# 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 |

### 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®) |

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) |

Arm description:

Patients receiving 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)

| **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 |

| | |
|---|---|
| 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®) |
|---|---|

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) |
|---|---|

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<br>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<br>Units: years | | | |
| arithmetic mean | 62.2 | 63.5 | 62.9 |
| standard deviation | ± 8.8 | ± 9.4 | ± 9.2 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 248 | 137 | 137 |
| Male | 124 | 50 | 50 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 746 | | |
| Age categorical<br>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] |
|---|---|

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 |
|---|---|

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 ≥ 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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 24.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | JTA-004 (Period 1) |

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) |

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) |

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) |

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) |

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) |

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:<br>- 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.<br>- Other sections were revised as a consequence of these changes. |
| 14 October 2020 | This amendment includes the following major changes:<br>- Additional clarifications were added to the visit schedule and procedures.<br>- 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).<br>- The statistical section was revised to align endpoint analysis with changes from Version 2.0 of the protocol, including:<br>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".<br>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).<br>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:<br>- 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