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	v2 (current)
This version publication date	04 September 2025
First version publication date	26 June 2025
Version creation reason	

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
Arm title	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.

Arm title	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.

Arm title	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.

Arm title	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.

Number of subjects in period 1	Placebo to ACZ885+LNA043 40 mg	Placebo to ACZ885	ACZ885 600 mg + 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	-

Number of subjects in period 1	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:	
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	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.	
Reporting group title	ACZ885 600 mg
Reporting group description:	
ACZ885 600 mg single dose intra-articular.	

Reporting group values	Placebo to ACZ885+LNA043 40 mg	Placebo to ACZ885	ACZ885 600 mg + LNA043 40 mg
Number of subjects	3	9	3
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 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 Units: years			
arithmetic mean	66.3	61.1	59.3
standard deviation	± 10.97	± 5.90	± 7.02
Sex: Female, Male Units: participants			
Female	1	7	1
Male	2	2	2
Race/Ethnicity, Customized 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 Units: Subjects			
In utero	0	0	
Preterm newborn infants (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 Units: years			
arithmetic mean	61.8		
standard deviation	± 8.55	-	
Sex: Female, Male Units: participants			
Female	7	16	
Male	1	7	
Race/Ethnicity, Customized 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:	
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	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.	
Reporting group title	ACZ885 600 mg
Reporting group description:	
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)[1][2]
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	Primary
End point timeframe:	
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: µL				
arithmetic mean (standard deviation)	108.33 (± 226.451)	-26.13 (± 65.204)		

Statistical analyses

No statistical analyses for this end point

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

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

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.

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)		

Statistical analyses

No statistical analyses for this end point

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

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

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: The end point is specific for the arms presented.

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	3	3		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum serum concentration (Cmax) of ANGPTL3 (Placebo to ACZ885+LNA043 versus ACZ885+LNA043)

End point title	Maximum serum concentration (Cmax) of ANGPTL3 (Placebo to ACZ885+LNA043 versus ACZ885+LNA043)[6]

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.
Cmax 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, Day 15, Day 43 and 60 minutes after first injection of LNA043 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: The end point is specific for the arms presented.

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	2	3		
Units: ng/mL				
arithmetic mean (standard deviation)	16.2 (± 2.47)	24.1 (± 7.32)		

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)[7]

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'. 999 = not measurable, below the lower limit of quantification of 2.74 ng/mL

End point type	Secondary

End point timeframe:

Pre-dose on Days 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: The end point is specific for the arms presented.

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: ng/mL				
arithmetic mean (standard deviation)				
Day 1	999 (± 999)	999 (± 999)		
Day 15	999 (± 999)	999 (± 999)		
Day 43	999 (± 999)	999 (± 999)		
Day 71	999 (± 999)	999 (± 999)		

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)[8]

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:

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

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: ng/mL				
arithmetic mean (standard deviation)	120 (± 999)	149 (± 999)		

Statistical analyses

No statistical analyses for this end point

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)[9]

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: The end point is specific for the arms presented.

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: 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)[10]

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:

[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		
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 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)[11]

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:

[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: 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: 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)[12]

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.

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: µL				
arithmetic mean (standard deviation)	152.78 (± 135.128)	20.54 (± 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 (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)[13]

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:

[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	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

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)[14]

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:

[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	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 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)[15]

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:

[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	6	7		
Units: min^-1				
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 versus Placebo to ACZ885)

End point title	Change in numeric rating scale (NRS) over time (ACZ885 versus Placebo to ACZ885)[16]

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:

[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	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 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)[17]

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)[18]

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

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)[19]

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)[20]

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)[21]

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, 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 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)	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	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.

Reporting group title	ACZ885 600 mg

Reporting group description:

ACZ885 600 mg single dose intra-articular.

Reporting group title	Total

Reporting group description:

Total

Serious adverse events	Placebo to ACZ885+LNA043 40 mg	Placebo to ACZ885	ACZ885 600 mg + LNA043 40 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 3 (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	Total	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 23 (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 %

Non-serious adverse events	Placebo to ACZ885+LNA043 40 mg	Placebo to ACZ885	ACZ885 600 mg + LNA043 40 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	2 / 9 (22.22%)	1 / 3 (33.33%)
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Bundle branch block right			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Body tinea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
COVID-19			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Oral herpes			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			

subjects affected / exposed	0 / 3 (0.00%)	1 / 9 (11.11%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 9 (0.00%)	0 / 3 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 9 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	ACZ885 600 mg	Total	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 8 (50.00%)	8 / 23 (34.78%)	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 8 (12.50%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Cardiac disorders			
Bundle branch block right			
subjects affected / exposed	0 / 8 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 8 (12.50%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 8 (12.50%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Body tinea			
subjects affected / exposed	0 / 8 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
COVID-19			

subjects affected / exposed	0 / 8 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Oral herpes			
subjects affected / exposed	1 / 8 (12.50%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Urinary tract infection			
subjects affected / exposed	1 / 8 (12.50%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	0 / 8 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	

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:

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: