Clinical trial results:
A randomized, placebo-controlled, patient and Investigator blinded, single dose, Proof of Concept study investigating the safety, tolerability and preliminary efficacy of intraarticular LNA043 in regenerating the articular cartilage of the knee at donor sites in patients undergoing autologous chondrocyte implantation

Summary

EudraCT number	2016-003418-28
Trial protocol	AT
Global end of trial date	05 April 2019

Results information

Result version number	v1 (current)
This version publication date	18 April 2020
First version publication date	18 April 2020

Trial information

Trial identification

Sponsor protocol code	CLNA043X2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03334812
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, 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	05 April 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 April 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of a single LNA043 i.a. injection in regenerating hyaline cartilage tissue at the donor sites of patients undergoing autologous chondrocyte implantation (ACI)
To assess safety and tolerability of a single LNA043 i.a. injection in patients undergoing ACI

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	18 October 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	Austria: 14
Worldwide total number of subjects	14
EEA total number of subjects	14

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)	14
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All patients were recruited from 3 clinical sites in Austria.

Pre-assignment

Screening details:

The original set up of this trial was for 2 cohorts of LNA043 (20 mg and 40 mg). The trial was terminated before any patient in the LNA043 40 mg cohort was randomized

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	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	LNA043 20mg

Arm description:

LNA043 20mg/3ml single dose

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

Dosage and administration details:

LNA043 was administered to the subject via i.a injection at the end of the arthroscopy performed for cartilage harvest.

Arm title	Matching placebo to 20mg

Arm description:

Matching placebo to 20mg/3ml, single dose

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:

Placebo was administered to the subject via i.a injection at the end of the arthroscopy performed for cartilage harvest.

Number of subjects in period 1	LNA043 20mg	Matching placebo to 20mg
Started	9	5
Completed	9	5

Baseline characteristics

Reporting groups	
Reporting group title	LNA043 20mg
Reporting group description:	
LNA043 20mg/3ml single dose	
Reporting group title	Matching placebo to 20mg
Reporting group description:	
Matching placebo to 20mg/3ml, single dose	

Reporting group values	LNA043 20mg	Matching placebo to 20mg	Total
Number of subjects	9	5	14
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)	9	5	14
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	31.0	39.4	
standard deviation	± 6.16	± 7.40	-
Sex: Female, Male Units: Participants			
Female	3	5	8
Male	6	0	6
Race/Ethnicity, Customized Units: Subjects			
White	9	5	14

End points

End points reporting groups

Reporting group title	LNA043 20mg
Reporting group description: LNA043 20mg/3ml single dose	
Reporting group title	Matching placebo to 20mg
Reporting group description: Matching placebo to 20mg/3ml, single dose	

Primary: Change from baseline to Week 4 in GAG content

End point title	Change from baseline to Week 4 in GAG content
End point description: Sodium MRI-based measurements of change from baseline in glycosaminoglycan (GAG) content were assessed from both defective sites and a nearby healthy cartilage region (as a reference tissue). Specifically, the ratio of normalized sodium signal in the surgically created defect (SCD or donor site) to healthy non-weight bearing region (HNWB), i.e. SCD/HNWB and the defect to be treated (DTBT or main lesion) to healthy weight bearing region (HWB), i.e. DTBT/HWB was of major interest	
End point type	Primary
End point timeframe: Baseline, Week 4	

End point values	LNA043 20mg	Matching placebo to 20mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	2		
Units: Ratio				
least squares mean (standard error)				
SCD/HNWB	0.24 (± 0.06)	0.06 (± 0.12)		
DTBT/HWB	0.08 (± 0.04)	0.09 (± 0.09)		

Statistical analyses

Statistical analysis title	LNA043 20mg vs. Placebo
Statistical analysis description: SCD/HNWB	
Comparison groups	Matching placebo to 20mg v LNA043 20mg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1219
Method	Mixed Effect Model Repeat Measurement
Parameter estimate	Mean difference (net)
Point estimate	0.18

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.51

Statistical analysis title	LNA043 20mg vs. Placebo
Statistical analysis description:	
DTBT/HWB	
Comparison groups	LNA043 20mg v Matching placebo to 20mg
Number of subjects included in analysis	9
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5438
Method	Mixed Effect Model Repeat Measurement
Parameter estimate	Mean difference (net)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.25

Primary: Bi-layer collagen organization based on MRI measurements at Week 4	
End point title	Bi-layer collagen organization based on MRI measurements at Week 4
End point description:	
MRI T2 maps were generated and zonal T2 ratios (superficial layer T2 / deep layer T2) were calculated to assess the collagen fiber organization in the surgically created defect (SCD) and defect to be treated (DTBT) cartilage regions.	
End point type	Primary
End point timeframe:	
Week 4	

End point values	LNA043 20mg	Matching placebo to 20mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	4		
Units: Ratio				
arithmetic mean (standard error)	1.01 (± 0.07)	0.95 (± 0.09)		

Statistical analyses

Statistical analysis title	LNA043 20mg vs. Placebo
Comparison groups	LNA043 20mg v Matching placebo to 20mg
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3067
Method	Mixed Effect Model Repeat Measurement
Parameter estimate	Mean difference (final values)
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.19
upper limit	0.31

Secondary: Change from baseline in International Cartilage Repair Society (ICRS) scoring

End point title	Change from baseline in International Cartilage Repair Society (ICRS) scoring

End point description:

Extent of the repair tissue at the donor site before surgery. Each criterion was evaluated based on the visual analog scale and graded from 0 (best) to 100 (worst).

End point type	Secondary

End point timeframe:

Week 4

End point values	LNA043 20mg	Matching placebo to 20mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	4		
Units: Unit on a scale				
arithmetic mean (standard error)				
Abnormal Calcification/Ossification	98.75 (± 1.05)	100.00 (± 1.48)		
Cell Morphology	61.43 (± 14.14)	56.67 (± 21.60)		
Chondrocyte clustering	85.71 (± 8.37)	85.00 (± 12.78)		
Inflammation	92.50 (± 2.15)	98.75 (± 3.04)		
Matrix Staining	57.14 (± 12.17)	25.00 (± 18.59)		
Overall assessment	49.29 (± 12.23)	55.00 (± 18.68)		
Tissue Morphology	71.43 (± 7.78)	65.00 (± 11.88)		
Vascularisation in repaired tissue	66.25 (± 12.88)	77.50 (± 18.21)		

Basal Integration	82.86 (± 10.64)	90.00 (± 16.26)		
Formation of a Tidemark	65.71 (± 18.15)	63.33 (± 27.72)		
Mid/Deep zone assessment	50.00 (± 14.56)	56.67 (± 22.24)		
Subcondral bone abnormalities/marrow fibrosis	73.75 (± 13.45)	77.50 (± 19.01)		
Surface Architecture	57.86 (± 11.33)	80.00 (± 17.31)		
Surface/Superficial assessment	56.43 (± 11.42)	83.33 (± 17.44)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of donor site refilling based on MRI measurements

End point title	Percentage of donor site refilling based on MRI measurements

End point description:

Extent of filling of the donor site over a longer term. Percentage change from baseline in refilling of cartilage defect based on 7T MRI for donor Region.

End point type	Secondary

End point timeframe:

Baseline, Week 4, Week 12 and Week 28

End point values	LNA043 20mg	Matching placebo to 20mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	4		
Units: Percent				
least squares mean (standard error)				
Week 4	64.38 (± 7.80)	38.15 (± 11.03)		
Week 12	60.25 (± 14.55)	32.44 (± 19.09)		
Week 28 (EOS)	86.53 (± 11.09)	62.73 (± 14.52)		

Statistical analyses

Statistical analysis title	LNA043 20mg vs. Placebo

Statistical analysis description:

Week 4

Comparison groups	LNA043 20mg v Matching placebo to 20mg

Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0404
Method	Mixed Effect Model Repeat Measurement
Parameter estimate	Mean difference (net)
Point estimate	26.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.86
upper limit	56.32

Statistical analysis title	LNA043 20mg vs. Placebo
Statistical analysis description:	
Week 12	
Comparison groups	LNA043 20mg v Matching placebo to 20mg
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1381
Method	Mixed Effect Model Repeat Measurement
Parameter estimate	Mean difference (net)
Point estimate	27.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.5
upper limit	82.1

Statistical analysis title	LNA043 20mg vs. Placebo
Statistical analysis description:	
Week 28 (EOS)	
Comparison groups	LNA043 20mg v Matching placebo to 20mg
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1168
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	23.8
Confidence interval	
level	Other: 96 %
sides	2-sided
lower limit	-19.3
upper limit	66.89

Secondary: Change from baseline in GAG content

End point title	Change from baseline in GAG content

End point description:

Sodium MRI-based measurements of change from baseline in glycosaminoglycan (GAG) content was assessed from both defective sites and a nearby healthy cartilage region (as a reference tissue). Specifically, the ratio of normalized sodium signal in the surgically created defect (SCD or donor site) to healthy non-weight bearing region (HNWB), i.e. SCD/HNWB was of major interest

End point type	Secondary

End point timeframe:

Baseline, Week 12 and Week 28

End point values	LNA043 20mg	Matching placebo to 20mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	4		
Units: Ratio				
least squares mean (standard error)				
SCD/HNWB - Week 12	0.14 (± 0.07)	0.15 (± 0.09)		
SCD/HNWB - Week 28	0.33 (± 0.10)	0.14 (± 0.14)		

Statistical analyses

Statistical analysis title	LNA043 20mg vs. Placebo

Statistical analysis description:

SCD/HNWB - Week 12

Comparison groups	LNA043 20mg v Matching placebo to 20mg
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5175
Method	Mixed Effect Model Repeat Measurement
Parameter estimate	Mean difference (net)
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.25

Statistical analysis title	LNA043 20mg vs. Placebo

Statistical analysis description:	
SCD/HNWB - Week 28	
Comparison groups	LNA043 20mg v Matching placebo to 20mg
Number of subjects included in analysis	11
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1476
Method	Mixed Effect Model Repeat Measurement
Parameter estimate	Mean difference (net)
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	0.6

Secondary: Bi-layer collagen organization based on MRI measurements

End point title	Bi-layer collagen organization based on MRI measurements
End point description:	
MRI T2 maps were generated and zonal T2 ratios (superficial layer T2 / deep layer T2) were calculated to assess the collagen fiber organization in the SCD cartilage region.	
End point type	Secondary
End point timeframe:	
Week 12 and Week 28	

End point values	LNA043 20mg	Matching placebo to 20mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	4		
Units: Ratio				
arithmetic mean (standard error)				
Week 12	1.44 (± 0.15)	1.57 (± 0.18)		
Week 28	1.33 (± 0.11)	1.45 (± 0.14)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK profile of LNA043 and of AngPTL3 in serum Cmax

End point title	PK profile of LNA043 and of AngPTL3 in serum Cmax
End point description:	
Local and systemic pharmacokinetics (PK) of LNA043 following a single i.a. administration	
End point type	Secondary

End point timeframe:

4 weeks

End point values	LNA043 20mg	Matching placebo to 20mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	5[1]		
Units: ng/mL				
arithmetic mean (standard deviation)				
LNA043	57.4 (± 22.1)	999 (± 999)		
AngPTL3	22.9 (± 9.03)	26.6 (± 7.62)		

Notes:

[1] - PK profile not assessed for LNA043 in Placebo Group (999)

Statistical analyses

No statistical analyses for this end point

Secondary: PK profile of LNA043 and of AngPTL3 in serum AUC

End point title	PK profile of LNA043 and of AngPTL3 in serum AUC

End point description:

Local and systemic pharmacokinetics (PK) of LNA043 following a single i.a. administration

End point type	Secondary

End point timeframe:

4 weeks

End point values	LNA043 20mg	Matching placebo to 20mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	5[2]		
Units: hr*ng/mL				
arithmetic mean (standard deviation)				
LNA043	821 (± 349)	999 (± 999)		
AngPTL3	3130 (± 1440)	3030 (± 1060)		

Notes:

[2] - PK profile not assessed for LNA043 in Placebo Group (999)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with anti-LNA043 antibodies in serum

End point title	Number of participants with anti-LNA043 antibodies in serum

End point description:

Potential immunogenicity of LNA043

End point type	Secondary

End point timeframe:

Baseline, Week 1, Week 4, Week 12 and Week 28

End point values	LNA043 20mg	Matching placebo to 20mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	5		
Units: Participants				
Day 1: anti-LNA043 antibodies present|YES	0	0		
Day 8: anti-LNA043 antibodies present|YES	0	0		
Day 29: anti-LNA043 antibodies present|YES	0	0		
Day 85: anti-LNA043 antibodies present|YES	0	0		
Day 197: anti-LNA043 antibodies present|YES	0	0		
Day 1: anti-LNA043 antibodies present|NO	9	5		
Day 8: anti-LNA043 antibodies present|NO	9	5		
Day 29: anti-LNA043 antibodies present|NO	9	5		
Day 85: anti-LNA043 antibodies present|NO	9	5		
Day 197: anti-LNA043 antibodies present|NO	9	5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were collected from the dose of study treatment until up to 28 weeks post treatment	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0
Reporting groups	
Reporting group title	LNA043 20mg
Reporting group description:	
LNA043 20mg	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Serious adverse events	LNA043 20mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	0 / 5 (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: 0 %

Non-serious adverse events	LNA043 20mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 9 (44.44%)	4 / 5 (80.00%)	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 9 (11.11%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	1 / 9 (11.11%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Traumatic haematoma			

subjects affected / exposed	1 / 9 (11.11%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 9 (22.22%)	0 / 5 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	1 / 9 (11.11%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 9 (11.11%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 9 (0.00%)	2 / 5 (40.00%)	
occurrences (all)	0	2	
Endocrine disorders			
Thyroid mass			
subjects affected / exposed	0 / 9 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 9 (11.11%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Joint range of motion decreased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 May 2017	The original protocol was amended to shift the baseline MRI from the screening epoch between days -14 and -1 to day 3, in the post-treatment follow-up epoch.
11 December 2017	To update specific protocol sections according the updated Investigator Brochure. To clarify the use of the 7 Tesla (7T) MRI as an exploratory medical device. To clarify about the site where the 7 Tesla MRI was performed, now defined specifically as the investigational site for medical device, and to describe how to report possible adverse device effects or serious adverse device effects associated with the 7 T MRI, if any; To increase the number of days between randomization and treatment to give more time to the sites to organize the activities for subject treatment: from 1 day to 7 days before treatment; To delete the PK sample collection 15 min after drug administration to simplify study procedures; To enlarge the interval within which performing the second surgery, from 3 to 5 days to simplify study procedures; To enlarge the interval within which performing the MRI before the surgery at Week 4, from 2 to 3 days to simplify study procedures.
24 May 2018	To add a second cohort to treat subjects with a single dose of 40 mg LNA043 or matching placebo, without increasing the number of total subjects to be enrolled and without stopping enrolment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported