



Clinical trial results:

A Multicenter, Randomized, Double-blind, Placebo- and Active-Controlled Phase III Study on the Safety and Efficacy of a Single Intra-articular Administration of JTA-004 in Symptomatic Knee Osteoarthritis. Summary

EudraCT number	2019-000796-16
Trial protocol	DK BE GB PL CZ
Global end of trial date	09 December 2021

Results information

Result version number	v1 (current)
This version publication date	11 March 2023
First version publication date	11 March 2023

Trial information

Trial identification

Sponsor protocol code	000014/BT
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bone Therapeutics S.A.
Sponsor organisation address	Rue Granbonpré 11 - Batiment H (bte 24), Mont-St-Guibert, Belgium, 1435
Public contact	JTA Clinical Trial Team, BioSenic SA (change in sponsor name on 26-Oct-22), info@biosenic.com
Scientific contact	JTA Clinical Trial Team, BioSenic SA (change in sponsor name on 26-Oct-22), info@biosenic.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	25 February 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 April 2021
Global end of trial reached?	Yes
Global end of trial date	09 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that treatment with JTA-004 leads to a reduction in knee pain intensity with respect to placebo in subjects suffering from symptomatic osteoarthritis (OA) of the knee at Month 3.

Protection of trial subjects:

Study commencement required prior written approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Clinical trial data were monitored at regular intervals by the Sponsor or their representative throughout the study to verify compliance to study protocol, completeness, accuracy and consistency of the data and adherence to local regulations on the conduct of clinical research.

Patients were discontinued from investigational product(s) (IP) in case of withdrawal of consent, violation of eligibility criteria, safety concerns (only if the Investigator has clearly determined that the subject's withdrawal would reduce the safety risks), lost to follow-up, lack of subject compliance to the clinical study protocol and lack of efficacy (early discontinuation for treatment failure).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 March 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 87
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Czechia: 142
Country: Number of subjects enrolled	Denmark: 184
Country: Number of subjects enrolled	Hong Kong: 213
Country: Number of subjects enrolled	Moldova, Republic of: 113
Worldwide total number of subjects	746
EEA total number of subjects	414

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)	420
From 65 to 84 years	322
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Informed consent was obtained before any protocol required assessments were performed. Subjects who signed informed consent, but fail to meet inclusion/exclusion criteria or withdrew consent prior to receiving any study medication were considered screen failures.

Period 1

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

Blinding implementation details:

Subjects with symptomatic knee OA who meet the eligibility criteria were randomized in a 2:1:1 ratio (JTA-004, placebo or active comparator) using an Interactive Web Response System (IWRS). Considering that the placebo and active comparator could be identified as such by the Investigator, IP injection was performed at Day 0 (Visit 2) by an unblinded Independent Physician/Injector, allowing the Investigator to remain blind.

Arms

Are arms mutually exclusive?	Yes
Arm title	JTA-004

Arm description:

Patients receiving one injection of 2 mL JTA-004 at visit 2 (Day 0) after randomization.

Arm type	Experimental
Investigational medicinal product name	JTA-004
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraarticular use

Dosage and administration details:

2mL intraarticular injection of JTA-004.

Arm title	Active comparator (Synvisc-One®)
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Arm description:

Patients receiving one injection of 6mL Synvisc-One® (Hylan G-F 20 (8 mg/mL; 48 mg/dose) at visit 2 (Day 0) after randomization.

Arm type	Active comparator
Investigational medicinal product name	Synvisc-One® (Hylan G-F 20 (8 mg/mL; 48 mg/dose))
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraarticular use

Dosage and administration details:

Synvisc-One® 6mL intraarticular injection (Hylan G-F 20 (8 mg/mL; 48 mg/dose))

Arm title	Placebo comparator (saline solution)
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Arm description:

Patients receiving one injection of 2mL of saline solution at visit 2 (Day 0) after randomization.

Arm type	Placebo
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Investigational medicinal product name	Saline solution (Sodium Chloride Injection BP 0.9% w/v)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraarticular use

Dosage and administration details:

2mL intraarticular injection of saline solution (Sodium Chloride Injection BP 0.9% w/v)

Number of subjects in period 1	JTA-004	Active comparator (Synvisc-One®)	Placebo comparator (saline solution)
Started	372	187	187
Completed	357	178	179
Not completed	15	9	8
Consent withdrawn by subject	5	7	3
Adverse event, non-fatal	1	-	-
Other	2	-	1
Month 6 Visit not done but study continued	-	1	-
Lost to follow-up	4	1	2
Lack of subject compliance	1	-	-
Violation of eligibility criteria	1	-	1
Lack of efficacy	1	-	1

Period 2

Period 2 title	Long-term follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Subjects with symptomatic knee OA who meet the eligibility criteria were randomized in a 2:1:1 ratio (JTA-004, placebo or active comparator) using an Interactive Web Response System (IWRS). Considering that the placebo and active comparator could be identified as such by the Investigator, IP injection was performed at Day 0 (Visit 2) by an unblinded Independent Physician/Injector, allowing the Investigator to remain blind.

Arms

Are arms mutually exclusive?	Yes
Arm title	JTA-004

Arm description:

Long-term follow-up of patients having received one injection of 2 mL JTA-004 at visit 2 (Day 0) after randomization

Arm type	Experimental
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Investigational medicinal product name	JTA-004
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraarticular use

Dosage and administration details:

2mL intraarticular injection of JTA-004 at visit 2 (Day 0) after randomization.

Arm title	Active comparator (Synvisc-One®)
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Arm description:

Long-term follow-up of patients having received one injection of 6mL Synvisc-One® (Hylan G-F 20 (8 mg/mL; 48 mg/dose) at visit 2 (Day 0) after randomization

Arm type	Active comparator
Investigational medicinal product name	Synvisc-One® (Hylan G-F 20 (8 mg/mL; 48 mg/dose))
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraarticular use

Dosage and administration details:

Synvisc-One® 6mL intraarticular injection (Hylan G-F 20 (8 mg/mL; 48 mg/dose)) at Day 0 (Visit 2) after randomization.

Arm title	Placebo comparator (saline solution)
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Arm description:

Long-term follow-up of patients having received one injection of 2mL of saline solution at visit 2 (Day 0) after randomization.

Arm type	Placebo
Investigational medicinal product name	Saline solution (Sodium Chloride Injection BP 0.9% w/v)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraarticular use

Dosage and administration details:

2mL intraarticular injection of saline solution (Sodium Chloride Injection BP 0.9% w/v) at Day 0 (Visit 2) after randomization.

Number of subjects in period 2	JTA-004	Active comparator (Synvisc-One®)	Placebo comparator (saline solution)
Started	357	178	179
Completed	342	171	174
Not completed	15	7	5
Consent withdrawn by subject	4	5	-
Other	1	-	-
Lost to follow-up	10	2	5

Baseline characteristics

Reporting groups

Reporting group title	JTA-004
Reporting group description: Patients receiving one injection of 2 mL JTA-004 at visit 2 (Day 0) after randomization.	
Reporting group title	Active comparator (Synvisc-One®)
Reporting group description: Patients receiving one injection of 6mL Synvisc-One® (Hylan G-F 20 (8 mg/mL; 48 mg/dose) at visit 2 (Day 0) after randomization.	
Reporting group title	Placebo comparator (saline solution)
Reporting group description: Patients receiving one injection of 2mL of saline solution at visit 2 (Day 0) after randomization.	

Reporting group values	JTA-004	Active comparator (Synvisc-One®)	Placebo comparator (saline solution)
Number of subjects	372	187	187
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)	214	103	103
From 65-84 years	157	81	84
85 years and over	1	3	0
Age continuous Units: years			
arithmetic mean	62.2	63.5	62.9
standard deviation	± 8.8	± 9.4	± 9.2
Gender categorical Units: Subjects			
Female	248	137	137
Male	124	50	50

Reporting group values	Total		
Number of subjects	746		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	420		
From 65-84 years	322		
85 years and over	4		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	522		
Male	224		

End points

End points reporting groups

Reporting group title	JTA-004
Reporting group description: Patients receiving one injection of 2 mL JTA-004 at visit 2 (Day 0) after randomization.	
Reporting group title	Active comparator (Synvisc-One®)
Reporting group description: Patients receiving one injection of 6mL Synvisc-One® (Hylan G-F 20 (8 mg/mL; 48 mg/dose) at visit 2 (Day 0) after randomization.	
Reporting group title	Placebo comparator (saline solution)
Reporting group description: Patients receiving one injection of 2mL of saline solution at visit 2 (Day 0) after randomization.	
Reporting group title	JTA-004
Reporting group description: Long-term follow-up of patients having received one injection of 2 mL JTA-004 at visit 2 (Day 0) after randomization	
Reporting group title	Active comparator (Synvisc-One®)
Reporting group description: Long-term follow-up of patients having received one injection of 6mL Synvisc-One® (Hylan G-F 20 (8 mg/mL; 48 mg/dose) at visit 2 (Day 0) after randomization	
Reporting group title	Placebo comparator (saline solution)
Reporting group description: Long-term follow-up of patients having received one injection of 2mL of saline solution at visit 2 (Day 0) after randomization.	

Primary: Mean changes from baseline in WOMAC pain score at month 3

End point title	Mean changes from baseline in WOMAC pain score at month
End point description: Primary Efficacy Variable: the efficacy of JTA-004 was evaluated as the mean changes from baseline at Month 3 of the WOMAC® VA3.1 Pain Subscale (subscale A) to demonstrate superiority of JTA-004 in comparison to placebo.	
End point type	Primary
End point timeframe: At month 3	

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: This is due to the fact that, in this trial, statistic comparisons were made either for JTA-004 Vs Placebo or for JTA-004 Vs active comparator, depending on the end-point, but never for JTA-004 Vs Placebo Vs active comparator (direct comparisons of the 3 arms for a same endpoint).

End point values	JTA-004	Placebo comparator (saline solution)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335 ^[2]	169 ^[3]		
Units: Pain score				
arithmetic mean (standard deviation)	-31.90 (± 20.68)	-29.27 (± 19.12)		

Notes:

[2] - Results from this endpoint are from the Full Analysis Set (FAS).

[3] - Results from this endpoint are from the Full Analysis Set (FAS).

Statistical analyses

Statistical analysis title	Difference (JTA-004 - Placebo)
Statistical analysis description: Change from Baseline in WOMAC® Pain Score at Month 3 - JTA-004 Versus Placebo (Main Analysis Based on MMRM) - Full Analysis Set (N=674)	
Comparison groups	JTA-004 v Placebo comparator (saline solution)
Number of subjects included in analysis	504
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.417
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.12
upper limit	2.12
Variability estimate	Standard error of the mean

Secondary: Mean changes from baseline in WOMAC pain score at month 6

End point title	Mean changes from baseline in WOMAC pain score at month
End point description: Mean changes from baseline in knee pain at Month 6 using the WOMAC® VA3.1 pain subscale (subscale A) between JTA-004 and placebo	
End point type	Secondary
End point timeframe: At month 6	

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: This is due to the fact that, in this trial, statistic comparisons were made either for JTA-004 Vs Placebo or for JTA-004 Vs active comparator, depending on the end-point, but never for JTA-004 Vs Placebo Vs active comparator (direct comparisons of the 3 arms for a same endpoint).

End point values	JTA-004	Placebo comparator (saline solution)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335 ^[5]	169 ^[6]		
Units: Womac pain score				
arithmetic mean (standard deviation)	-33.31 (± 20.40)	-29.19 (± 18.41)		

Notes:

[5] - Results presented here are from the Full Analysis Set (FAS)

[6] - Results presented here are from the Full Analysis Set (FAS)

Statistical analyses

Statistical analysis title	Difference (JTA-004 - Placebo)
Comparison groups	Placebo comparator (saline solution) v JTA-004
Number of subjects included in analysis	504
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.154
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.28
upper limit	0.99
Variability estimate	Standard error of the mean

Secondary: Mean changes from baseline in WOMAC pain score at month 3

End point title	Mean changes from baseline in WOMAC pain score at month
End point description:	
Non-inferiority test comparing mean changes from baseline in knee pain at Month 3 using the WOMAC® VA3.1 pain subscale (subscale A) between JTA-004 and active control.	
End point type	Secondary
End point timeframe:	
At month 3	

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: This is due to the fact that, in this trial, statistic comparisons were made either for JTA-004 Vs Placebo or for JTA-004 Vs active comparator, depending on the end-point, but never for JTA-004 Vs Placebo Vs active comparator (direct comparisons of the 3 arms for a same endpoint).

End point values	JTA-004	Active comparator (Synvisc-One®)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	324 ^[8]	163 ^[9]		
Units: Pain score				
arithmetic mean (standard deviation)	-31.90 (± 20.68)	-34.22 (± 19.51)		

Notes:

[8] - Results presented here are from Full Analysis Set (FAS). 11 patients were missing.

[9] - Results presented here were from Full Analysis Set (FAS). 7 patients were missing.

Statistical analyses

Statistical analysis title	Difference JTA-004 Versus Active Comparator
Comparison groups	JTA-004 v Active comparator (Synvisc-One®)
Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.193
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.22
upper limit	6.02
Variability estimate	Standard error of the mean

Secondary: Mean changes from baseline in WOMAC physical function at month 3

End point title	Mean changes from baseline in WOMAC physical function at month 3 ^[10]
End point description:	
Mean changes from baseline in knee physical function at Month 3 using the WOMAC® VA3.1 physical function subscale (subscale C) between JTA-004 and placebo.	
End point type	Secondary
End point timeframe:	
At month 3.	

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: This is due to the fact that, in this trial, statistic comparisons were made either for JTA-004 Vs Placebo or for JTA-004 Vs active comparator, depending on the end-point, but never for JTA-004 Vs Placebo Vs active comparator (direct comparisons of the 3 arms for a same endpoint).

End point values	JTA-004	Placebo comparator (saline solution)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323 ^[11]	163 ^[12]		
Units: Physical function score				
arithmetic mean (standard deviation)	-24.35 (± 22.11)	-24.28 (± 20.59)		

Notes:

[11] - Results presented here are from Full Analysis Set (FAS). 12 patients were missing.

[12] - Results presented here are from Full Analysis Set (FAS). 6 patients were missing.

Statistical analyses

Statistical analysis title	Difference JTA-004 Versus Placebo
Comparison groups	JTA-004 v Placebo comparator (saline solution)
Number of subjects included in analysis	486
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.682
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.31
upper limit	2.82
Variability estimate	Standard error of the mean

Secondary: Mean changes in PGA at month 3

End point title	Mean changes in PGA at month 3 ^[13]
End point description:	Mean changes from baseline in PGA at Month 3) between JTA-004 and placebo.
End point type	Secondary
End point timeframe:	
At month 3	

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: This is due to the fact that, in this trial, statistic comparisons were made either for JTA-004 Vs Placebo or for JTA-004 Vs active comparator, depending on the end-point, but never for JTA-004 Vs Placebo Vs active comparator (direct comparisons of the 3 arms for a same endpoint).

End point values	JTA-004	Placebo comparator (saline solution)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	324 ^[14]	164 ^[15]		
Units: Patient Global Assessment				
arithmetic mean (standard deviation)	-2.16 (± 2.30)	-1.88 (± 2.32)		

Notes:

[14] - Results presented here are from Full Analysis Set (FAS). 11 patients were missing.

[15] - Results presented here are from Full Analysis Set (FAS). 5 patients were missing.

Statistical analyses

Statistical analysis title	Difference JTA-004 versus Placebo
Comparison groups	JTA-004 v Placebo comparator (saline solution)
Number of subjects included in analysis	488
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.106
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.72
upper limit	0.07
Variability estimate	Standard error of the mean

Secondary: Mean changes from baseline in WOMAC physical function at month 6

End point title	Mean changes from baseline in WOMAC physical function at month 6 ^[16]
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End point description:

Mean changes from baseline in knee physical function at Month 6 using the WOMAC® VA3.1 physical function subscale (subscale C) between JTA-004 and placebo.

End point type	Secondary
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End point timeframe:

At month 6.

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: This is due to the fact that, in this trial, statistic comparisons were made either for JTA-004 Vs Placebo or for JTA-004 Vs active comparator, depending on the end-point, but never for JTA-004 Vs Placebo Vs active comparator (direct comparisons of the 3 arms for a same endpoint).

End point values	JTA-004	Placebo comparator (saline solution)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	322 ^[17]	163 ^[18]		
Units: Physical function score				
arithmetic mean (standard deviation)	-25.28 (± 21.29)	-23.27 (± 20.78)		

Notes:

[17] - Results presented here are from Full Analysis Set (FAS). 13 patients were missing.

[18] - Results presented here are from Full Analysis Set (FAS). 6 patients were missing.

Statistical analyses

Statistical analysis title	Difference JTA-004 versus Placebo
Comparison groups	JTA-004 v Placebo comparator (saline solution)

Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.227
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.67
upper limit	1.35
Variability estimate	Standard error of the mean

Secondary: Mean changes from baseline in subject global health and well-being score at month 3

End point title	Mean changes from baseline in subject global health and well-being score at month 3 ^[19]
End point description:	Mean changes from baseline in subject global health and well-being score at Month 3 using the EQ-5D-5L questionnaire between JTA-004 and placebo.
End point type	Secondary
End point timeframe:	At month 3.

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: This is due to the fact that, in this trial, statistic comparisons were made either for JTA-004 Vs Placebo or for JTA-004 Vs active comparator, depending on the end-point, but never for JTA-004 Vs Placebo Vs active comparator (direct comparisons of the 3 arms for a same endpoint).

End point values	JTA-004	Placebo comparator (saline solution)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	325 ^[20]	162 ^[21]		
Units: Utility score				
arithmetic mean (standard deviation)	0.0829 (± 0.1882)	0.0825 (± 0.1843)		

Notes:

[20] - Results presented here are from Full Analysis Set (FAS). 10 patients were missing.

[21] - Results presented here are from Full Analysis Set (FAS). 7 patients were missing.

Statistical analyses

Statistical analysis title	Difference JTA-004 versus Placebo
Comparison groups	JTA-004 v Placebo comparator (saline solution)

Number of subjects included in analysis	487
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.732
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.005
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.0236
upper limit	0.0335
Variability estimate	Standard error of the mean

Secondary: Responder rates at month 3

End point title	Responder rates at month 3 ^[22]
End point description:	Responder rates (defined as $\geq 30\%$ pain intensity reduction) at Month 3 between JTA-004 and placebo.
End point type	Secondary
End point timeframe:	At month 3.

Notes:

[22] - 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: This is due to the fact that, in this trial, statistic comparisons were made either for JTA-004 Vs Placebo or for JTA-004 Vs active comparator, depending on the end-point, but never for JTA-004 Vs Placebo Vs active comparator (direct comparisons of the 3 arms for a same endpoint).

End point values	JTA-004	Placebo comparator (saline solution)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335 ^[23]	169 ^[24]		
Units: Responder	250	122		

Notes:

[23] - Results presented here are from Full Analysis Set (FAS)

[24] - Results presented here are from Full Analysis Set (FAS)

Statistical analyses

Statistical analysis title	Common relative risk JTA-004 versus Placebo
Comparison groups	JTA-004 v Placebo comparator (saline solution)
Number of subjects included in analysis	504
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.606
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk ratio (RR)
Point estimate	1.03

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.15

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From injection at day 0 until month 6 (period 1): reporting of serious adverse events and non-serious adverse events.

From month 6 until month 12 (period 2, long-term follow-up): reporting of serious adverse events only.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	JTA-004 (Period 1)
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Reporting group description:

One injection of 2 mL JTA-004 at visit 2 (Day 0) after randomization. Safety Analysis Set (SAS).

Reporting group title	Active comparator (Synvisc-One®) (Period 1)
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Reporting group description:

One injection of 6mL Synvisc-One® (Hylan G-F 20 (8 mg/mL; 48 mg/dose) at visit 2 (Day 0) after randomization. Safety Analysis Set (SAS).

Reporting group title	Placebo comparator (saline solution) (Period 1)
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Reporting group description:

One injection of 2mL of saline solution at visit 2 (Day 0) after randomization. Safety Analysis Set (SAS).

Reporting group title	JTA-004 (Period 2)
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Reporting group description:

Long-term safety follow-up. Only SAEs were reported. Safety Analysis Set (SAS).

Reporting group title	Active comparator (Synvisc-One®) (Period 2)
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Reporting group description:

Long-term safety follow-up. Only SAEs were reported. Safety Analysis Set (SAS).

Reporting group title	Placebo comparator (saline solution) (Period 2)
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Reporting group description:

Long-term safety follow-up. Only SAEs were reported. Safety Analysis Set (SAS).

Serious adverse events	JTA-004 (Period 1)	Active comparator (Synvisc-One®) (Period 1)	Placebo comparator (saline solution) (Period 1)
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 371 (1.89%)	6 / 187 (3.21%)	4 / 185 (2.16%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Parathyroid tumour benign			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural			

complications			
Facial bones fracture			
subjects affected / exposed	0 / 371 (0.00%)	1 / 187 (0.53%)	0 / 185 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 371 (0.00%)	1 / 187 (0.53%)	0 / 185 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Patella fracture			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (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
Tibia fracture			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 371 (0.27%)	0 / 187 (0.00%)	0 / 185 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Sinus node dysfunction			
subjects affected / exposed	0 / 371 (0.00%)	1 / 187 (0.53%)	0 / 185 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (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
Surgical and medical procedures			
Knee arthroplasty			

subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (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
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 371 (0.00%)	1 / 187 (0.53%)	0 / 185 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated inguinal hernia			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 371 (0.27%)	0 / 187 (0.00%)	0 / 185 (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
Skin and subcutaneous tissue disorders			
Excessive skin			
subjects affected / exposed	1 / 371 (0.27%)	0 / 187 (0.00%)	0 / 185 (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
Renal and urinary disorders			
Renal artery stenosis			
subjects affected / exposed	1 / 371 (0.27%)	0 / 187 (0.00%)	0 / 185 (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
Stress urinary incontinence			

subjects affected / exposed	1 / 371 (0.27%)	0 / 187 (0.00%)	0 / 185 (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
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 371 (0.00%)	1 / 187 (0.53%)	0 / 185 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (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
Osteoarthritis			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (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
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	3 / 371 (0.81%)	1 / 187 (0.53%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess limb			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			
subjects affected / exposed	0 / 371 (0.00%)	1 / 187 (0.53%)	0 / 185 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	1 / 371 (0.27%)	0 / 187 (0.00%)	0 / 185 (0.00%)
occurrences causally related to treatment / all	0 / 15	0 / 4	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Incision site abscess			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	1 / 185 (0.54%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	JTA-004 (Period 2)	Active comparator (Synvisc-One®) (Period 2)	Placebo comparator (saline solution) (Period 2)
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 371 (1.08%)	1 / 187 (0.53%)	0 / 185 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Parathyroid tumour benign			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (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
Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (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
Femoral neck fracture			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (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
Patella fracture			
subjects affected / exposed	1 / 371 (0.27%)	0 / 187 (0.00%)	0 / 185 (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
Tibia fracture			

subjects affected / exposed	1 / 371 (0.27%)	0 / 187 (0.00%)	0 / 185 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (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
Cardiac disorders			
Sinus node dysfunction			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (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
Acute myocardial infarction			
subjects affected / exposed	1 / 371 (0.27%)	0 / 187 (0.00%)	0 / 185 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Knee arthroplasty			
subjects affected / exposed	1 / 371 (0.27%)	0 / 187 (0.00%)	0 / 185 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (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
Ileus			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (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
Incarcerated inguinal hernia			

subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (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
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (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
Skin and subcutaneous tissue disorders			
Excessive skin			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (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
Renal and urinary disorders			
Renal artery stenosis			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (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
Stress urinary incontinence			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (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
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (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
Neck pain			
subjects affected / exposed	0 / 371 (0.00%)	1 / 187 (0.53%)	0 / 185 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			

subjects affected / exposed	1 / 371 (0.27%)	0 / 187 (0.00%)	0 / 185 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (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
Abscess limb			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (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
Arthritis bacterial			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (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
COVID-19			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (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
Incision site abscess			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (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
Pneumonia			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (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

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

Non-serious adverse events	JTA-004 (Period 1)	Active comparator (Synvisc-One®) (Period 1)	Placebo comparator (saline solution) (Period 1)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	162 / 371 (43.67%)	96 / 187 (51.34%)	65 / 185 (35.14%)
Nervous system disorders			
Headache			
subjects affected / exposed	53 / 371 (14.29%)	32 / 187 (17.11%)	21 / 185 (11.35%)
occurrences (all)	53	32	21
General disorders and administration site conditions			
Injection site joint pain			
subjects affected / exposed	14 / 371 (3.77%)	10 / 187 (5.35%)	4 / 185 (2.16%)
occurrences (all)	14	10	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	51 / 371 (13.75%)	30 / 187 (16.04%)	19 / 185 (10.27%)
occurrences (all)	51	30	19
Back pain			
subjects affected / exposed	30 / 371 (8.09%)	12 / 187 (6.42%)	15 / 185 (8.11%)
occurrences (all)	30	12	15
Pain in extremity			
subjects affected / exposed	14 / 371 (3.77%)	12 / 187 (6.42%)	6 / 185 (3.24%)
occurrences (all)	14	12	6

Non-serious adverse events	JTA-004 (Period 2)	Active comparator (Synvisc-One®) (Period 2)	Placebo comparator (saline solution) (Period 2)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (0.00%)
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Injection site joint pain			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 371 (0.00%)	0 / 187 (0.00%)	0 / 185 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 June 2020	This amendment includes the following major changes: <ul style="list-style-type: none">- Inclusion criterion #4 and exclusion criterion #7 were modified in order to align eligibility criteria (previously based on a VAS assessment of knee pain) and the primary endpoint based on WOMAC® V3.1 pain subscale.- Other sections were revised as a consequence of these changes.
14 October 2020	This amendment includes the following major changes: <ul style="list-style-type: none">- Additional clarifications were added to the visit schedule and procedures.- The description of the criteria for assessment of relationship of AEs to IMP were aligned to what was specified in the eCRF (unrelated/unlikely related/ possibly related/related/unknown).- The statistical section was revised to align endpoint analysis with changes from Version 2.0 of the protocol, including: The stratification classes associated with the target knee pain at baseline (VAS) were reworded from "≥40 - <59 mm / ≥59- <70 mm / ≥70 mm" to " <59 mm / ≥59- <70 mm / ≥70 mm". The number of subjects to be treated was increased from 676 to 742, considering that some subjects enrolled under protocol Version 1.1 would be excluded from the main analysis (as they had a baseline WOMAC® V3.1 pain subscale score out of the range defined in Version 2.0 (i.e. target knee pain ≥ 200 mm and ≤ 400 mm). Text clarifications regarding the hypotheses used for sample size calculation and the timing of analysis.
06 April 2021	The amendment includes the following major changes: <ul style="list-style-type: none">- The last protocol amendment allowed monitoring activities on some data points (specifically on-site data cleaning for the primary endpoint analysis at Month 6 and for the final analysis at Month 12) to be performed remotely using electronic equipment. This amendment was related to the context of the COVID-19 pandemic. All eligible data points were prospectively defined in the Clinical Monitoring Plan.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported