



Clinical trial results:

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

Summary

EudraCT number	2016-004052-30
Trial protocol	SE CZ DK
Global end of trial date	06 September 2022

Results information

Result version number	v1 (current)
This version publication date	20 September 2023
First version publication date	20 September 2023

Trial information

Trial identification

Sponsor protocol code	CLNA043X2202
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis AG, 41 613241111, Novartis.email@Novartis.com
Scientific contact	Clinical Disclosure Office, Novartis 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	06 September 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this two-part study was to assess the efficacy, safety, and tolerability of multiple intra-articular (i.a.) injections of LNA043, in regenerating the articular surface in subjects at an early stage of osteoarthritis with cartilage lesions in the knee (Part A) and subjects at a more advanced stage of knee osteoarthritis K&L grade 2 or 3 (Part B).

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	12 September 2017
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: 49
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	United States: 87
Worldwide total number of subjects	141
EEA total number of subjects	54

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)	106

From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 142 participants were randomized, but only 141 received treatment. One participant in Part B was discontinued due to poor veins that were not adequate for blood samples.

Period 1

Period 1 title	Treatment Period Part A and Part B
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	LNA043 20 mg Part A

Arm description:

Part A: a single intra-articular injection of 20 mg LNA043 was administered weekly for 4 weeks for participants with focal cartilage lesions of the knee.

Arm type	Experimental
Investigational medicinal product name	LNA043
Investigational medicinal product code	LNA043A
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intraarticular use

Dosage and administration details:

LNA043 20 mg intra-articular injection

Arm title	Placebo Part A
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Arm description:

Part A: a single intra-articular injection of matching placebo (0 mg) was administered weekly for 4 weeks for participants with focal cartilage lesions of the knee

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intraarticular use

Dosage and administration details:

Matching placebo 0 mg intra-articular injection

Arm title	LNA043 20 mg Part B
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Arm description:

Part B: a single intra-articular injection of 20 mg LNA043 was administered every 4 weeks from Week 1 to Week 13 (4 injections) for participants with osteoarthritis.

Arm type	Experimental
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Investigational medicinal product name	LNA043
Investigational medicinal product code	LNA043A
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intraarticular use
Dosage and administration details: LNA043 20 mg intra-articular injection	
Arm title	LNA043 40 mg Part B

Arm description:

Part B: a single intra-articular injection of 40 mg LNA043 was administered every 4 weeks from Week 1 to Week 13 (4 injections) for participants with osteoarthritis.

Arm type	Experimental
Investigational medicinal product name	LNA043
Investigational medicinal product code	LNA043A
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intraarticular use
Dosage and administration details: LNA043 40 mg intra-articular injection	
Arm title	Placebo Part B

Arm description:

Part B: a single intra-articular injection of matching placebo (0 mg) was administered every 4 weeks from Week 1 to Week 13 (4 injections) for participants with osteoarthritis

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intraarticular use
Dosage and administration details: Matching placebo 0 mg intra-articular injection	

Number of subjects in period 1	LNA043 20 mg Part A	Placebo Part A	LNA043 20 mg Part B
Started	43	15	27
Completed	42	15	27
Not completed	1	0	0
PI decision based on poor veins for blood sampling	-	-	-
Patient discontinued tx, entered followup	1	-	-

Number of subjects in period 1	LNA043 40 mg Part B	Placebo Part B
Started	27	29
Completed	26	29
Not completed	1	0
PI decision based on poor veins for blood sampling	1	-
Patient discontinued tx, entered followup	-	-

Period 2

Period 2 title	Post-treatment follow-up Parts A and B
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	LNA043 20 mg Part A

Arm description:

Part A: a single intra-articular injection of 20 mg LNA043 was administered weekly for 4 weeks for participants with focal cartilage lesions of the knee.

Arm type	Experimental
Investigational medicinal product name	LNA043
Investigational medicinal product code	LNA043A
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intraarticular use

Dosage and administration details:

LNA043 20 mg intra-articular injection

Arm title	Placebo Part A
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Arm description:

Part A: a single intra-articular injection of matching placebo (0 mg) was administered weekly for 4 weeks for participants with focal cartilage lesions of the knee

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intraarticular use

Dosage and administration details:

Matching placebo 0 mg intra-articular injection

Arm title	LNA043 20 mg Part B
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Arm description:

Part B: a single intra-articular injection of 20 mg LNA043 was administered every 4 weeks from Week 1 to Week 13 (4 injections) for participants with osteoarthritis.

Arm type	Experimental
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Investigational medicinal product name	LNA043
Investigational medicinal product code	LNA043A
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intraarticular use
Dosage and administration details: LNA043 20 mg intra-articular injection	
Arm title	LNA043 40 mg Part B

Arm description:

Part B: a single intra-articular injection of 40 mg LNA043 was administered every 4 weeks from Week 1 to Week 13 (4 injections) for participants with osteoarthritis.

Arm type	Experimental
Investigational medicinal product name	LNA043
Investigational medicinal product code	LNA043A
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intraarticular use
Dosage and administration details: LNA043 40 mg intra-articular injection	
Arm title	Placebo Part B

Arm description:

Part B: a single intra-articular injection of matching placebo (0 mg) was administered every 4 weeks from Week 1 to Week 13 (4 injections) for participants with osteoarthritis

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intraarticular use
Dosage and administration details: Matching placebo 0 mg intra-articular injection	

Number of subjects in period 2^[1]	LNA043 20 mg Part A	Placebo Part A	LNA043 20 mg Part B
Started	41	15	27
Completed	39	15	24
Not completed	2	0	3
No longer required treatment	-	-	-
Lost to follow-up	1	-	2
Subject/guardian decision	1	-	1

Number of subjects in period 2^[1]	LNA043 40 mg Part B	Placebo Part B
Started	26	29
Completed	25	28
Not completed	1	1
No longer required treatment	1	-

Lost to follow-up	-	1
Subject/guardian decision	-	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: One participant discontinued the treatment period but entered the follow up period.

Baseline characteristics

Reporting groups

Reporting group title	LNA043 20 mg Part A
Reporting group description: Part A: a single intra-articular injection of 20 mg LNA043 was administered weekly for 4 weeks for participants with focal cartilage lesions of the knee.	
Reporting group title	Placebo Part A
Reporting group description: Part A: a single intra-articular injection of matching placebo (0 mg) was administered weekly for 4 weeks for participants with focal cartilage lesions of the knee	
Reporting group title	LNA043 20 mg Part B
Reporting group description: Part B: a single intra-articular injection of 20 mg LNA043 was administered every 4 weeks from Week 1 to Week 13 (4 injections) for participants with osteoarthritis.	
Reporting group title	LNA043 40 mg Part B
Reporting group description: Part B: a single intra-articular injection of 40 mg LNA043 was administered every 4 weeks from Week 1 to Week 13 (4 injections) for participants with osteoarthritis.	
Reporting group title	Placebo Part B
Reporting group description: Part B: a single intra-articular injection of matching placebo (0 mg) was administered every 4 weeks from Week 1 to Week 13 (4 injections) for participants with osteoarthritis	

Reporting group values	LNA043 20 mg Part A	Placebo Part A	LNA043 20 mg Part B
Number of subjects	43	15	27
Age Categorical Units: participants			
18-64 years	43	15	18
65 - 76	0	0	9
Sex: Female, Male Units:			
Female	21	5	19
Male	22	10	8
Race/Ethnicity, Customized Units: Subjects			
Asian	1	1	0
White	42	11	20
American Indian or Alaska Native	0	1	0
Black or African	0	1	7
American Unknow	0	1	0
Other	0	0	0

Reporting group values	LNA043 40 mg Part B	Placebo Part B	Total
Number of subjects	27	29	141
Age Categorical Units: participants			
18-64 years	15	15	106
65 - 76	12	14	35

Sex: Female, Male			
Units:			
Female	20	21	86
Male	7	8	55
Race/Ethnicity, Customized			
Units: Subjects			
Asian	0	1	3
White	26	24	123
American Indian or Alaska Native	0	0	1
Black or African	1	3	12
American Unknow	0	0	1
Other	0	1	1

End points

End points reporting groups

Reporting group title	LNA043 20 mg Part A
Reporting group description: Part A: a single intra-articular injection of 20 mg LNA043 was administered weekly for 4 weeks for participants with focal cartilage lesions of the knee.	
Reporting group title	Placebo Part A
Reporting group description: Part A: a single intra-articular injection of matching placebo (0 mg) was administered weekly for 4 weeks for participants with focal cartilage lesions of the knee	
Reporting group title	LNA043 20 mg Part B
Reporting group description: Part B: a single intra-articular injection of 20 mg LNA043 was administered every 4 weeks from Week 1 to Week 13 (4 injections) for participants with osteoarthritis.	
Reporting group title	LNA043 40 mg Part B
Reporting group description: Part B: a single intra-articular injection of 40 mg LNA043 was administered every 4 weeks from Week 1 to Week 13 (4 injections) for participants with osteoarthritis.	
Reporting group title	Placebo Part B
Reporting group description: Part B: a single intra-articular injection of matching placebo (0 mg) was administered every 4 weeks from Week 1 to Week 13 (4 injections) for participants with osteoarthritis	
Reporting group title	LNA043 20 mg Part A
Reporting group description: Part A: a single intra-articular injection of 20 mg LNA043 was administered weekly for 4 weeks for participants with focal cartilage lesions of the knee.	
Reporting group title	Placebo Part A
Reporting group description: Part A: a single intra-articular injection of matching placebo (0 mg) was administered weekly for 4 weeks for participants with focal cartilage lesions of the knee	
Reporting group title	LNA043 20 mg Part B
Reporting group description: Part B: a single intra-articular injection of 20 mg LNA043 was administered every 4 weeks from Week 1 to Week 13 (4 injections) for participants with osteoarthritis.	
Reporting group title	LNA043 40 mg Part B
Reporting group description: Part B: a single intra-articular injection of 40 mg LNA043 was administered every 4 weeks from Week 1 to Week 13 (4 injections) for participants with osteoarthritis.	
Reporting group title	Placebo Part B
Reporting group description: Part B: a single intra-articular injection of matching placebo (0 mg) was administered every 4 weeks from Week 1 to Week 13 (4 injections) for participants with osteoarthritis	

Primary: Change from baseline in articular cartilage collagen organization in the overall cartilage (femoral and patellar lesions) - Part A

End point title	Change from baseline in articular cartilage collagen organization in the overall cartilage (femoral and patellar lesions) - Part A ^[1]
End point description: Collagen fibril organization in articular cartilage evaluated by Magnetic Resonance Imaging (MRI) from the cartilage mean T2 relaxation time (with lower values indicative of higher quality). The area of interest is the focal cartilage lesion.	

End point type	Primary
End point timeframe:	
Baseline up to Week 16, Week 28	
Notes:	
[1] - 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: Estimated mean difference was provided.	

End point values	LNA043 20 mg Part A	Placebo Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	15		
Units: ms				
arithmetic mean (standard error)				
Week 16 n=43,14	3.28 (± 9.78)	2.79 (± 16.37)		
Week 28 n=39,15	5.66 (± 9.90)	1.98 (± 15.97)		

Statistical analyses

Statistical analysis title	Week 16
Comparison groups	LNA043 20 mg Part A v Placebo Part A
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.48
Confidence interval	
level	90 %
sides	2-sided
lower limit	-30.73
upper limit	31.69

Statistical analysis title	Week 28
Comparison groups	LNA043 20 mg Part A v Placebo Part A
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	3.68
Confidence interval	
level	90 %
sides	2-sided
lower limit	-27.04
upper limit	34.4

Primary: Change from baseline in articular cartilage collagen organization in the deep cartilage layer (femoral and patellar lesions) - Part A

End point title	Change from baseline in articular cartilage collagen organization in the deep cartilage layer (femoral and patellar lesions) - Part A ^[2]
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End point description:

Collagen fibril organization in articular cartilage evaluated by MRI from the cartilage mean T2 relaxation time (with lower values indicative of higher quality). The area of interest is the focal cartilage lesion.

End point type	Primary
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End point timeframe:

Baseline up to Week 16, Week 28

Notes:

[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: Estimated mean difference was provided.

End point values	LNA043 20 mg Part A	Placebo Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	15		
Units: ms				
arithmetic mean (standard error)				
Week 16 n=41,14	5.30 (± 9.17)	3.61 (± 15.46)		
Week 28 n=39,15	7.86 (± 9.36)	1.90 (± 15.08)		

Statistical analyses

Statistical analysis title	Week 28
Comparison groups	LNA043 20 mg Part A v Placebo Part A
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	5.97
Confidence interval	
level	90 %
sides	2-sided
lower limit	-23.03
upper limit	34.97

Statistical analysis title	Week 16
Comparison groups	LNA043 20 mg Part A v Placebo Part A

Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.69
Confidence interval	
level	90 %
sides	2-sided
lower limit	-27.7
upper limit	31.08

Primary: Change from baseline in articular cartilage collagen organization in the superficial cartilage layer (femoral and patellar lesions) - Part A

End point title	Change from baseline in articular cartilage collagen organization in the superficial cartilage layer (femoral and patellar lesions) - Part A ^[3]
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End point description:

Collagen fibril organization in articular cartilage evaluated by MRI from the cartilage mean T2 relaxation time (with lower values indicative of higher quality).The area of interest is the focal cartilage lesion.

End point type	Primary
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End point timeframe:

Baseline up to Week 16, Week 28

Notes:

[3] - 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: Estimated mean difference was provided.

End point values	LNA043 20 mg Part A	Placebo Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	15		
Units: ms				
arithmetic mean (standard error)				
Week 16 n=17,7	-13.05 (± 15.68)	-13.93 (± 24.73)		
Week 28 n=16,9	-10.45 (± 16.61)	-12.73 (± 22.09)		

Statistical analyses

Statistical analysis title	Week 28
Comparison groups	LNA043 20 mg Part A v Placebo Part A

Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	2.27
Confidence interval	
level	90 %
sides	2-sided
lower limit	-43.11
upper limit	47.65

Statistical analysis title	Week 16
Comparison groups	LNA043 20 mg Part A v Placebo Part A
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.88
Confidence interval	
level	90 %
sides	2-sided
lower limit	-47.27
upper limit	49.04

Primary: Change from baseline of LNA043 to placebo in cartilage volume in the femoral medial index region (mm3) - Part B

End point title	Change from baseline of LNA043 to placebo in cartilage volume in the femoral medial index region (mm3) - Part B ^[4]
End point description:	MRI based quantitative assessment using an automated segmentation algorithm
End point type	Primary
End point timeframe:	Baseline, Week 29, Week 53

Notes:

[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: Estimated mean difference was provided.

End point values	LNA043 20 mg Part B	LNA043 40 mg Part B	Placebo Part B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	27	29	
Units: mm3				
arithmetic mean (standard error)				
Week 29 n=12,13,13	45.52 (± 61.90)	-12.79 (± 60.38)	-154.7 (± 60.25)	

Week 53 n=11,13,7	75.64 ($\pm$ 54.48)	-36.52 ($\pm$ 51.21)	-152.7 ($\pm$ 67.72)	
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Statistical analyses

Statistical analysis title	Week 29
Comparison groups	LNA043 20 mg Part B v Placebo Part B
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0131
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	200.18
Confidence interval	
level	90 %
sides	2-sided
lower limit	54.53
upper limit	345.83

Statistical analysis title	Week 53
Comparison groups	LNA043 20 mg Part B v Placebo Part B
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0067
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	228.27
Confidence interval	
level	90 %
sides	2-sided
lower limit	80.87
upper limit	375.67

Statistical analysis title	Week 53
Comparison groups	LNA043 40 mg Part B v Placebo Part B

Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0931
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	116.21
Confidence interval	
level	90 %
sides	2-sided
lower limit	-29.52
upper limit	261.94

Statistical analysis title	Week 29
Comparison groups	LNA043 40 mg Part B v Placebo Part B
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0544
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	141.87
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.83
upper limit	287.56

Primary: Change from baseline of LNA043 to placebo in cartilage thickness in the femoral medial index region (mm) - Part B

End point title	Change from baseline of LNA043 to placebo in cartilage thickness in the femoral medial index region (mm) - Part B ^[5]
End point description:	MRI based quantitative assessment using an automated segmentation algorithm.
End point type	Primary
End point timeframe:	Baseline, Week 29, Week 53

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: Estimated mean difference was provided.

End point values	LNA043 20 mg Part B	LNA043 40 mg Part B	Placebo Part B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	27	29	
Units: mm				
arithmetic mean (standard error)				
Week 29 n=12,13,13	0.01 ($\pm$ 0.02)	0.02 ($\pm$ 0.02)	-0.04 ($\pm$ 0.02)	
Week 53 n=11,13,7	-0.01 ($\pm$ 0.02)	-0.00 ($\pm$ 0.02)	-0.02 ($\pm$ 0.03)	

Statistical analyses

Statistical analysis title	Week 29
Comparison groups	LNA043 20 mg Part B v Placebo Part B
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0574
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.05
Confidence interval	
level	90 %
sides	2-sided
lower limit	0
upper limit	0.1

Statistical analysis title	Week 53
Comparison groups	LNA043 20 mg Part B v Placebo Part B
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3864
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.05
upper limit	0.07

Statistical analysis title	Week 53
Comparison groups	LNA043 40 mg Part B v Placebo Part B

Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.329
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.05
upper limit	0.08

Statistical analysis title	Week 29
Comparison groups	LNA043 40 mg Part B v Placebo Part B
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0248
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.06
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.01
upper limit	0.11

Secondary: Change from baseline of LNA043 to placebo in cartilage defect volume (mm3) for both groups of patients (femoral and patellar lesions) - Part A

End point title	Change from baseline of LNA043 to placebo in cartilage defect volume (mm3) for both groups of patients (femoral and patellar lesions) - Part A ^[6]
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End point description:

Cartilage volume data were generated from the manual segmentation of the cartilage defect that was identified in MR images.

End point type	Secondary
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End point timeframe:

Baseline up to Week 16, Week 28

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: Estimated mean difference was provided.

End point values	LNA043 20 mg Part A	Placebo Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	15		
Units: mm				
arithmetic mean (standard error)				
Week 16 n=40,14	-2.42 (± 8.27)	-7.17 (± 13.64)		
Week 28 n=39,15	-11.88 (± 8.27)	-4.57 (± 13.45)		

Statistical analyses

Statistical analysis title	Week 16
Comparison groups	LNA043 20 mg Part A v Placebo Part A
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6184
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	4.75
Confidence interval	
level	90 %
sides	2-sided
lower limit	-21.36
upper limit	30.85

Statistical analysis title	Week 28
Comparison groups	LNA043 20 mg Part A v Placebo Part A
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3194
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-7.32
Confidence interval	
level	90 %
sides	2-sided
lower limit	-33.16
upper limit	18.53

Secondary: Change from baseline in cartilage mean T2 relaxation time as a marker of collagen organization in the medial femoral index region - Overall Part B

End point title	Change from baseline in cartilage mean T2 relaxation time as a marker of collagen organization in the medial femoral index region - Overall Part B ^[7]
End point description:	Collagen fibril organisation in articular cartilage evaluated by MRI from the cartilage mean T2 relaxation time (with lower values indicative of higher quality). The area of interest is the femoral medial index region comprising the anterior, central and posterior aspects of the femoral condyle.
End point type	Secondary
End point timeframe:	Baseline, Week 29, Week 53

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: Estimated mean difference was provided.

End point values	LNA043 20 mg Part B	LNA043 40 mg Part B	Placebo Part B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	27	29	
Units: ms				
arithmetic mean (standard error)				
Week 29 n=21,21,25	-1.59 (± 2.25)	-5.07 (± 2.26)	-4.97 (± 2.07)	
Week 53 n=20,22,22	-4.23 (± 2.29)	-10.53 (± 2.25)	-3.09 (± 2.18)	

Statistical analyses

Statistical analysis title	Week 29
Comparison groups	LNA043 20 mg Part B v Placebo Part B
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	3.38
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.72
upper limit	8.47

Statistical analysis title	Week 29
Comparison groups	LNA043 40 mg Part B v Placebo Part B

Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-5.22
upper limit	5.01

Statistical analysis title	Week 53
Comparison groups	LNA043 20 mg Part B v Placebo Part B
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.14
Confidence interval	
level	90 %
sides	2-sided
lower limit	-6.42
upper limit	4.15

Statistical analysis title	Week 53
Comparison groups	LNA043 40 mg Part B v Placebo Part B
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-7.44
Confidence interval	
level	90 %
sides	2-sided
lower limit	-12.68
upper limit	-2.2

Secondary: Change from baseline in cartilage mean T2 relaxation time as a marker of collagen organization in the median femoral index region - Deep Part B

End point title	Change from baseline in cartilage mean T2 relaxation time as a marker of collagen organization in the median femoral index
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End point description:

Collagen fibril organisation in articular cartilage evaluated by MRI from the cartilage mean T2 relaxation time (with lower values indicative of higher quality). The area of interest is the femoral medial index region comprising the anterior, central and posterior aspects of the femoral condyle.

End point type	Secondary
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End point timeframe:

Baseline, Week 29, Week 53

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: Estimated mean difference was provided.

End point values	LNA043 20 mg Part B	LNA043 40 mg Part B	Placebo Part B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	27	29	
Units: ms				
arithmetic mean (standard error)				
Week 29 n=21,21,25	-3.80 (± 2.47)	-5.07 (± 2.49)	-5.89 (± 2.26)	
Week 53 n=20,22,22	-3.93 (± 2.53)	-12.17 (± 2.54)	-6.21 (± 2.41)	

Statistical analyses

Statistical analysis title	Week 29
Comparison groups	LNA043 20 mg Part B v Placebo Part B
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	2.09
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.49
upper limit	7.66

Statistical analysis title	Week 53
Comparison groups	LNA043 40 mg Part B v Placebo Part B
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-5.96

Confidence interval	
level	90 %
sides	2-sided
lower limit	-11.81
upper limit	-0.1

Statistical analysis title	Week 53
Comparison groups	LNA043 20 mg Part B v Placebo Part B
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	2.29
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3.54
upper limit	8.11

Statistical analysis title	Week 29
Comparison groups	LNA043 40 mg Part B v Placebo Part B
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.82
Confidence interval	
level	90 %
sides	2-sided
lower limit	-4.82
upper limit	6.45

Secondary: Incidence of immunogenicity (IG) Part A

End point title	Incidence of immunogenicity (IG) Part A ^[9]
End point description:	
A validated ligand binding assay were used for the detection of anti-LNA043 antibodies, and cross-reactivity to ANGPTL3 and ANGPTL4.	
End point type	Secondary
End point timeframe:	
Week 1,3,8,16,28	

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: No analysis was done

End point values	LNA043 20 mg Part A	Placebo Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	15		
Units: participants				
Week 1 (Day 1) Predose	0	0		
Week 3 (Day 15) Pre-dose	0	0		
Week 8 (Day 50)	0	0		
Week 16 (Day 106)	0	0		
Week 28 (Day 190)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in cartilage mean T2 relaxation time as a marker of collagen organization in the medial femoral index region - Superficial Part B

End point title	Change from baseline in cartilage mean T2 relaxation time as a marker of collagen organization in the medial femoral index region - Superficial Part B ^[10]
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End point description:

Collagen fibril organisation in articular cartilage evaluated by MRI from the cartilage mean T2 relaxation time (with lower values indicative of higher quality). The area of interest is the femoral medial index region comprising the anterior, central and posterior aspects of the femoral condyle.

End point type	Secondary
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End point timeframe:

Baseline, Week 29, Week 53

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: Estimated mean difference was provided.

End point values	LNA043 20 mg Part B	LNA043 40 mg Part B	Placebo Part B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	27	29	
Units: ms				
arithmetic mean (standard error)				
Week 29 n=21,21,25	-0.06 (± 2.51)	-4.16 (± 2.51)	-3.53 (± 2.30)	
Week 53 n=20,22,22	-3.54 (± 2.36)	-9.07 (± 2.36)	-0.91 (± 2.25)	

Statistical analyses

Statistical analysis title	Week 29
Comparison groups	LNA043 20 mg Part B v Placebo Part B
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	3.47
Confidence interval	
level	90 %
sides	2-sided
lower limit	-2.21
upper limit	9.15

Statistical analysis title	Week 53
Comparison groups	LNA043 40 mg Part B v Placebo Part B
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-8.16
Confidence interval	
level	90 %
sides	2-sided
lower limit	-13.61
upper limit	-2.72

Statistical analysis title	Week 53
Comparison groups	LNA043 20 mg Part B v Placebo Part B
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-2.63
Confidence interval	
level	90 %
sides	2-sided
lower limit	-8.07
upper limit	2.82

Statistical analysis title	Week 29
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Comparison groups	LNA043 40 mg Part B v Placebo Part B
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.63
Confidence interval	
level	90 %
sides	2-sided
lower limit	-6.31
upper limit	5.04

Secondary: Incidence of immunogenicity (IG) Part B

End point title	Incidence of immunogenicity (IG) Part B ^[11]
End point description: A validated ligand binding assay were used for the detection of anti-LNA043 antibodies, and cross-reactivity to ANGPTL3 and ANGPTL4.	
End point type	Secondary
End point timeframe: Week 1,5,9,13,17,29,53	

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: No analysis was done

End point values	LNA043 20 mg Part B	LNA043 40 mg Part B	Placebo Part B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	27	29	
Units: participants				
Week 1 (Day 1) Predose	0	0	0	
Week 5 Pre-dose	0	0	0	
Week 9	0	0	0	
Week 13	0	0	0	
Week 17	0	0	0	
Week 29	0	0	0	
Week 53	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Serum concentrations of LNA043 - Part A

End point title	Serum concentrations of LNA043 - Part A ^[12]
End point description: Concentrations for LNA043 were determined by a validated LC-MS/MS method; the anticipated LLOQ	

was 10ng/mL in serum. Concentrations below the LLOQ were reported as "zero"

End point type	Secondary
End point timeframe:	
Week 1: 0 (pre-dose), 0.25 hours, 1, 2 hours post dose; Weeks 2, 3, 4: 0 hour (pre dose), 1 hour post dose	
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: No analysis was done	

End point values	LNA043 20 mg Part A			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 1, 0 hour pre-dose n=43,	0.00 (± 0.00)			
Week 1, 0.25 hour post dose n=6	24.9 (± 16.3)			
Week 1, 1 hour post dose n=7	65.1 (± 30.2)			
Week 1, 2 hours post dose n=41	64.9 (± 37.5)			
Week 2, 0 hour pre dose n=42	0.00 (± 0.00)			
Week 2, 1 hour post dose n=43	48.1 (± 32.9)			
Week 3, 0 hour pre dose n=41	0.00 (± 0.00)			
Week 3, 1 hour post dose n=39	51.0 (± 37.6)			
Week 4, 0 hour pre dose n=42	3.00 (± 19.4)			
Week 4, 1 hour post dose n=41	52.9 (± 38.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum concentrations of ANGPTL3 - Part A

End point title	Serum concentrations of ANGPTL3 - Part A ^[13]
End point description:	
Validated bioanalytical assays were used to determine ANGPTL3 in serum with an LLOQ of 2.13 ng/mL. Concentrations below the LLOQ were reported as "zero"	
End point type	Secondary
End point timeframe:	
Week 1: 0 (pre-dose), 0.25 hours, 1, 2 hours post dose; Weeks 2, 3, 4: 0 hour (pre dose), 1 hour post dose	
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: No analysis done	

End point values	LNA043 20 mg Part A	Placebo Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	15		
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 1, 0 hour pre-dose n=41,14	19.1 (± 9.29)	23.3 (± 8.55)		
Week 1, 0.25 hour post dose n=6,2	20.8 (± 8.12)	20.4 (± 6.36)		
Week 1, 1 hour post dose n=7,2	19.7 (± 8.65)	18.2 (± 3.32)		
Week 1, 2 hours post dose n=40,15	18.9 (± 9.38)	24.3 (± 9.52)		
Week 2,0 hour pre dose n=42,15	18.9 (± 10.3)	21.7 (± 10.2)		
Week 2, 1 hour post dose n=42,15	18.3 (± 8.06)	19.7 (± 9.58)		
Week 3, 0 hour pre dose n=42,14	19.1 (± 7.79)	24.2 (± 9.95)		
Week 3, 1 hour post dose n=39,14	18.5 (± 7.35)	28.9 (± 16.4)		
Week 4, 0 hour pre dose n=42,15	19.6 (± 8.71)	21.0 (± 7.11)		
Week 4, 1 hour post dose n=41,15	19.6 (± 7.87)	22.6 (± 9.06)		

Statistical analyses

No statistical analyses for this end point

Secondary: Synovial Fluid concentrations of LNA043 - Part A

End point title	Synovial Fluid concentrations of LNA043 - Part A ^[14]
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End point description:

Concentrations for LNA043 were determined by a validated LC-MS/MS method; the anticipated LLOQ was 10ng/mL in synovial fluid. Concentrations below the LLOQ were reported as "zero".

End point type	Secondary
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End point timeframe:

Weeks 1,2,3,4: 0 hour (pre-dose)

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: No analysis was done

End point values	LNA043 20 mg Part A			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[15]			
Units: ng/mL				
arithmetic mean (standard deviation)	()			

Notes:

[15] - LNA043 Stability in synovial fluid could not be demonstrated.

Statistical analyses

No statistical analyses for this end point

Secondary: Synovial Fluid concentrations of ANGPTL3 - Part A

End point title	Synovial Fluid concentrations of ANGPTL3 - Part A ^[16]
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End point description:

Validated bioanalytical assays were used to determine ANGPTL3 in synovial fluid with an LLOQ of 2.74 ng/mL. Concentrations below the LLOQ were reported as "zero".

End point type Secondary

End point timeframe:

Weeks 1,2,3,4: 0 hour (pre-dose)

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: No analysis was done

End point values	LNA043 20 mg Part A	Placebo Part A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	15		
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 1, 0 hour pre-dose n=8,3	0.00 (± 0.00)	00.0 (± 00.0)		
Week 2, 0 hour pre dose n=11,5	0.00 (± 0.00)	00.0 (± 00.0)		
Week 3, 0 hour pre dose n=13,4	0.616 (± 2.22)	00.0 (± 00.0)		
Week 4, 0 hour pre dose n=15,3	1.42 (± 5.50)	00.0 (± 00.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Serum concentrations of ANGPTL3 - Part B

End point title Serum concentrations of ANGPTL3 - Part B^[17]

End point description:

Validated bioanalytical assays were used to determine ANGPTL3 in serum with an LLOQ of 2.13 ng/mL. Concentrations below the LLOQ were reported as "zero".

End point type Secondary

End point timeframe:

Week 1: 0 (pre-dose), 1, 2 hours post dose; Weeks 2, 3, 4: 0 hour (pre dose), 1 hour post dose

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: No analysis was done

End point values	LNA043 20 mg Part B	LNA043 40 mg Part B	Placebo Part B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	26	29	
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 1, 0 hour pre-dose n=27,26,29	25.3 (± 11.1)	21.9 (± 9.09)	26.6 (± 14.0)	
Week 1, 2 hours post dose n=24,24,26	26.0 (± 12.8)	23.9 (± 10.6)	27.6 (± 13.1)	
Week 5, 1 hour post dose n=26,26,28	21.8 (± 9.80)	23.3 (± 9.97)	26.2 (± 10.8)	
Week 13, 1 hour post dose n=27,25,28	22.9 (± 8.72)	22.5 (± 8.39)	24.8 (± 11.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Serum concentrations of LNA043 - Part B

End point title	Serum concentrations of LNA043 - Part B ^[18]
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End point description:

Concentrations for LNA043 were determined by a validated LC-MS/MS method; the anticipated LLOQ was 10ng/mL in serum. Concentrations below the LLOQ were reported as "zero"

End point type	Secondary
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End point timeframe:

Week 1: 0 (pre-dose), 2 hours post dose; Weeks 5 and 13: 1 hour post dose

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: No analysis was done

End point values	LNA043 20 mg Part B	LNA043 40 mg Part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 1, 0 hours pre-dose n=27,26	3.48 (± 18.1)	7.96 (± 40.6)		
Week 1, 2 hours post dose n=24,24,	76.4 (± 51.0)	158 (± 94.0)		
Week 5, 1 hour post dose n=27,26	55.6 (± 47.0)	101 (± 74.2)		
Week 13, 1 hour post dose n=27,25	59.5 (± 53.0)	118 (± 78.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Synovial Fluid concentrations of LNA043 Part B

End point title	Synovial Fluid concentrations of LNA043 Part B ^[19]
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End point description:

Concentrations for LNA043 were determined by a validated LC-MS/MS method; the anticipated LLOQ was 10ng/mL in synovial fluid. Concentrations below the LLOQ were reported as "zero".

End point type	Secondary
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End point timeframe:

Weeks 1,5,9,13: 0 hour (pre-dose)

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: No analysis was done

End point values	LNA043 20 mg Part B	LNA043 40 mg Part B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 1, 0 hours pre dose n=9,5	28.9 (± 86.7)	0.00 (± 0.00)		
Week 5, 0 hours pre dose n=10,5	368 (± 1160)	18.1 (± 40.6)		
Week 9, 0 hours pre-dose n=11,6	0.00 (± 0.00)	43600 (± 90900)		
Week 13, 0 hours pre dose n=8,4	0.00 (± 0.00)	199000 (± 398000)		

Statistical analyses

No statistical analyses for this end point

Secondary: Synovial Fluid concentrations of ANGPTL3 - Part B

End point title	Synovial Fluid concentrations of ANGPTL3 - Part B ^[20]
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End point description:

Validated bioanalytical assays were used to determine ANGPTL3 in synovial fluid with an LLOQ of 2.74 ng/mL. Concentrations below the LLOQ were reported as "zero".

End point type	Secondary
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End point timeframe:

Weeks 1,5.9.13: 0 hour (pre-dose)

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: No analysis was done

End point values	LNA043 20 mg Part B	LNA043 40 mg Part B	Placebo Part B	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	27	29	
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 1, 0 hour pre-dose n=8,3,8	0.00 (± 0.00)	0.00 (± 0.00)	0.00 (± 0.00)	
0.00Week 5,,0 hour pre dose n=10,5,12	1.00 (± 3.16)	4.38 (± 9.79)	1.57 (± 5.43)	
Week 9,, 0 hour pre dose n=8,4,9	0.00 (± 0.00)	0.00 (± 0.00)	0.00 (± 0.00)	
Week 13, 0 hour pre dose n=7,4,8	0.00 (± 0.00)	1.87 (± 3.74)	0.890 (± 2.52)	

Statistical analyses

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 of 99 days plus 30 days post treatment, up to maximum duration of approximately 129 days.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	LNA043 20mg
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Reporting group description:

LNA043 20mg

Reporting group title	PLACEBO
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Reporting group description:

PLACEBO

Reporting group title	Total-Part A
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Reporting group description:

Total-Part A

Reporting group title	Total-Part B
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Reporting group description:

Total-Part B

Reporting group title	LNA043 40mg@in Part B
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Reporting group description:

LNA043 40mg@in Part B

Reporting group title	PLACEBO@in Part B
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Reporting group description:

PLACEBO@in Part B

Reporting group title	LNA043 20mg@in Part B
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Reporting group description:

LNA043 20mg@in Part B

Serious adverse events	LNA043 20mg	PLACEBO	Total-Part A
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 43 (0.00%)	0 / 15 (0.00%)	0 / 58 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	0 / 43 (0.00%)	0 / 15 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Total-Part B	LNA043 40mg@in Part B	PLACEBO@in Part B
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 83 (1.20%)	0 / 27 (0.00%)	0 / 29 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 27 (0.00%)	0 / 29 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	LNA043 20mg@in Part B		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 27 (3.70%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	LNA043 20mg	PLACEBO	Total-Part A
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 43 (44.19%)	7 / 15 (46.67%)	26 / 58 (44.83%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 43 (0.00%)	0 / 15 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 43 (0.00%)	0 / 15 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			

Injection site haematoma subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 15 (0.00%) 0	0 / 58 (0.00%) 0
Injection site erythema subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 15 (0.00%) 0	0 / 58 (0.00%) 0
Injection site bruising subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 15 (0.00%) 0	0 / 58 (0.00%) 0
Inflammation subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 15 (0.00%) 0	1 / 58 (1.72%) 1
Injection site joint erythema subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 15 (0.00%) 0	0 / 58 (0.00%) 0
Peripheral swelling subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 15 (0.00%) 0	0 / 58 (0.00%) 0
Injection site joint pain subjects affected / exposed occurrences (all)	2 / 43 (4.65%) 2	0 / 15 (0.00%) 0	2 / 58 (3.45%) 2
Pyrexia subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 15 (0.00%) 0	1 / 58 (1.72%) 1
Vessel puncture site haemorrhage subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 15 (0.00%) 0	1 / 58 (1.72%) 1
Reproductive system and breast disorders Atrophic vulvovaginitis subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 15 (0.00%) 0	0 / 58 (0.00%) 0
Ovulation pain subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 15 (0.00%) 0	1 / 58 (1.72%) 1
Respiratory, thoracic and mediastinal disorders			

Nasal congestion subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	1 / 15 (6.67%) 1	1 / 58 (1.72%) 1
Psychiatric disorders Sleep disorder subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 15 (0.00%) 0	0 / 58 (0.00%) 0
Investigations Cardiac murmur subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 15 (0.00%) 0	0 / 58 (0.00%) 0
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 15 (0.00%) 0	1 / 58 (1.72%) 1
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 15 (0.00%) 0	0 / 58 (0.00%) 0
Haematology test abnormal subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 15 (0.00%) 0	0 / 58 (0.00%) 0
Urine protein/creatinine ratio increased subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 15 (0.00%) 0	0 / 58 (0.00%) 0
SARS-CoV-2 test positive subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 15 (0.00%) 0	0 / 58 (0.00%) 0
Injury, poisoning and procedural complications Tooth fracture subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 15 (0.00%) 0	0 / 58 (0.00%) 0
Tendon injury subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 15 (0.00%) 0	0 / 58 (0.00%) 0
Skin abrasion			

subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 15 (0.00%) 0	0 / 58 (0.00%) 0
Limb injury subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 15 (0.00%) 0	1 / 58 (1.72%) 1
Ligament sprain subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 15 (0.00%) 0	0 / 58 (0.00%) 0
Fall subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	1 / 15 (6.67%) 1	2 / 58 (3.45%) 2
Traumatic haematoma subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 15 (0.00%) 0	0 / 58 (0.00%) 0
Nervous system disorders Syncope subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 15 (0.00%) 0	0 / 58 (0.00%) 0
Paraesthesia subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 15 (0.00%) 0	1 / 58 (1.72%) 1
Headache subjects affected / exposed occurrences (all)	6 / 43 (13.95%) 9	1 / 15 (6.67%) 1	7 / 58 (12.07%) 10
Dizziness subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 15 (0.00%) 0	1 / 58 (1.72%) 1
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 15 (0.00%) 0	0 / 58 (0.00%) 0
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 15 (0.00%) 0	1 / 58 (1.72%) 1
Dental caries			

subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	1 / 15 (6.67%) 1	1 / 58 (1.72%) 1
Skin and subcutaneous tissue disorders			
Lichenoid keratosis			
subjects affected / exposed	0 / 43 (0.00%)	0 / 15 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Eczema			
subjects affected / exposed	0 / 43 (0.00%)	0 / 15 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Dermatitis contact			
subjects affected / exposed	0 / 43 (0.00%)	0 / 15 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	1 / 43 (2.33%)	0 / 15 (0.00%)	1 / 58 (1.72%)
occurrences (all)	1	0	1
Renal and urinary disorders			
Microalbuminuria			
subjects affected / exposed	0 / 43 (0.00%)	0 / 15 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	0 / 43 (0.00%)	0 / 15 (0.00%)	0 / 58 (0.00%)
occurrences (all)	0	0	0
Arthralgia			
subjects affected / exposed	3 / 43 (6.98%)	1 / 15 (6.67%)	4 / 58 (6.90%)
occurrences (all)	3	1	4
Back pain			
subjects affected / exposed	1 / 43 (2.33%)	1 / 15 (6.67%)	2 / 58 (3.45%)
occurrences (all)	1	1	2
Joint swelling			
subjects affected / exposed	4 / 43 (9.30%)	0 / 15 (0.00%)	4 / 58 (6.90%)
occurrences (all)	7	0	7
Pain in extremity			
subjects affected / exposed	1 / 43 (2.33%)	0 / 15 (0.00%)	1 / 58 (1.72%)
occurrences (all)	1	0	1
Neck pain			

subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 15 (0.00%) 0	0 / 58 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 15 (0.00%) 0	1 / 58 (1.72%) 1
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 15 (0.00%) 0	0 / 58 (0.00%) 0
COVID-19 pneumonia subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 15 (0.00%) 0	0 / 58 (0.00%) 0
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	1 / 15 (6.67%) 1	1 / 58 (1.72%) 1
Herpes zoster subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 15 (0.00%) 0	1 / 58 (1.72%) 1
Infected dermal cyst subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 15 (0.00%) 0	0 / 58 (0.00%) 0
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 43 (0.00%) 0	0 / 15 (0.00%) 0	0 / 58 (0.00%) 0
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	1 / 15 (6.67%) 1	2 / 58 (3.45%) 2
Tonsillitis subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	0 / 15 (0.00%) 0	1 / 58 (1.72%) 1
Respiratory tract infection viral subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1	1 / 15 (6.67%) 1	2 / 58 (3.45%) 2

Non-serious adverse events	Total-Part B	LNA043 40mg@in Part B	PLACEBO@in Part B
Total subjects affected by non-serious adverse events			

subjects affected / exposed	31 / 83 (37.35%)	15 / 27 (55.56%)	10 / 29 (34.48%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 83 (1.20%)	0 / 27 (0.00%)	1 / 29 (3.45%)
occurrences (all)	1	0	1
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 83 (1.20%)	1 / 27 (3.70%)	0 / 29 (0.00%)
occurrences (all)	1	1	0
General disorders and administration site conditions			
Injection site haematoma			
subjects affected / exposed	1 / 83 (1.20%)	1 / 27 (3.70%)	0 / 29 (0.00%)
occurrences (all)	1	1	0
Injection site erythema			
subjects affected / exposed	1 / 83 (1.20%)	1 / 27 (3.70%)	0 / 29 (0.00%)
occurrences (all)	1	1	0
Injection site bruising			
subjects affected / exposed	1 / 83 (1.20%)	0 / 27 (0.00%)	1 / 29 (3.45%)
occurrences (all)	1	0	1
Inflammation			
subjects affected / exposed	0 / 83 (0.00%)	0 / 27 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Injection site joint erythema			
subjects affected / exposed	1 / 83 (1.20%)	1 / 27 (3.70%)	0 / 29 (0.00%)
occurrences (all)	1	1	0
Peripheral swelling			
subjects affected / exposed	1 / 83 (1.20%)	1 / 27 (3.70%)	0 / 29 (0.00%)
occurrences (all)	1	1	0
Injection site joint pain			
subjects affected / exposed	2 / 83 (2.41%)	1 / 27 (3.70%)	1 / 29 (3.45%)
occurrences (all)	2	1	1
Pyrexia			
subjects affected / exposed	0 / 83 (0.00%)	0 / 27 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Vessel puncture site haemorrhage			

subjects affected / exposed occurrences (all)	0 / 83 (0.00%) 0	0 / 27 (0.00%) 0	0 / 29 (0.00%) 0
Reproductive system and breast disorders			
Atrophic vulvovaginitis subjects affected / exposed occurrences (all)	1 / 83 (1.20%) 1	1 / 27 (3.70%) 1	0 / 29 (0.00%) 0
Ovulation pain subjects affected / exposed occurrences (all)	0 / 83 (0.00%) 0	0 / 27 (0.00%) 0	0 / 29 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Nasal congestion subjects affected / exposed occurrences (all)	0 / 83 (0.00%) 0	0 / 27 (0.00%) 0	0 / 29 (0.00%) 0
Psychiatric disorders			
Sleep disorder subjects affected / exposed occurrences (all)	1 / 83 (1.20%) 1	1 / 27 (3.70%) 1	0 / 29 (0.00%) 0
Investigations			
Cardiac murmur subjects affected / exposed occurrences (all)	1 / 83 (1.20%) 1	1 / 27 (3.70%) 1	0 / 29 (0.00%) 0
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	2 / 83 (2.41%) 2	1 / 27 (3.70%) 1	0 / 29 (0.00%) 0
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 83 (1.20%) 1	1 / 27 (3.70%) 1	0 / 29 (0.00%) 0
Haematology test abnormal subjects affected / exposed occurrences (all)	1 / 83 (1.20%) 1	0 / 27 (0.00%) 0	0 / 29 (0.00%) 0
Urine protein/creatinine ratio increased subjects affected / exposed occurrences (all)	2 / 83 (2.41%) 2	1 / 27 (3.70%) 1	1 / 29 (3.45%) 1
SARS-CoV-2 test positive			

subjects affected / exposed occurrences (all)	1 / 83 (1.20%) 1	0 / 27 (0.00%) 0	0 / 29 (0.00%) 0
Injury, poisoning and procedural complications			
Tooth fracture			
subjects affected / exposed	1 / 83 (1.20%)	0 / 27 (0.00%)	1 / 29 (3.45%)
occurrences (all)	1	0	1
Tendon injury			
subjects affected / exposed	1 / 83 (1.20%)	0 / 27 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0
Skin abrasion			
subjects affected / exposed	1 / 83 (1.20%)	0 / 27 (0.00%)	1 / 29 (3.45%)
occurrences (all)	1	0	1
Limb injury			
subjects affected / exposed	0 / 83 (0.00%)	0 / 27 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	1 / 83 (1.20%)	1 / 27 (3.70%)	0 / 29 (0.00%)
occurrences (all)	1	1	0
Fall			
subjects affected / exposed	0 / 83 (0.00%)	0 / 27 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Traumatic haematoma			
subjects affected / exposed	1 / 83 (1.20%)	1 / 27 (3.70%)	0 / 29 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 83 (1.20%)	1 / 27 (3.70%)	0 / 29 (0.00%)
occurrences (all)	1	1	0
Paraesthesia			
subjects affected / exposed	0 / 83 (0.00%)	0 / 27 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	0 / 83 (0.00%)	0 / 27 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Dizziness			

subjects affected / exposed occurrences (all)	0 / 83 (0.00%) 0	0 / 27 (0.00%) 0	0 / 29 (0.00%) 0
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 83 (1.20%) 1	0 / 27 (0.00%) 0	1 / 29 (3.45%) 1
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Dental caries subjects affected / exposed occurrences (all)	0 / 83 (0.00%) 0 0 / 83 (0.00%) 0	0 / 27 (0.00%) 0 0 / 27 (0.00%) 0	0 / 29 (0.00%) 0 0 / 29 (0.00%) 0
Skin and subcutaneous tissue disorders Lichenoid keratosis subjects affected / exposed occurrences (all) Eczema subjects affected / exposed occurrences (all) Dermatitis contact subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	1 / 83 (1.20%) 1 1 / 83 (1.20%) 1 1 / 83 (1.20%) 1 1 / 83 (1.20%) 1	0 / 27 (0.00%) 0 1 / 27 (3.70%) 1 1 / 27 (3.70%) 1 0 / 27 (0.00%) 0	1 / 29 (3.45%) 1 0 / 29 (0.00%) 0 0 / 29 (0.00%) 0 1 / 29 (3.45%) 1
Renal and urinary disorders Microalbuminuria subjects affected / exposed occurrences (all)	1 / 83 (1.20%) 1	1 / 27 (3.70%) 1	0 / 29 (0.00%) 0
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all) Arthralgia	1 / 83 (1.20%) 1	0 / 27 (0.00%) 0	1 / 29 (3.45%) 1

subjects affected / exposed	6 / 83 (7.23%)	4 / 27 (14.81%)	1 / 29 (3.45%)
occurrences (all)	9	7	1
Back pain			
subjects affected / exposed	1 / 83 (1.20%)	0 / 27 (0.00%)	1 / 29 (3.45%)
occurrences (all)	1	0	1
Joint swelling			
subjects affected / exposed	5 / 83 (6.02%)	1 / 27 (3.70%)	3 / 29 (10.34%)
occurrences (all)	5	1	3
Pain in extremity			
subjects affected / exposed	1 / 83 (1.20%)	1 / 27 (3.70%)	0 / 29 (0.00%)
occurrences (all)	1	1	0
Neck pain			
subjects affected / exposed	1 / 83 (1.20%)	0 / 27 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	1 / 83 (1.20%)	1 / 27 (3.70%)	0 / 29 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 83 (1.20%)	1 / 27 (3.70%)	0 / 29 (0.00%)
occurrences (all)	1	1	0
COVID-19 pneumonia			
subjects affected / exposed	1 / 83 (1.20%)	0 / 27 (0.00%)	0 / 29 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	0 / 83 (0.00%)	0 / 27 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			
subjects affected / exposed	0 / 83 (0.00%)	0 / 27 (0.00%)	0 / 29 (0.00%)
occurrences (all)	0	0	0
Infected dermal cyst			
subjects affected / exposed	1 / 83 (1.20%)	1 / 27 (3.70%)	0 / 29 (0.00%)
occurrences (all)	1	1	0
Urinary tract infection			
subjects affected / exposed	1 / 83 (1.20%)	1 / 27 (3.70%)	0 / 29 (0.00%)
occurrences (all)	1	1	0

Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 83 (0.00%) 0	0 / 27 (0.00%) 0	0 / 29 (0.00%) 0
Tonsillitis subjects affected / exposed occurrences (all)	0 / 83 (0.00%) 0	0 / 27 (0.00%) 0	0 / 29 (0.00%) 0
Respiratory tract infection viral subjects affected / exposed occurrences (all)	0 / 83 (0.00%) 0	0 / 27 (0.00%) 0	0 / 29 (0.00%) 0

Non-serious adverse events	LNA043 20mg@in Part B		
Total subjects affected by non-serious adverse events subjects affected / exposed	6 / 27 (22.22%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Squamous cell carcinoma of skin subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Vascular disorders Haematoma subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
General disorders and administration site conditions Injection site haematoma subjects affected / exposed occurrences (all) Injection site erythema subjects affected / exposed occurrences (all) Injection site bruising subjects affected / exposed occurrences (all) Inflammation subjects affected / exposed occurrences (all) Injection site joint erythema	0 / 27 (0.00%) 0 0 / 27 (0.00%) 0 0 / 27 (0.00%) 0 0 / 27 (0.00%) 0		

subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Peripheral swelling			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Injection site joint pain			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Vessel puncture site haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Atrophic vulvovaginitis			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Ovulation pain			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Nasal congestion			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Investigations			
Cardiac murmur			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Blood creatine phosphokinase increased			

subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Alanine aminotransferase increased			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Haematology test abnormal			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Urine protein/creatinine ratio increased			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
SARS-CoV-2 test positive			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Tooth fracture			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Tendon injury			
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	1		
Skin abrasion			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Limb injury			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Ligament sprain			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Traumatic haematoma			

subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Paraesthesia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Dental caries			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Lichenoid keratosis			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Eczema			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Dermatitis contact			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Rash			

subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Renal and urinary disorders Microalbuminuria subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0		
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Joint swelling subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Neck pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0 1 / 27 (3.70%) 1 0 / 27 (0.00%) 0 1 / 27 (3.70%) 1 0 / 27 (0.00%) 0 1 / 27 (3.70%) 1 0 / 27 (0.00%) 0		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) COVID-19 pneumonia subjects affected / exposed occurrences (all) Gastroenteritis	0 / 27 (0.00%) 0 1 / 27 (3.70%) 1		

subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Herpes zoster			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Infected dermal cyst			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Tonsillitis			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		
Respiratory tract infection viral			
subjects affected / exposed	0 / 27 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 May 2017	Amendment 01 was generated in response to request from the State Institute for Drug Control (SUKL) in Czech Republic during the CTA review, in order to add more specific definition of the primary efficacy endpoint and details on the blinding levels of the MRI assessments, as well as an update of the wording for the exclusion criterion 9 for more clarity.
01 June 2017	Amendment 02 is to introduce clarifications requested by health authorities at CTA review regarding the End of Trial definition and the corresponding activities. In adjustment to local practices, inclusion criterion n°5 is updated to allow arthroscopic confirmation of the symptomatic, single, partial thickness articular cartilage defect of one knee, grade II or IIIA according to the ICRS classification, localized to either the femoral condyles/femoral trochlea or to the patella, performed within 9 months before screening visit. In order to improve clarity, exclusion criterion n°13 is updated to allow enrolment of bipolar lesions if the tibial lesion does not exceed ICRS grade 1, and for exclusion criterion n°16, definition is specified. Exclusion criteria n°17 and n°18 are updated regarding the requirement for imaging diagnostics no longer limited to 9 month. The restraints regarding prohibited medication are updated to adjust the time frame towards the dosing start, to reduce patient's burden.
01 December 2017	Amendment 03 is to adjust the screening period and the eligibility criteria following input from investigators. Furthermore, the number of PK samples to be collected is lowered, as additional PK and safety information from the First-in-Human study has become available, Section 1.3 is updated accordingly. Also, clarification is added regarding the restriction of rescue medications during follow-up visits to prevent any bias for patient-related outcomes.
01 July 2019	Amendment 04 is to add a 52-week visit schedule for clinical and MRI evaluations
01 March 2020	Amendment 05 is to add a Part B to the study protocol with the aim of: (i) evaluating monthly dosing efficacy, safety and tolerability; (ii) exploring dose-dependence by testing multiple doses of 40 mg and 20 mg dose levels; (iii) broadening the population by including Kellgren & Lawrence (K&L) 2-3 patients, based on the positive results of the X2201 study and the positive IA of the current study; (iv) adding additional safety measures (e.g., post-dosing monitoring extended to 3 hours; more stringent stopping rules, with patients who experience any grade hypersensitivity reaction not to be re-dosed), following the Urgent Safety Measure (USM) implemented in August 2019.
01 July 2020	Amendment 06 is generated in response to the request from the Danish Medicines Agency (DKMA) to include monthly pregnancy testing, to match it with the duration of LNA043 pharmacodynamic effect. Additionally, a modification of the stopping rule related to acute allergic reactions is included, with the aim of extending safety monitoring, by adding criteria to pause the study should one (1) fatal or life-threatening event occur. Lastly, the assessment of the Benefit/Risk concluded the absence of additional risks related to COVID-19.

01 December 2020	Amendment 07 is generated to address the request from the U.S. Food and Drug Administration (FDA) to collect safety ECG monitoring (around Tmax) to provide information on whether a QT study would be required for the LNA043 program. Additionally, a modification of the radiologic selection criteria is introduced to better match the population expected to benefit from LNA043.
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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.

For several outcomes there was a loss in samples size, which may limit the interpretability of results. Due to some errors in calculations that require re- analysis, some p values will be updated and provided at a later time.

Notes: