |  |  |
| Units: score on scale                |                   |                 |  |  |
| arithmetic mean (standard deviation) |                   |                 |  |  |
| Day 15 (n=8,8)                       | 11.9 (± 23.87)    | 18.4 (± 18.35)  |  |  |
| Day 29 (n=8,8)                       | 14.3 (± 24.74)    | 25.7 (± 20.72)  |  |  |
| Day 43 (n=8,8)                       | 9.7 (± 17.04)     | 26.1 (± 19.79)  |  |  |
| Day 57 (n=8,8)                       | 16.7 (± 28.06)    | 31.8 (± 21.99)  |  |  |
| Day 71 (n=7,8)                       | 16.8 (± 22.30)    | 28.7 (± 19.40)  |  |  |
| Day 85 (n=7,8)                       | 14.7 (± 23.05)    | 23.7 (± 19.26)  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in Knee Injury and Osteoarthritis Outcome Score (KOOS) Function in daily living (ADL) subscale over time (ACZ885+LNA043 versus ACZ885, and ACZ885+LNA043 versus Placebo to ACZ885+LNA043)

|                 |  |
|-----------------|--|
| End point title | Change in Knee Injury and Osteoarthritis Outcome Score (KOOS) Function in daily living (ADL) subscale over time (ACZ885+LNA043 versus ACZ885, and ACZ885+LNA043 versus Placebo to ACZ885+LNA043) <sup>[21]</sup> |
|-----------------|--|

End point description:

The KOOS questionnaire is a commonly used instrument to assess the patient's perception about their knee and associated problems. The original KOOS consists of 5 subscales. One of those is the KOOS Function in Daily Living (ADL) subscale consisting of 17 questions with a recall of 7 days. Each question has 5 standardized answer options with a score from 0 to 4. A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale. The Number of Subjects Analyzed differs as stated on the category column, in case of difference from Number of subjects that started the Arm.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Day 15, 29, 43, 57, 71, 85, 197 and 365

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The end point is specific for the arms presented.

| End point values                     | Placebo to<br>ACZ885+LNA0<br>43 40 mg | ACZ885 600<br>mg + LNA043<br>40 mg | ACZ885 600<br>mg |  |
|--------------------------------------|---------------------------------------|------------------------------------|------------------|--|
| Subject group type                   | Reporting group                       | Reporting group                    | Reporting group  |  |
| Number of subjects analysed          | 2                                     | 3                                  | 8                |  |
| Units: score on scale                |                                       |                                    |                  |  |
| arithmetic mean (standard deviation) |                                       |                                    |                  |  |
| Day 15 (n=2,3,8)                     | 37.5 (± 34.32)                        | 2.9 (± 8.82)                       | 18.4 (± 18.35)   |  |
| Day 29 (n=2,3,8)                     | 42.6 (± 20.80)                        | 17.2 (± 4.49)                      | 25.7 (± 20.72)   |  |
| Day 43 (n=2,3,8)                     | 41.9 (± 28.08)                        | 16.2 (± 11.76)                     | 26.1 (± 19.79)   |  |
| Day 57 (n=2,3,8)                     | 40.4 (± 19.76)                        | 19.1 (± 8.95)                      | 31.8 (± 21.99)   |  |
| Day 71 (n=2,3,8)                     | 43.4 (± 23.92)                        | 20.6 (± 10.29)                     | 28.7 (± 19.40)   |  |
| Day 85 (n=2,3,8)                     | 41.9 (± 19.76)                        | 28.4 (± 15.09)                     | 23.7 (± 19.26)   |  |
| Day 197 (n=2,3,8)                    | 50.7 (± 19.76)                        | 36.8 (± 1.47)                      | 27.4 (± 23.92)   |  |
| Day 365 (n=2,3,6)                    | 44.9 (± 26.00)                        | 42.2 (± 13.34)                     | 33.6 (± 23.79)   |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until end of study treatment plus follow up period, up to a maximum duration of approximately 52 weeks.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 27.1 |
|--------------------|------|

### Reporting groups

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Placebo to ACZ885+LNA043 40 mg |
|-----------------------|--------------------------------|

Reporting group description:

Placebo to ACZ885 single dose intra-articular (i.a) followed by LNA043 40 mg administrated i.a every four weeks, three times.

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Placebo to ACZ885 |
|-----------------------|-------------------|

Reporting group description:

Placebo to ACZ885 single dose intra-articular.

|                       |       |
|-----------------------|-------|
| Reporting group title | Total |
|-----------------------|-------|

Reporting group description:

Total

|                       |               |
|-----------------------|---------------|
| Reporting group title | ACZ885 600 mg |
|-----------------------|---------------|

Reporting group description:

ACZ885 600 mg single dose intra-articular.

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | ACZ885 600 mg + LNA043 40 mg |
|-----------------------|------------------------------|

Reporting group description:

ACZ885 600 mg single dose i.a. followed by LNA043 40 mg administrated i.a every four weeks, three times.

| Serious adverse events                            | Placebo to ACZ885+LNA043 40 mg | Placebo to ACZ885 | Total          |
|---|--------------------------------|-------------------|----------------|
| Total subjects affected by serious adverse events |                                |                   |                |
| subjects affected / exposed                       | 0 / 3 (0.00%)                  | 0 / 9 (0.00%)     | 0 / 23 (0.00%) |
| number of deaths (all causes)                     | 0                              | 0                 | 0              |
| number of deaths resulting from adverse events    | 0                              | 0                 | 0              |

| Serious adverse events                            | ACZ885 600 mg | ACZ885 600 mg + LNA043 40 mg |  |
|---|---------------|------------------------------|--|
| Total subjects affected by serious adverse events |               |                              |  |
| subjects affected / exposed                       | 0 / 8 (0.00%) | 0 / 3 (0.00%)                |  |
| number of deaths (all causes)                     | 0             | 0                            |  |
| number of deaths resulting from adverse events    | 0             | 0                            |  |

Frequency threshold for reporting non-serious adverse events: 5 %

| <b>Non-serious adverse events</b>                        | Placebo to<br>ACZ885+LNA043 40<br>mg | Placebo to ACZ885 | Total           |
|--|--------------------------------------|-------------------|-----------------|
| Total subjects affected by non-serious<br>adverse events |                                      |                   |                 |
| subjects affected / exposed                              | 1 / 3 (33.33%)                       | 2 / 9 (22.22%)    | 8 / 23 (34.78%) |
| Investigations   |                                      |                   |                 |
| Blood creatine phosphokinase<br>increased                |                                      |                   |                 |
| subjects affected / exposed                              | 0 / 3 (0.00%)                        | 0 / 9 (0.00%)     | 1 / 23 (4.35%)  |
| occurrences (all)  | 0                                    | 0                 | 1               |
| Cardiac disorders  |                                      |                   |                 |
| Bundle branch block right                                |                                      |                   |                 |
| subjects affected / exposed                              | 0 / 3 (0.00%)                        | 0 / 9 (0.00%)     | 1 / 23 (4.35%)  |
| occurrences (all)  | 0                                    | 0                 | 1               |
| Respiratory, thoracic and mediastinal<br>disorders       |                                      |                   |                 |
| Cough  |                                      |                   |                 |
| subjects affected / exposed                              | 0 / 3 (0.00%)                        | 0 / 9 (0.00%)     | 1 / 23 (4.35%)  |
| occurrences (all)  | 0                                    | 0                 | 1               |
| Infections and infestations                              |                                      |                   |                 |
| Abscess limb   |                                      |                   |                 |
| subjects affected / exposed                              | 0 / 3 (0.00%)                        | 0 / 9 (0.00%)     | 1 / 23 (4.35%)  |
| occurrences (all)  | 0                                    | 0                 | 1               |
| Nasopharyngitis  |                                      |                   |                 |
| subjects affected / exposed                              | 0 / 3 (0.00%)                        | 0 / 9 (0.00%)     | 1 / 23 (4.35%)  |
| occurrences (all)  | 0                                    | 0                 | 1               |
| COVID-19   |                                      |                   |                 |
| subjects affected / exposed                              | 0 / 3 (0.00%)                        | 0 / 9 (0.00%)     | 1 / 23 (4.35%)  |
| occurrences (all)  | 0                                    | 0                 | 1               |
| Body tinea   |                                      |                   |                 |
| subjects affected / exposed                              | 0 / 3 (0.00%)                        | 1 / 9 (11.11%)    | 1 / 23 (4.35%)  |
| occurrences (all)  | 0                                    | 1                 | 1               |
| Oral herpes  |                                      |                   |                 |
| subjects affected / exposed                              | 0 / 3 (0.00%)                        | 0 / 9 (0.00%)     | 1 / 23 (4.35%)  |
| occurrences (all)  | 0                                    | 0                 | 1               |
| Rhinitis   |                                      |                   |                 |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 3 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 1 / 23 (4.35%)<br>1 |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 3 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 | 1 / 23 (4.35%)<br>1 |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 3 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  | 1 / 23 (4.35%)<br>1 |
| Metabolism and nutrition disorders<br>Hypophosphataemia<br>subjects affected / exposed<br>occurrences (all) | 1 / 3 (33.33%)<br>1 | 0 / 9 (0.00%)<br>0  | 1 / 23 (4.35%)<br>1 |

| <b>Non-serious adverse events</b>   | ACZ885 600 mg       | ACZ885 600 mg +<br>LNA043 40 mg |  |
|---|---------------------|---------------------------------|--|
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed                         | 4 / 8 (50.00%)      | 1 / 3 (33.33%)                  |  |
| Investigations<br>Blood creatine phosphokinase<br>increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 8 (12.50%)<br>1 | 0 / 3 (0.00%)<br>0              |  |
| Cardiac disorders<br>Bundle branch block right<br>subjects affected / exposed<br>occurrences (all)              | 0 / 8 (0.00%)<br>0  | 1 / 3 (33.33%)<br>1             |  |
| Respiratory, thoracic and mediastinal<br>disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all) | 1 / 8 (12.50%)<br>1 | 0 / 3 (0.00%)<br>0              |  |
| Infections and infestations<br>Abscess limb<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 8 (12.50%)<br>1 | 0 / 3 (0.00%)<br>0              |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)   | 1 / 8 (12.50%)<br>1 | 0 / 3 (0.00%)<br>0              |  |
| COVID-19  |                     |                                 |  |



|                                    |                |                |  |
|------------------------------------|----------------|----------------|--|
| subjects affected / exposed        | 0 / 8 (0.00%)  | 1 / 3 (33.33%) |  |
| occurrences (all)                  | 0              | 1              |  |
| Body tinea                         |                |                |  |
| subjects affected / exposed        | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  |  |
| occurrences (all)                  | 0              | 0              |  |
| Oral herpes                        |                |                |  |
| subjects affected / exposed        | 1 / 8 (12.50%) | 0 / 3 (0.00%)  |  |
| occurrences (all)                  | 1              | 0              |  |
| Rhinitis                           |                |                |  |
| subjects affected / exposed        | 1 / 8 (12.50%) | 0 / 3 (0.00%)  |  |
| occurrences (all)                  | 1              | 0              |  |
| Upper respiratory tract infection  |                |                |  |
| subjects affected / exposed        | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  |  |
| occurrences (all)                  | 0              | 0              |  |
| Urinary tract infection            |                |                |  |
| subjects affected / exposed        | 1 / 8 (12.50%) | 0 / 3 (0.00%)  |  |
| occurrences (all)                  | 1              | 0              |  |
| Metabolism and nutrition disorders |                |                |  |
| Hypophosphataemia                  |                |                |  |
| subjects affected / exposed        | 0 / 8 (0.00%)  | 0 / 3 (0.00%)  |  |
| occurrences (all)                  | 0              | 0              |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 15 December 2021 | This amendment was generated to investigate differences in pain endpoints between all the four treatment arms (also comparing TA3 vs TA1 and TA3 vs TA4).   |
| 08 December 2022 | This amendment was generated to clarify permissible re-screening scenarios and to specify the required period of contraception use for women of child-bearing potential after the last investigational drug administration. The amendment also describes an Informed Consent Form used for healthy volunteers during the MRI qualification process, if required by local regulations. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The small sample size overall and the difference in group sizes do not allow a valid interpretation of the data regarding efficacy, pharmacokinetics and immunogenicity.

Notes: