Bone Therapeutics

Clinical Study Report

CLINICAL STUDY REPORT

Study JTA-KOA1

EudraCT number: 2015-002117-30

Protocol Number: 000010/BT

A Two-stage 6-month, Multicentre, Randomised, Double-blind, Controlled Study on the Safety and Efficacy of a Single Intra-articular Administration of JTA-004 in Patients with Symptomatic Knee Osteoarthritis

Sponsor

Bone Therapeutics S.A.
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TITLE PAGE

Study title: A Two-stage 6-month, Multicentre, Randomised, Double-blind, Controlled Study on the Safety and Efficacy of a Single Intra-articular Administration of JTA-004 in Patients with Symptomatic Knee Osteoarthritis

Name of test drug/investigational product: JTA-004

Indication studied: Treatment of symptomatic osteoarthritis of the knee with Kellgren-Lawrence grade II and III.

Study description: Prospective, randomised, double-blind controlled trial including 3 test strengths and 1 reference product to select the best test product and demonstrate its superiority compared to the reference treatment in patients suffering from symptomatic osteoarthritis of the knee.

Sponsor: Bone Therapeutics S.A., B-6041 Gosselies, Belgium

Protocol Identification: 000010/BT

Clinical Phase: Two-stage Phase II/III trial

Study Initiation Date *(first patient enrolled)*: 24 March 2016

Study Completion Date (*last patient completed last visit [Visit #5]*): 27 April 2018

Data Base Lock Date: 12 July 2018

Coordinating Investigator: Pr. T Appelboom, Hôpitaux Iris Sud Molière Longchamp, Forest, Belgium

Medical Officer: Dr. O. Godeaux, Bone Therapeutics S.A., Gosselies, Belgium

Sponsor Signatory: Dr. O. Godeaux, Bone Therapeutics S.A., Gosselies, Belgium

GCP Statement: This study was performed in compliance with ICH Good Clinical Practice (GCP) including the archiving of essential documents

Date of report: 07 June 2019

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SYNOPSIS

Name of Sponsor	Bone Therapeutics S.A.
Name of Product	JTA-004
Name of Active Ingredients	Sodium hyaluronate *N*-(2,6-dichlorophenyl)-4,5-dihydro-1*H*-imidazol-2-amine (clonidine) Human plasma
Indication (phase)	Treatment of symptomatic osteoarthritis (OA) of the knee with Kellgren-Lawrence grade II and III (Two-stage Phase II/III)
Title of Study	A Two-stage 6-month, Multicentre, Randomised, Double-blind, Controlled Study on the Safety and Efficacy of Single Intra-articular Administration of JTA-004 in Patients with Symptomatic Knee Osteoarthritis
REPORT PARTICULARS	
Report date	15 May 2019
Period of study	24 March 2016 to 27 April 2018

Protocol and Amendments

Protocol V02	**Initial**	**26 January 2016**
Protocol V03	Amendment 1	23 September 2016
Protocol V04	Amendment 2	10 May 2017

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OBJECTIVES
The objective of this study was to assess the safety and efficacy of JTA-004 (as a single intra-articular [IA] administration) in patients suffering from symptomatic OA of the knee until the end of the study period (Month 6). Primary study objectives were (i) the selection of the best JTA-004 strength and (ii) the superiority assessment of the efficacy of the best JTA-004 strength with respect to the Reference. They were determined as follows: - For selection of best JTA-004 strength (interim analysis), by comparing the different JTA-004 groups to each other with respect to the Western Ontario McMaster Universities (WOMAC®) VA3.1 Pain Subscale Score (mean differences between Baseline and Month 3) based on the point estimates and the 90% confidence intervals (CIs), - For superiority assessment, by comparing the best JTA-004 strength and Reference on the mean differences in WOMAC® VA3.1 Pain Subscale Score between Baseline and Month 6.

METHODOLOGY	
Study Design	Prospective, randomised, double-blind controlled two-stage Phase II/III trial
Treatments:	JTA-004 is a single administration enhanced viscosupplement which is reconstituted prior to use. The control treatment, Synvisc-One®, is a sterile viscoelastic solution provided in a ready-to-use syringe.
Treatment Duration	Single IA administration
Study Drug and Formulation	JTA-004 is composed of three active substances: - hyaluronic acid (HA) - *N*-(2,6-dichlorophenyl)-4,5-dihydro-1*H*-imidazol-2-amine (clonidine) - human plasma Three different strengths: JTA-004 50 (2ml), JTA-004 50 (4ml) and JTA-004 100 (2ml) were used. For the JTA-004 50 (2ml) and JTA-004 100 (2ml) study groups, the sodium hyaluronate content was 20 mg and the concentration of clonidine was 50 µg/ml and 100 µg/ml, respectively. For the JTA-004 50 (4 ml) study group, the sodium hyaluronate content was 40 mg and the concentration of clonidine was 50 µg/ml. JTA-004 was provided in kits containing vials of the freeze-dried JTA-004 and of the resuspension solution and all elements needed for the reconstitution of the product. One kit by patient was provided for JTA-004 50 (2ml) and JTA-004 100 (2ml) while two kits by patient were provided for JTA-004 50 (4ml).
Product Codes and Lot Numbers	Subjects in the JTA-004 50 study groups received either lot number 20160128 or 20161117. Subjects in the JTA-004 100 (2ml) study group received either lot number 20160204 or 20170202. Subjects in the Reference group received commercial lots of Synvisc-One® (Genzyme Europe BV): lot numbers 1028-260216A-BT, 1028-290216A-BT, 1028-020816A-BT, 1028-080317A-BT and 1028-020617A-BT were used.
Dose and Route of Administration	JTA-004 (as one of three different formulations: JTA-004 50 (2ml), JTA-004 50 (4ml) and JTA-004 100 (2ml)) or Reference product was given percutaneously in the knee, as a single IA administration.
Concomitant and Excluded Therapy:	Throughout the clinical trial, the Investigator could prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in the exclusion criteria. If excluded treatments were required, patients were withdrawn from the study.

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SUBJECT POPULATION	
Number Planned; Number Analysed	The protocol planned for treatment of a total of 164 subjects (41 subjects per treatment group). All 164 treated subjects were included in the analysis of safety; 150 (91.5%) were included in the analysis of efficacy.
Major Inclusion Criteria	Men and women, aged 50 to 79 years old, diagnosed with primary knee OA having a previous insufficient/failed response to analgesics and/or nonsteroidal anti-inflammatory drugs (NSAIDs).
ASSESSMENTS	
Efficacy	*Clinical Evaluation:* The following clinical assessments were performed: - WOMAC® VA3.1: WOMAC® Osteoarthritis Index is a tri-dimensional, self-administered, patient-centred health status questionnaire for knee disease severity and osteonecrosis symptoms. Patients were assessed at each follow-up visit from the Baseline/treatment visit to the end of the study follow-up at Month 6. To this end, each Investigational Site received validated WOMAC® Indexes in the language of the patient and the WOMAC® Index User Guide in English. - Well-Being using the Short-Form health survey (SF-12 questionnaire): the SF-12 questionnaire is the abridged form of the SF-36 questionnaire and takes into account the physical elements of health, psychological aspects and a subjective perception of health. - Consumption of analgesics and NSAIDs: at each follow-up visit from the Baseline/treatment visit to the end of the study follow-up at Month 6, patients were assessed for the consumption of analgesics and NSAIDs compared to the previous visit using the patient open questionnaire. In order to avoid bias, (self-reported) clinical evaluation was the first procedure during a study visit before discussing with the Principal Investigator or the Study Nurse/Coordinator. The patient had to complete the questionnaires alone without any outside intervention.
Safety	Physical examination, vital signs, haematology, serum chemistry, coagulation parameters, adverse event (AE) monitoring, and concomitant medications.
For the Schedule of Study Assessments, see Table 1 of the protocol, which is in Section **Error! Reference source not found.** of this final report.	
STATISTICAL METHODS AND ANALYSIS	
Efficacy	**Interim Analysis** An interim analysis to select the best JTA-004 strength was to be conducted on Month 3 data from 26 patients from each study group. Thus, the interim analysis was performed when 29 patients in each treatment group had been included (for a total of 116 included patients), which took into account an estimated drop-out rate of 10% at Month 3. The decisions for selecting the best JTA-004 strength at the interim analysis was based on the most promising p-value (conditional error approach; Koenig *et al.*, 2008).

	Final Analysis on Selected JTA Group The planned analyses were to be performed on the best JTA-004 strength identified at the time of the interim analysis: *Primary Endpoint* The primary endpoint is the WOMAC® VA3.1 Pain Subscale (subscale A): the individual changes in WOMAC® VA3.1 Pain Subscale Score between Baseline and Month 6 were calculated and compared by analysis of covariance (ANCOVA), adjusted for baseline value, to the Reference group. *Secondary Endpoints* The secondary efficacy endpoints were: - WOMAC® VA3.1 Pain Subscale (WOMAC® subscale A) at Month 3 - WOMAC® VA3.1 Total Score over time *Exploratory Endpoints* The exploratory endpoints were: - WOMAC® VA3.1 Total Score at Month 6 - WOMAC® VA3.1 Pain Subscale (WOMAC® subscale A) evolution over time - WOMAC® VA3.1 Stiffness Subscale (WOMAC® subscale B) at Month 6 and over time - WOMAC® VA3.1 Physical Function Subscale (WOMAC® subscale C) at Month 6 and over time - Well-being scores (SF-12 questionnaire: physical and mental component summary scores) at Month 6 and over time - Consumption of analgesics and NSAIDs at Month 6 and over time ***Post-hoc* Analyses on Non-selected and Pooled JTA Groups** A *post-hoc* analysis of efficacy for non-selected JTA-004 groups compared to the Reference group was performed using all the same endpoints as for the selected JTA-004 group. A second *post-hoc* analysis, in which the data from all 3 JTA-004 treatment groups were pooled for comparison with the Reference group, was performed to determine whether JTA-004 could provide statistically significant benefit over the Reference product. The analysis was performed for the WOMAC® Total Score and WOMAC® subscales A, B and C scores at Month 3 and Month 6.
Safety	Occurrence of any AEs and serious adverse events (SAEs), related or not to the product or the procedure, using patient open questionnaire, physical examination (including vital signs), and laboratory measurements.
STUDY POPULATION RESULTS	
Demographics	The mean age at enrolment was 62.7 years (Standard Deviation [SD]: 7.5 years). Overall, 68.3% of the patients were female and 31.7% were male. The mean height and weight at enrolment were 1.6 m (SD: 0.10 m) and 79.2 kg (SD: 14.5 kg), respectively, for a mean Body Mass Index (BMI) of 28.5 kg/m^2 (SD: 3.9 kg/m^2). This distribution was comparable within each treatment group.
Patient Populations	• Screened: 229 patients • Randomised: 173 (75.5%) patients • Treated: 164 (71.6%) patients (41 subjects in each treatment group) • Completed: 147 (89.6%) patients

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EFFICACY RESULTS	
Interim Analysis	A total of 116 patients were included at the time of the interim analysis (29 per group). The difference between each JTA-004 strength and the Reference group in mean Change from Baseline in WOMAC® Pain Subscale Score at Month 3 from ANCOVA analysis (adjusted for the differences in Baseline values) was in favour of JTA-004 for all strengths. The difference was the largest for the JTA-004 50 (4 ml) group. The difference was still in favour of JTA-004 for all strengths at Month 6. However, the largest difference was observed for the JTA-004 100 (2 ml) group. The same pattern, *i.e.*, largest difference for the treatment group JTA-004 50 (4 ml) at Month 3 and for the treatment group JTA-004 100 (2 ml) at Month 6, was also observed for the WOMAC® Physical Function Subscale Score and the WOMAC® Total Score. As the study primary endpoint was the difference in WOMAC® VA3.1 Pain Subscale Score at Month 6, the Independent Data Monitoring Committee (IDMC) selected JTA-004 100 (2 ml) as the most effective JTA-004 strength with respect to the predefined decision rules.
Primary Variable	**<u>WOMAC® VA3.1 Pain Subscale Score at Month 6</u>** The primary analysis was conducted on the Full Analysis Set (FAS), which included a total of 82 patients - 41 patients in the JTA-004 100 (2ml) group (group selected at interim analysis) and 41 patients in the Reference group. At Month 6, the mean WOMAC® Pain Subscale Score had decreased with respect to Baseline in both groups. The mean Change from Baseline was -26.7 mm (SD: 28.9 mm) in the JTA-004 100 (2ml) group and -11.3 mm (SD: 27.9 mm) in the Reference group. As shown in Synopsis Figure 1, the adjusted mean Change from Baseline at Month 6 was -23.6 mm (SE: 4.6 mm) for the JTA-004 100 (2ml) group and -14.1 mm (SE: 4.3 mm) for the Reference group; the difference in mean Change from Baseline between the JTA-004 100 (2ml) group and the Reference group was -9.49 mm (adjusted 95% CI:-22.21; 3.23). The difference between groups was not statistically significant (p = 0.141).

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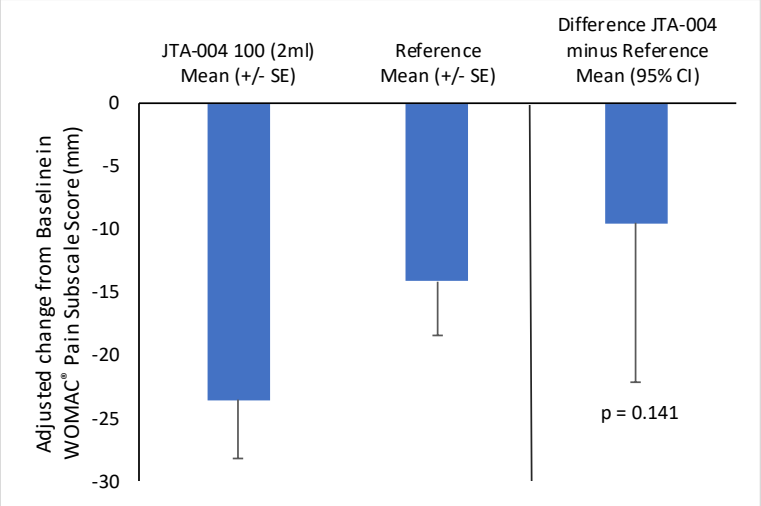
Primary Variable (continued)

Synopsis Figure 1: WOMAC® Pain Subscale Score - Change from Baseline at Month 6 - FAS



Source: Section 10A, Table 14.2.1.1.

Data from predefined supportive analyses in different patient populations (Per Protocol (PP) and the FAS [with missing values imputed]) confirmed the primary analysis; whereas the differences in adjusted mean WOMAC® Pain Subscale Score at Month 6 invariably favoured the JTA-004 100 (2ml) group, the p values for the difference between groups were >0.05.

Secondary Variables

WOMAC® VA3.1 Pain Subscale Score at Month 3

The mean Change from Baseline in Pain Subscale Score was -29.8 mm in the JTA-004 100 (2ml) group and -12.5 mm in the Reference group (Synopsis Table 1). The difference between the 2 groups (in adjusted mean change) was -11.63 mm, which was not statistically significant (p value > 0.025).

Synopsis Table 1: WOMAC® Pain Subscale Score - Change from Baseline at Month 3 - FAS

	JTA-004 100 (2ml) (N=41)	**Reference (N=41)**
n	35	40
Mean ± SD	-29.8 ± 24.2	-12.5 ± 24.9
Difference between treatments (JTA-004 – Reference) in Change from Baseline at Visit 4 (Month 3)		
Adjusted Mean (Standard Error [SE])	-11.63 (5.50)	
Adjusted CI	[-22.60 ; -0.66]	
p-value	0.038	

Source: Section 10A, Table 14.2.2.2.1.1 and Table 14.2.2.2.3.1.

WOMAC® VA3.1 Total Score over time

Observed differences in mean Total Score were consistently smaller in the Reference group with respect to the JTA-004 100 (2 ml) group (Synopsis Table 2). However, none of the differences between treatment groups were statistically significant (all p-values were > 0.05).

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Secondary Variables (continued)

Synopsis Table 2: WOMAC® Total Score - Change from Baseline Over Time - FAS

	JTA-004 100 (2ml) (N=41)	**Reference (N=41)**
Visit 3 (Week 2)		
Change from Baseline in WOMAC Total score		
n	41	41
Mean ± SD	-22.7 ± 22.9	-17.7 ± 19.2
Difference between treatments (JTA-004 – Reference) in Change from Baseline at Visit 3 (Week 2)		
Adjusted Mean (SE)	-1.48 (4.35)	
Adjusted CI	[-12.70 ; 9.74]	
p-value	0.997	
Visit 4 (Month 3)		
Change from Baseline in WOMAC Total score		
n	34	40
Mean ± SD	-27.7 ± 23.3	-17.1 ± 24.2
Difference between treatments (JTA-004 – Reference) in Change from Baseline at Visit 4 (Month 3)		
Adjusted Mean (SE)	-2.94 (5.30)	
Adjusted CI	[-16.52 ; 10.65]	
p-value	0.972	
Visit 5 (Month 6 / Early Termination)		
Change from Baseline in WOMAC Total Score		
n	35	39
Mean ± SD	-26.8 ± 27.3	-14.0 ± 26.9
Difference between treatments (JTA-004 – Reference) in Change from Baseline at Visit 5 (Month 6)		
Adjusted Mean (SE)	-7.17 (5.96)	
Adjusted CI	[-22.28 ; 7.94]	
p-value	0.599	

Source: Section 10A, Table 14.2.2.2.1.1 and Table 14.2.2.2.5.1.

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***Post hoc* Analyses**

Non selected group analysis (first *post hoc* analysis)

WOMAC® VA3.1 Pain Subscale Score at Month 6

At Month 6, the mean WOMAC® Pain Subscale Score had decreased in all groups (Synopsis Table 3).

The differences between the JTA-004 groups and the Reference group in mean Change from Baseline were in favour of the JTA-004 groups, when adjusted for Baseline value. However, none of the differences between groups were statistically significant ($p > 0.05$).

Synopsis Table 3: WOMAC® Pain Subscale Score - Change from Baseline at Month 6 - FAS (non selected groups)

	JTA-004 50 (2 ml) (N=41)	**JTA-004 50 (4 ml) (N=41)**	**Reference (N=41)**
Change from Baseline in WOMAC Pain Subscale at Visit 5 (Month 6)			
n	36	40	39
Mean ± SD	-29.2 ± 29.5	-27.1 ± 29.4	-11.3 ± 27.9
Difference between treatments (JTA-004 – Reference) in Change from Baseline at Visit 5 (Month 6)			
Adjusted Mean (SE)	-11.63 (6.02)	-11.42 (5.78)	-
Adjusted CI	[-23.64 ; 0.38]	[-22.94 ; 0.09]	-
p-value	0.057	0.052	-

Source: Section 10B, Table 14.2.1.1, Section 10C, Table 14.2.1.1 and Section 10D, Table 14.2.2.2.1.1.

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***Post-hoc* analyses (continued)**

WOMAC® VA3.1 Pain Subscale Score at Month 3

The mean Change from Baseline in Pain Subscale Score was -25.5 mm in the JTA-004 50 (2ml) group, -30.2 mm in JTA-004 50 (4ml) group, and -12.5 mm in the Reference group (Synopsis Table 4).

For the JTA-004 50 (4ml) group, the p value for the adjusted mean difference in Change from Baseline was <0.05, indicating statistical significance. However, for the JTA-004 50 (2ml) group, the adjusted mean difference with respect to the Reference group was not statistically significant.

Synopsis Table 4: WOMAC® Pain Subscale Score - Change from Baseline at Month 3 - FAS (non selected groups)

	JTA-004 50 (2 ml) (N=41)	**JTA-004 50 (4 ml) (N=41)**	**Reference (N=41)**
Change from Baseline in WOMAC Pain Subscale			
n	39	41	40
Mean ± SD	-25.5 ± 30.2	-30.2 ± 28.1	-12.5 ± 24.9
Difference between treatments (JTA-004 – Reference) in Change from Baseline at Visit 4 (Month 3)			
Adjusted Mean (SE)	-9.13 (5.72)	-13.81 (5.15)	-
Adjusted CI	[-20.52 ; 2.25]	[-24.05 ; -3.57]	-
p-value	0.114	0.009	-

Source: Section 10B, Table 14.2.2.2.3.1; Section 10C, Table 14.2.2.2.3.1; Section 10D, Table 14.2.2.2.1.1.

WOMAC® VA3.1 Total Score over time

Observed differences in mean Total Score were consistently smaller in the Reference group with respect to the JTA-004 groups (Synopsis Table 5). However, none of the differences were statistically significant; the p-values for both groups were > 0.05 at all time points.

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***Post-hoc* analyses (continued)**

Synopsis Table 5: WOMAC® Total Score - Change from Baseline Over Time - FAS (non selected groups)

	JTA-004 50 (2 ml) (N=41)	**JTA-004 50 (4 ml) (N=41)**	**Reference (N=41)**
Visit 3 (Week 2)			
Change from Baseline in WOMAC Total Score			
n	39	39	41
Mean ± SD	-22.5 ± 23.2	-17.8 ± 22.6	-17.7 ± 19.2
Difference between treatments (JTA-004 – Reference) in Change from Baseline at Visit 3 (Week 2)			
Adjusted Mean (SE)	-3.03 (4.45)	1.26 (4.36)	-
Adjusted CI	[-14.50 ; 8.43]	[-9.94 ; 12.45]	-
p-value	0.942	0.998	-
Visit 4 (Month 3)			
Change from Baseline in WOMAC Total Score			
n	38	41	40
Mean ± SD	-24.3 ± 28.8	-29.7 ± 27.6	-17.1 ± 24.2
Difference between treatments (JTA-004 – Reference) in Change from Baseline at Visit 4 (Month 3)			
Adjusted Mean (SE)	-4.34 (5.44)	-10.55 (5.05)	-
Adjusted CI	[-18.21 ; 9.54]	[-23.42 ; 2.32]	-
p-value	0.878	0.143	-
Visit 5 (Month 6 / Early Termination)			
Change from Baseline in WOMAC Total Score			
n	36	40	39
Mean ± SD	-29.5 ± 30.9	-25.8 ± 30.1	-14.0 ± 26.9
Difference between treatments (JTA-004 – Reference) in Change from Baseline at Visit 5 (Month 6)			
Adjusted Mean (SE)	-11.49 (5.84)	-10.11 (5.68)	-
Adjusted CI	[-26.29 ; 3.32]	[-24.47 ; 4.24]	-
p-value	0.177	0.246	-

Source: Section 10B, Table 14.2.2.2.5.1; Section 10C, Table 14.2.2.2.5.1; Section 10D, Table 14.2.2.2.1.1.

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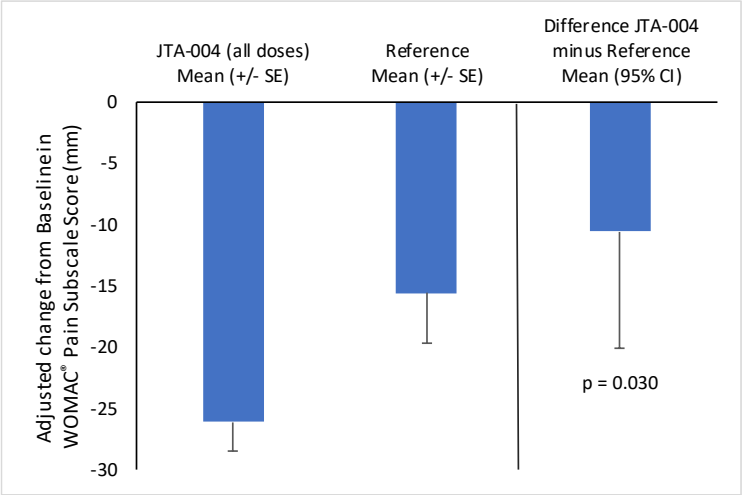
***Post-hoc* analyses (continued)**	**Pooled analysis (second *post hoc* analysis)** All differences (in WOMAC® Total Score and WOMAC® subscales A, B and C scores) between groups at Month 3 and Month 6 were in favour of the pooled JTA-004 groups. The difference between the pooled JTA-004 groups and the Reference group was statistically significant for Pain Subscale Score (p = 0.014) and Physical Function Subscale Score (p = 0.040) at Month 3. In line with the study primary endpoint, the difference in Pain Subscale Score at Month 6 was statistically significant (p =0.030). At Month 6, the adjusted mean Change from Baseline in Pain Subscale Score was -26.1 mm (SE: 2.4 mm) for the pooled JTA-004 groups and -15.6 mm (SE: 4.1 mm) for the Reference group; the difference in mean Change from Baseline between the pooled JTA-004 groups and the Reference group was -10.57 mm (adjusted 95% CI:-20.08; -1.06) (Synopsis Figure 2). ***Synopsis Figure 2: Mean Change from Baseline in WOMAC® Pain Subscale Score at Month 6 - Analysis of Covariance - FAS (pooled JTA groups)***  Source: Section 10E, Page 2/5.
SAFETY RESULTS	
Extent of Exposure	All 123 subjects randomised to the JTA groups received the full dose of study treatment. One subject randomised to the Reference group did not receive the entire volume of the study drug (5 ml instead of 6 ml). The mean duration of follow-up for the 164 treated patients was 6.3 months (SD: 1.0 month).
All AEs	During the study period, 116 (70.7%) patients experienced a total of 292 emergent AEs with no significant differences between groups. Among these emergent AEs, 49 were considered related to treatment: 5 events in 3 patients in the JTA-004 50 (2ml) group, 15 events in 12 patients in the JTA-004 50 (4ml) group, 12 events in 8 patients in the JTA-004 100 (2ml) group, and 17 events in 11 patients in the Reference group. There was a trend for fewer related events in the JTA-004 50 (2ml) group. The most frequently reported AEs considered as either related to the study treatment or to study procedure across all study groups were arthralgia, injection site pain and hypotension (6 patients (7.3%) in the JTA-004 50 (4ml) and JTA-004 100 (2ml) groups had mild and short-lasting hypotension after injection)

Deaths and Other Serious AEs	No death was reported during the study. Eight patients experienced a total of 11 emergent SAEs: 4 events in 4 patients in the JTA 004 50 (2ml) group, 1 event in 1 patient in the JTA 004 50 (4ml) group, 5 events in 2 patients in the JTA 004 100 (2ml) group, and 1 event in 1 patient in the Reference group. None of the events was reported by more than a single patient. One patient (0113 in the JTA-004 100 [2ml] group) experienced 3 emergent SAEs considered as possibly related to study treatment or procedure: one event of acute osteomyelitis and two events of chronic osteomyelitis. The event of acute osteomyelitis was reported as a Suspected Unexpected Serious Adverse Reaction (SUSAR) by the Sponsor as a precautionary measure but upon complete review of the case, the event was assessed as not related to trial medication or study procedure by the Sponsor.
AEs with NCI Toxicity of Grade 3 or 4	Seven emergent AEs were reported as severe: 1 in the JTA 004 50 (4ml) group and 6 in the JTA 004 100 (2ml) group. Of the severe events, 3 (one event of acute osteomyelitis and two events of chronic osteomyelitis reported for patient 0113) were considered as possibly related to study treatment or procedure by the Investigator. The events were assessed as not related to trial medication or study procedure by the Sponsor.
Laboratory Results	Twenty-one abnormal values (after Baseline) were considered as clinically significant in 10 patients (6.3%) with no significant differences between groups. Fourteen of these values were reported as adverse events.
Vital Signs and Physical Findings	Vital signs remained stable over the course of follow-up; no clinically relevant changes from Baseline in any parameter were observed (with the exception of the 6 mild cases of hypotension after treatment reported as adverse events, see above). Individual patient values were in line with what could be expected in this population.
CONCLUSIONS	
Efficacy	As shown by the amplitude of the SD, the inter-patient variability was large for all clinical endpoints assessed in this study. There was also a statistically significant difference in pain at baseline between the reference and the JTA groups, this was taken into account in the adjusted mean difference calculation. Notably due to these factors, the strength chosen at the time of the interim analysis (JTA-004 100 (2ml)) could not be demonstrated statistically to be superior to the Reference treatment with regards to the change in WOMAC® VA3.1 Pain Subscale Scores at Month 6 (primary efficacy endpoint), although the observed change in mean Pain Score was greater in the JTA-004 100 (2ml) group than in the Reference group. All observed differences in the secondary and exploratory efficacy endpoints with respect to Baseline values were also greater in the JTA-004 100 (2ml) group than in the Reference group. However, none of the differences between treatment groups were statistically significant. *Post-hoc* analyses of the other non-selected strengths (JTA-004 50 (2ml) and JTA-004 50 (4ml)) provided similar results, and no clear benefit of one JTA-004 strength over another could be evidenced. However, pooled analysis of all JTA-004 strengths did indicate statistical significance for the pooled JTA-004 groups over the Reference therapy for Pain Subscale Scores at Month 3 (similar to the key secondary efficacy endpoint) and at Month 6 (similar to the primary efficacy endpoint), indicating that further clinical development of JTA-004 is warranted.
Safety	JTA-004 was shown to be well tolerated at all strengths evaluated. There was a trend for fewer treatment-related events in the JTA-004 50 (2ml), notably no cases of post injection hypotension. Therefore, this strength was selected to go further in Phase III.

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Conclusion	The present study showed that JTA-004 was well tolerated at all strengths evaluated. This study provides preliminary evidence of the efficacy of JTA-004 in the treatment of symptomatic osteoarthritis of the knee, although the results do not indicate a statistically significant benefit of one specific strength of JTA-004 with respect to the Reference therapy. Nevertheless, the observed differences between the JTA-004 groups and the Reference group which were consistently in favour of JTA-004, and the statistically significant superiority of the pooled JTA-004 strengths versus the Reference group in the *post hoc* analyses, support further clinical development of JTA-004 in this indication with the JTA-004 50 (2ml) strength which showed a trend for a more favourable safety profile.