Osteoarthritis and Cartilage xxx (xxxx) xxx–xxx

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

A single intra-articular injection of JTA-004, a combination of human plasma, hyaluronic acid, and clonidine, versus placebo in symptomatic knee osteoarthritis: A Phase 3 trial☆

Asger Reinstrup Bihlet [a] * [1], Yves Henrotin [b] [1], Edith Ming Chu Lau [c], Peter Alexandersen [d], Olivier Godeaux [e], Helene Rovsing [f], François Rieger [h], Carole Nicco [g] [h]

[a] NBCD A/S, Telefonvej 8D, Søborg 2860, Denmark
[b] Musculoskeletal Innovative Research Lab, University of Liège, Belgium
[c] Hong Kong Center for Clinical Research, Hong Kong
[d] Sanos Clinic Syddanmark, Vejle, Denmark
[e] ZAM Consulting srl, formerly Bone Therapeutics S.A., Mont-St-Guibert, Belgium
[f] Sanos Clinic Nordjylland, Gandrup, Denmark
[g] Université Paris Cité, Paris, France
[h] Medsenic, Strasbourg, France

ARTICLE INFO

Article history:
Received 17 June 2025
Accepted 22 September 2025

Keywords:
Knee osteoarthritis
Randomized controlled trials
Clonidine
Inflammation
Hyaluronic acid
Viscosupplement

ABSTRACT

Objectives: Intra-articular treatments for osteoarthritis (OA) are limited by their efficacy, safety, or duration of response. JTA-004 is a potential novel treatment for OA for intra-articular (IA) injection, combining hyaluronic acid (HA) and clonidine with human plasma to enhance the effects of HA. The objectives of the trial were to evaluate the efficacy and safety of JTA-004 in participants with symptomatic knee OA, where the primary objective was evaluating the efficacy of JTA-004 in terms of WOMAC pain, compared to placebo.

Design: The trial was a multicenter, Phase 3, randomized, double-blind, placebo- and active-controlled clinical trial, evaluating the efficacy and safety of a single IA injection of JTA-004, compared to saline (primary hypothesis) and an HA-comparator (Synvisc-One®) (secondary hypothesis) in knee OA with a Kellgren-Lawrence grade of 2 or 3. For the secondary hypothesis, non-inferiority of JTA-004 to active comparator by comparing the 2 treatment groups on the mean differences in WOMAC pain with a non-inferiority margin of $\Delta = 10$ mm. Primary efficacy endpoint was the change from baseline in WOMAC pain to Month 3. The main secondary efficacy endpoints included changes from baseline in WOMAC function and stiffness at Months 3 and 6, OMERACT-OARSI responder rates, global assessments, and use of rescue medication. Safety assessments were based on adverse events (AE) reporting, and post-injection vital signs.

Results: A total of 746 participants were randomized, of which 687 (92.1%) completed the trial. The results indicated no significant differences in the primary endpoint between JTA-004 and placebo (LSmean difference: −1.50 mm, 95%CI 5.12; 2.12, p= 0.42) or Synvisc-One® (LSmean difference: 2.40, 95% CI: −1.22; 6.02, p=0.20) nor in either of the efficacy outcomes of the main study population. The safety and tolerability of

☆ Trial registration number: Clinicaltrials.gov (NCT04333160) and the EudraCT database (2019–000796–16).

* Corresponding author.
E-mail addresses: abi@nbcd.com (A.R. Bihlet), yhenrotin@uliege.be (Y. Henrotin), edith.lau@hkccr.co (E.M.C. Lau), pal@sanosclinic.com (P. Alexandersen), ogodeaux@zam-consulting.com (O. Godeaux), hel@sanosclinic.com (H. Rovsing), rieger.meds@gmail.com (F. Rieger), carole.nicco@u-paris.fr (C. Nicco).

[1] Co-primary authors contributing equally to the manuscript.

https://doi.org/10.1016/j.joca.2025.09.015

Please cite this article as: A.R. Bihlet et al., A single intra-articular injection of JTA-004, a combination of human plasma, hyaluronic acid, and clonidine, versus placebo in symptomatic knee osteoarthritis: A Phase 3 trial, Osteoarthritis and Cartilage, https://doi.org/10.1016/j.joca.2025.09.015

JTA-004 was good, and there were no differences in the frequency of any of the reported AEs or trial discontinuations between the study groups.

Conclusions: A single IA injection of JTA-004 was not superior to a saline solution (LSmean difference: −1.50 mm, 95%CI 5.12; 2.12, p= 0.42) or Synvisc-One® (LSmean difference: 2.40, 95% CI: −1.22; 6.02, p=0.20) for the treatment of OA symptoms in the overall study population.

Introduction

Currently approved pharmacological treatments for osteoarthritis (OA) are limited to symptom-modifiers, oral analgesics such as paracetamol/acetaminophen with modest efficacy [1] and NSAIDs with a good efficacy profile but risks of serious safety issues associated with long-term use [2,3]. Intra-articular injections to alleviate symptoms include corticosteroids, which are known to be highly efficacious but with short duration of action and risks of deleterious joint structural effects [4,5]. New treatments addressing these shortcomings of existing treatments are in high demand, and as a potential solution, combinations of existing treatment modalities to enhance the effects of the individual components and induce a longer duration of action could be of great value for patients suffering from OA.

JTA-004 is a fixed-dose viscosupplement combination product consisting of hyaluronan, human plasma, and clonidine for IA injection.

HA is a well-known treatment modality used in OA for its beneficial yet modest effects on symptoms [6,7]. The content of plasma coagulation factors from human plasma in JTA-004 is intended to facilitate in situ gel formation, which is triggered by the presence of the excipient calcium once in contact with the synovial fluid. In the formed gel, plasma proteins contained in JTA-004 (albumin, globulins, and fibrin) are expected to aggregate and form a tenuous polymeric network entangling the long HA chains [8–11].

Apart from platelet-rich plasma and particular preparations containing low-molecular weight fraction of human serum albumin [12,13], no data to evaluate the efficacy and safety of IA human plasma as a single agent exist. Studies indicate that plasma proteins and HA may act as boundary lubricants for articular cartilage [14]. The HA primarily appears to provide the viscous response where the bovine serum albumin adds interfacial elasticity. In addition, globular proteins can exhibit bulk aggregation that affects bulk rheology [15]. Moreover, in a study conducted on explanted femoral heads from early and advanced OA subjects treated with HA and γ–globulin solutions, in advanced stage OA, both HA and γ–globulin significantly improved cartilage frictional behavior [16].

In addition, JTA-004 contains clonidine, an α-adrenoreceptor agonist intended to enhance short-term pain relief through analgesic action. Clonidine is used off-label in arthroscopy/knee surgery practice to relieve pain after IA injection [17–19], but apart from the previous trial evaluating JTA-004, the use of clonidine in a clinical trial in knee OA has not previously been described in the literature.

Results from preclinical experiment with JTA-004 in an anterior cruciate ligament tear model of OA indicated that JTA-004 was associated with a protective effect, reducing significantly osteolysis and/or osteophytes (data on file).

Previously, a Phase 2 clinical study was conducted to assess the safety and efficacy of JTA-004 (as a single IA administration) until 6 months after injection in subjects suffering from symptomatic OA of the knee. The study showed that JTA-004 viscosupplement was well tolerated in all formulations evaluated. The results did not reach a statistically significant benefit of one specific formulation of JTA-004 with respect to the reference therapy, however, the observed differences between the JTA-004 groups and the reference group were consistently in favor of JTA-004 up to 6 months [20].

Based on the evidence described above, the objective of this trial was to evaluate the efficacy and safety of IA injections of JTA-004 in patients with knee OA in a large multicenter Phase 3 trial.

Patients and methods

Study design

The trial was a randomized, placebo-controlled, double-blind, active-comparator Phase 3 trial, evaluating a single IA injection of either JTA-004, a commercially available hyaluronic acid product (HA) viscosupplement (Synvisc-One®), or isotonic saline solution.

The total trial duration was 12 months, with the primary endpoint assessment at Month 3. Participants were randomized 2:1:1 between JTA-004, Synvisc-One®, or saline solution. The trial was performed in 23 sites across six European countries and Hong Kong. The main inclusion criteria were meeting the American College of Rheumatology (ACR) clinical and radiographic criteria for femorotibial OA [21], with a radiographic Kellgren-Lawrence Grade of 2 or 3, a Western Ontario and McMaster University Arthritis Index (WOMAC), version VA3.1 pain subscale score of ≥ 40 mm and ≤ 80 mm (out of 100 mm) at screening and baseline, insufficient/failed response or intolerance to analgesics and/or non-steroidal anti-inflammatory drugs (NSAIDs). The inclusion criterion concerning WOMAC pain was amended in Protocol Version 2.0 early in the trial after 66 participants had been randomized, from requiring the defined threshold to be present only at the screening visit to be required at both the screening and baseline visits to ensure the main analysis population had the intended baseline level of pain (40 out of 100 mm).

The main exclusion criteria were body mass index ≥40 kg/m^2, history of knee trauma or recent surgery within 12 months, presence of other painful conditions likely to interfere with the study endpoints, WOMAC pain score of the non-target knee exceeding that of the target knee at screening or baseline, presence of neuropathic pain or fibromyalgia, recent IA injection of HA (6 months), platelet-rich plasma (6 months), or corticosteroids (4 months). Any use of analgesic medication was prohibited during the trial, except for rescue medication (paracetamol or ibuprofen) dispensed as a part of the protocol.

Trial site visits were performed for screening, baseline (Day 0), where the IA injection of the Investigational Medicinal Product (IMP) was performed, Month 1, Month 3, Month 6, and Month 12, and phone visits on Day 1, Day 14, Month 2, and Month 5 for collection of reported adverse events (AEs) and changes in concomitant medication.

The primary endpoint was the change from baseline in WOMAC VA3.1 pain sub-score at Month 3 between JTA-004 and saline solution (placebo). The key secondary endpoints included change from baseline in WOMAC pain at Month 6 between JTA-004 and placebo, change from baseline in WOMAC pain at Month 3 between JTA-004 and Synvisc-One®, change from baseline in the WOMAC physical

function sub-scale at Month 3 between JTA-004 and placebo, change from baseline in Patient Global Assessment (PGA) at Month 3 between JTA-004 and placebo, change from baseline in the WOMAC physical function sub-scale at Month 6 between JTA-004 and placebo, change from baseline in subject global health and well-being score at Month 3 using the EQ-5D-5L questionnaire between JTA-004 and placebo, and the differences between JTA-004 and placebo in responder rate (defined as ≥ 30% pain intensity reduction) at Month 3. The key secondary endpoints were sequentially tested in this particular order, as further described below. The 30 % reduction in WOMAC pain was selected based on several literature reports using this cut-off [22–25]. Other endpoints included changes from baseline in WOMAC subscores, PGA, Investigator Global Assessment (IGA), EQ-5D at different time points up to Month 6, and rescue medication up to Month 6 and 12. Safety endpoints included AEs and vital signs, including a 2-hour assessment following the IA injection to monitor the risk of hypotension hypothetically associated with clonidine. All AEs were reported and collected during the period starting from informed consent until Month 6. In contrast, only serious AEs (SAEs) were collected in the period from Month 6 to Month 12.

The trial was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonization—Good Clinical Practice (ICH-GCP). The protocol was approved by all relevant competent authorities and ethics committees. All subjects gave their informed consent to participate. The trial was prospectively registered in clinicaltrials.gov (NCT04333160) and the EudraCT database (2019–000796–16).

Radiography

All radiographs were posteroanterior knee X-rays obtained using a fixed-flexion frame to evaluate the Kellgren-Lawrence (KL) grade at the time of screening.

At least two experienced musculoskeletal radiologists read the radiographs centrally. In case of disagreement on the KL grade, a third senior radiologist provided the decisive assessment. All personnel involved in the acquisition and reading of any image in the trial remained blinded to treatment allocation throughout the trial. A follow-up X-ray was performed at Month 12, and evaluated for changes in structural severity and OA structural features.

Investigational product, administration, randomization, and blinding

Each dose of JTA-004 viscosupplement was a 2 mL fixed-dose combination of 118.8 mg of a commercially available allogeneic human plasma protein product (OctaplasLG®), 20 mg sodium hyaluronate, and 100 µg clonidine HCl. The IMP was supplied in kits, each containing one vial of freeze-dried powder and one vial of water for injection used for resuspension of the IMP. The active comparator was Hylan G-F 20 8 mg/mL (Synvisc-One®, Genzyme Corporation) in a ready-to-use syringe containing 6 mL of product. The comparator was isotonic saline. The preparation of the IMP for injection and the subsequent injection was performed by dedicated unblinded personnel (pharmacists and physician injectors) with no other involvement in the trial conduct or interactions with the participants. As the appearance of the three treatment groups differed, appropriate measures were taken to conceal the appearance of the syringe and contents of the syringe for the participant during the injection procedure. The use of ultrasound guidance for the injection procedure was allowed but not mandatory. Any extractable synovial fluid was extracted before the injection of the IMP.

Randomization was performed using an Integrated Web-Response System (IWRS). The IWRS determined the treatment group of the participant and allocated a treatment number to the subject to associate a specific treatment to a specific subject. The IWRS was accessible through a secure website to authorized users with valid individual login and password. Stratification was performed according to the following criteria: (1) Body Mass Index (BMI): ≤30 kg/m^2 / > 30 kg/m^2, (2) target knee pain at baseline (VAS): < 59 mm / ≥59 - < 70 mm / ≥70 mm and (3) knee pain distribution: unilateral/bilateral. If pain at the contralateral knee is ≤ 30 mm, the subject will be randomized as unilateral, and if pain at the contralateral knee is > 30 mm, the subject will be randomized as bilateral.

Outcome assessments

For the patient-reported outcome measures, symptoms of OA were assessed using WOMAC, version VA3.1, where participants scored their symptoms in three categories of pain, stiffness, and functional impairment on a Visual Analogue Scale 0–100 mm in each of the 24 questions, evaluated at Screening, Baseline, and Months 1, 3, 6, and 12. The WOMAC data was normalized to a 0–100 scale for each subscale for ease of interpretation. An Investigator Global Assessment, a Patient Global Assessment, and EQ-5D-5L quality of life assessment was performed at Baseline and Months 1, 3, 6, and 12. The patient-reported outcome assessments were collected directly from the participants using an electronic patient-reported outcomes system.

In addition, a general pain evaluation (single question) was collected at Baseline (Day 1) and each day through to Day 15 for evaluation of the day-to-day pain developments during the first fourteen days of the trial, in addition to Months 1, 3, 6 and 12.

The target knee was determined based on the eligibility criteria as specified above. If both knees were eligible based on pain level and KL grade, the knee with the higher baseline pain level, as measured by WOMAC pain, was selected. If both knees had identical WOMAC pain scores, the target knee was determined by the investigator.

Safety data was comprised of reported AEs and vital signs collected at study visits. All AEs were reported in the period from informed consent until the Month 6 visit. As per study protocol, only SAEs were reported between Month 6 and Month 12 of the trial. To evaluate the hypothetical potential for hypotension caused by systemic exposure to clonidine, vital signs (blood pressure and heart rate) monitoring at 15, 30, 45, 60, and 120 min after the IMP injection was performed at the baseline visit.

Statistical methods

Sample size

Assuming a mean between-group difference of $\delta 1$ = 10 mm on a 0–100 mm transformed scale, in favor of JTA-004 compared to placebo with a standard deviation (SD) of 30 mm [20] and using a 2-sided Student t-test with a statistical power of 90% and significance level (α) of 0.05, a sample size of 286 evaluable subjects in the JTA-004 group and 143 evaluable subjects in the placebo group (allocation ratio 2:1) would allow rejecting the null hypothesis in favor of the alternative hypothesis (superiority of JTA-004 to placebo). Additionally, assuming a mean between-group difference of δ_2 = 0 mm between JTA-004 and active comparator with a SD of 30 mm, a non-inferiority margin of Δ = 10 mm and using a 1-sided Student t-test with a statistical power of 90% and significance level (α) of 0.025, a sample size of 286 evaluable subjects in the JTA-004 group and 143 evaluable subjects in the active comparator group (allocation ratio 2:1) would allow rejecting the null hypothesis in favor of the alternative hypothesis (non-inferiority of JTA-004 to active comparator). A total number of 572 evaluable subjects will be required for analysis with an allocation ratio of 2:1:1 for JTA-004 (286 evaluable subjects),

placebo (143 evaluable subjects), and active comparator (143 evaluable subjects), respectively.

Considering the 66 subjects included before protocol version 2.0 who were excluded from the main analysis (as having baseline WOMAC pain out of range as per protocol version 2.0) and were replaced, and an estimated rate of non-evaluable subjects around 15%, a total number of 742 treated subjects was required.

Analysis sets

The Intention-to-Treat (ITT) population included all subjects who were randomized into the study, regardless of whether the IMP was administered. This population was used to report participant disposition and as an additional efficacy set. In addition, a Modified Intent-to-Treat (mITT) population was defined: The mITT population included all subjects with a baseline target knee pain between 40 and 80 mm out of 100 mm on WOMAC pain and who received the IMP. This population was used as an additional efficacy set.

The full analysis set (FAS) included all randomized and treated subjects having a baseline and a post-baseline efficacy assessment of WOMAC (i.e., score available at baseline and score available at Month 1, Month 3, or Month 6 visit) with a baseline target knee pain between 40 and 80 mm (out of 100 mm) on WOMAC pain. This population was used for the primary analysis of the efficacy endpoints. Analyses in these populations were performed according to the randomization group regardless of the study treatment received. The Per Protocol Set (PPS) comprises subjects from the FAS without significant protocol deviation(s) excluding from PPS. The primary and other efficacy endpoints was analyzed using the PPS in addition to the FAS. The Safety (SAF) Population comprised all subjects who received the IMP whatever the protocol version under which they were included.

Data analysis

Primary endpoint analysis

Mean changes from baseline to Month 3 in the WOMAC pain subscale score were compared between JTA-004 and placebo treatment groups using a Mixed Model for Repeated Measurements (MMRM). The MMRM included treatment group and timepoint as fixed factors as well as stratification factors, treatment by timepoint interaction, and WOMAC pain score at baseline as covariate. Three timepoints were considered in the model: Month 1 (Visit 3), Month 3 (Visit 4) and Month 6 (Visit 5). All treatment groups were included in the model.

The treatment comparisons were carried out using contrasts on the treatment factor by time effect. The within-subject variance-covariance matrix will be assumed to be unstructured.

The primary endpoint was tested with a 2-sided type I error rate 0.05. The MMRM model analysed all available data, assuming that any missing data is missing-at-random, and did not utilize imputation of missing data.

Secondary endpoint analyses

If the primary comparison of JTA-004 viscosupplement vs placebo results in a statistically significant improvement in knee pain at Month 3, then subsequent comparisons would be tested for the key secondary endpoints using a serial gatekeeping procedure with pre-specified hierarchical order as listed above. To control the overall type I error rate at 2-sided 0.05, each hypothesis regarding the key secondary endpoint was formally tested only if the previous hypothesis in the pre-specified hierarchical order is the key secondary endpoint was formally tested only if the previous hypothesis in the pre-specified hierarchical order was tested significantly. If a test was not significant (at a one-sided 0.025 significance level for a non-inferiority test or a 2-sided 0.05 significance level for the superiority test), the serial gatekeeping procedure stopped (the result of the test as well as the next tests of the sequence cannot be claimed significant). Analyses of continuous key secondary endpoints were performed in the same manner as the main analyses of the primary endpoint. For non-inferiority claims, JTA-004 was considered to be non-inferior to active comparator if the upper bound of the 95% CI of the difference between JTA-004 and active comparator at Month 3 using the WOMAC® VA3.1 pain subscale (subscale A) is inferior to 10 mm. Responder rates at Month 3 were compared between treatment groups using the Cochran-Mantel-Haenszel test with adjustment for stratification factors.

The Safety Analysis Set summarized safety data descriptively overall and by treatment group. All analyses were performed using SAS software.

Results

Analysis of populations and baseline characteristics

A total of 1.890 participants were screened between March 2020 and December 2020; 746 were randomized and included in the Intent-to-treat (ITT) group, of which 372 were allocated to the JTA-004 group, 187 to the Synvisc-One® group, and 187 to the saline solution group (Fig. 1). The FAS included 674 participants: 335 in the JTA-004 group, 170 in the Synvisc-One® group, and 169 in the saline solution group (Fig. 1). In the FAS, 50.3 % had unilateral OA, and 49.7 % had bilateral OA, with no differences in the distribution of OA laterality between treatment groups.

The main reasons for screen failure were not meeting the radiographic inclusion criteria of KL grade of 2 or 3, and/or the specified pain criteria, together accounting for the majority of screen failures. The treatment groups were well-balanced regarding the primary baseline demographics, with a slightly lower proportion of women in the JTA-004 group as compared to the remaining groups, as shown in Table 1 below.

Efficacy outcomes

The main efficacy outcomes are shown in Table 2 and illustrated in Fig. 2.

Primary endpoint

All treatment groups observed a reduction in WOMAC pain during the trial. However, the primary endpoint of the trial was not met, as no difference (LSmean difference: −1.50 mm, 95% CI 5.12; 2.12, p= 0.42) was observed in the change from baseline in WOMAC pain at Month 3 between JTA-004 (LSMean −31.90 SD: 20.68) and placebo −29.27, SD: 19.12),. Therefore, any subsequent statistical testing was considered exploratory.

Key secondary endpoints

In line with the primary efficacy, no significant differences between JTA-004 and placebo were observed at any time points analyzed.

Safety

An overview of the most frequently reported AEs, including SAEs, are shown in Table 3. There were no AEs with a markedly higher incidence in the JTA-004-group compared to saline or Synvisc-One®-groups, indicating a good tolerability and safety. The most frequently reported events were headache and arthralgia. A total of 29 SAEs were reported, with no noticeable difference between frequency

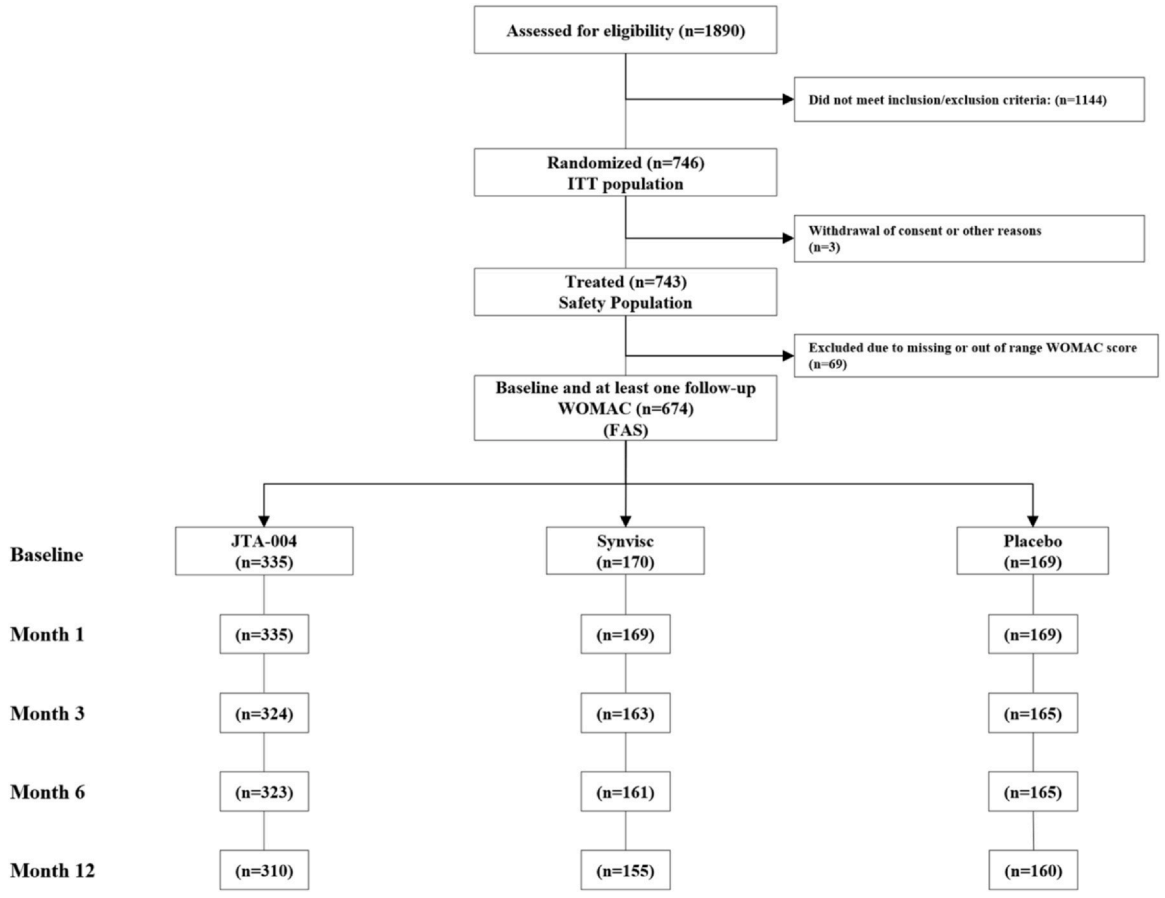

Fig. 1 Osteoarthritis and Cartilage

Study populations and analysis sets. Abbreviations: FAS, Full Analysis Set; ITT, Intention-to-Treat; WOMAC, Western Ontario and McMaster University Arthritis Index.

		JTA-004 (n=335)	Synvisc-One (N=170)	Placebo (N=169)	Total (N=674)
Sex, n(%)	Male	111 (33.1%)	47 (27.6%)	46 (27.2%)	204 (30.3%)
	Female	224 (66.9%)	123 (72.4%)	123 (72.8%)	470 (69.7%)
Age, years,	mean (SD)	62.0 (8.6)	63.0 (9.5)	62.6 (9.3)	62.4 (9.0)
	< 65 years, n (%)	195 (58.2%)	96 (56.5%)	97 (57.4%)	388 (57.6%)
	≥ 65 years, n (%)	140 (41.8%)	74 (43.5%)	72 (42.6%)	286 (42.4%)
Body Mass Index, kg/m^2	Mean (SD)	29.9 (4.8)	29.6 (4.6)	29.7 (4.9)	29.8 (4.8)
Target knee WOMAC pain subscore, 0–100 mm	Mean (SD)	58.1 (8.6)	58.1 (7.5)	56.7 (8.4)	57.8 (8.3)
Unilateral knee OA	N, (%)	170 (50.7%)	85 (50.0%)	84 (49.7%)	339 (50.3%)
Target knee Kellgren-Lawrence Grade (0–4)	Grade 2	141 (42.1%)	85 (50.0%)	74 (43.8%)	300 (44.5%)
	Grade 3	194 (57.9%)	85 (50.0%)	95 (56.2%)	374 (55.5%)

Abbreviations: OA: Osteoarthritis. SD: Standard Deviation. WOMAC: Western Ontario and McMaster University Arthritis Index.

Table 1 Osteoarthritis and Cartilage

Baseline characteristics.

between the treatment groups. No SAEs were reported as related to the investigational product.

As shown in Table 4, a total of 59 participants (7.9 %) discontinued the trial prematurely, with no apparent differences between groups. There were no deaths in the trial. From Month 6 to Month 12, knee arthroplasty was performed in 0.5% of the patients in the JTA group, 0.5% of the patients in the active control group and 0% of the patients in the placebo group.

	JTA-004			Synvisc-One®	Saline
	N=335			N=170	N=169
Primary Endpoint	LSMean (SD)	Difference to saline solution, (95 % CI, p-value)	Difference to Synvisc® (95 % CI, p-value)	LSMean (SD)	LSMean (SD)
WOMAC pain, CFB to Month 3	−31.90 (20.68)	−1.50 [.5.12; 2.12] 0.417	2.40 [−1.22; 6.02] 0.193	−34.22 (19.51)	−29.27 (19.12)
Secondary Endpoints					
WOMAC pain CFB to Month 6	−33.31 (20.40)	−2.64 [−6.28; 0.99] 0.154	0.45 [−3.19; 4.09] 0.808	−33.48 (20.77)	−29.19 (18.41)
WOMAC function, CFB to Month 3	−24.35 (22.11)	−0.74 [−4.31; 2.82] 0.682	0.66 [−2.92; 4.24] 0.717	−23.21 (21.99)	−24.28 (20.59)
WOMAC function, CFB to Month 3	−25.28 (21.29)	−2.16 [−5.67; 1.35] 0.227	−1.23 [−4.76; 2.31] 0.496	−22.06 (22.27)	−23.27 (20.78)
WOMAC stiffness, CFB to Month 3	−23.25 (24.19)	0.45 [−3.41; 4.31] 0.820	1.17 [−2.71; 5.05] 0.555	−20.94 (25.15)	−24.82 (24.85)
PGA, CFB to Month 3	−2.16 (2.30)	−0.32 [−0.72; 0.07] 0.106	0.21 [−0.18; 0.60] 0.296	−2.25 (2.49)	−1.88 (2.32)
IGA, CFB to Month 3	−1.91 (2.10)	−0.14 [−0.49; 0.20] 0.409	−0.36 [−0.70; −0.01] 0.043	−1.48 (2.05)	−1.79 (2.20)
EQ−5D VAS CFB to Month 3	6.77 (20.79)	1.40 [−1.86; 4.66] 0.983	−1.12 [−4.36; 2.13] 0.499	6.77 (20.79)	6.02 (22.31)
≥30 % responder on WOMAC pain at Month 3, n (%)	250 (74.6%)			130 (76.5%)	122 (72.2%)
Any consumption of rescue medication	241 (71.9%)			128 (75.3%)	118 (69.8%)
Mean daily consumption, Paracetamol, mg (SD)	171.8 (387.9)	−25.7 [−98.9; 47.6] 0.491	2.0 [−71.2; 75.3] 0.956	171.9 (394.4)	199.0 (397.5)
Mean daily consumption, ibuprofen, mg (SD)	34.8 (80.9)	−14.7 [−31.4; 1.9] 0.083	5.8 [−10.7; 22.4] 0.489	29.6 (75.9)	49.8 (115.1)
OMERACT OARSI Responder status at 3 M, n (%)	261 (77.9%)			132 (77.6%)	128 (75.7%)

CFB: Change from baseline. SD: Standard deviation. WOMAC: Western Ontario and McMasters Osteoarthritis index. All WOMAC subscales normalized to a 0–100 scale. PGA: Patient Global Assessment (0–10). IGA: Investigator Global Assessment (0–10).

Table 2

Osteoarthritis and Cartilage

Overview of efficacy outcomes.

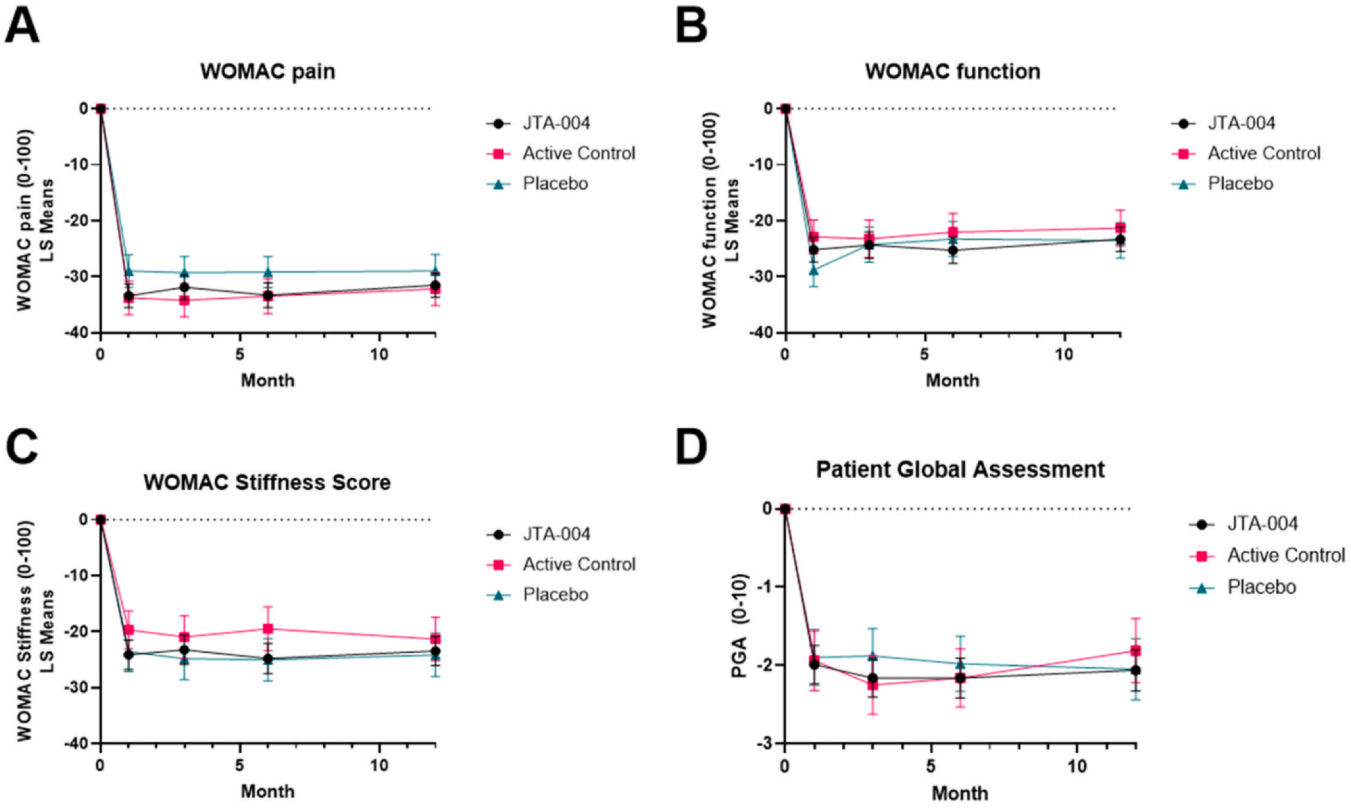

Fig. 2

Osteoarthritis and Cartilage

Main efficacy outcomes over the course of the trial. Least square means (LSMeans) change from baseline in the four main efficacy outcomes. A: WOMAC pain. B: WOMAC Function. C: WOMAC Stiffness. D: Patient Global Assessment. Error bars are 95 % confidence intervals. PGA: Patient Global Assessment.

A: Treatment-Emergent AEs reported during the first 6 months with a frequency of at least 3 % in any treatment group Safety population			
	JTA-004	**Synvisc-One®**	**Saline solution**
System Organ Class Preferred Term	N=371 N (%) E	N=187 N (%) E	N=185 N (%) E
Musculoskeletal and connective tissue disorders	113 (30.5%) 188	66 (35.3%) 104	48 (25.9%) 85
Arthralgia	51 (13.7%) 66	30 (16.0%) 42	19 (10.3%) 28
Back pain	30 (8.1%) 36	12 (6.4%) 19	15 (8.1%) 29
Pain in extremity	14 (3.8%) 16	12 (6.4%) 16	6 (3.2%) 7
Nervous system disorders	66 (17.8%) 117	37 (19.8%) 57	26 (14.1%) 52
Headache	53 (14.3%) 98	32 (17.1%) 48	21 (11.4%) 40
Infections and infestations	60 (16.2%) 76	30 (16.0%) 35	28 (15.1%) 35
COVID−19	15 (4.0%) 16	4 (2.1%) 4	7 (3.8%) 7
Nasopharyngitis	5 (1.3%) 6	4 (2.1%) 5	8 (4.3%) 9
Gastrointestinal disorders	32 (8.6%) 40	17 (9.1%) 20	21 (11.4%) 24
Toothache	9 (2.4%) 11	8 (4.3%) 9	8 (4.3%) 8
General disorders and administration site conditions	29 (7.8%) 33	20 (10.7%) 23	14 (7.6%) 15
Injection site joint pain	14 (3.8%) 14	10 (5.3%) 10	4 (2.2%) 4
B: Treatment-emergent serious adverse events: SAEs in System Organ Classes with frequency of at least 1 %			
Any Treatment-emergent serious adverse events (SAEs)	11 (3.0%) 14	7 (3.7%) 8	4 (2.2%) 7
Musculoskeletal and connective tissue disorders	1 (0.3%) 1	2 (1.1%) 2	0 (0.0%) 0
Intervertebral disc protrusion	0 (0.0%) 0	1 (0.5%) 1	0 (0.0%) 0
Neck pain	0 (0.0%) 0	1 (0.5%) 1	0 (0.0%) 0
Osteoarthritis	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Infections and infestations	4 (1.1%) 4	2 (1.1%) 2	3 (1.6%) 4
COVID−19 pneumonia	3 (0.8%) 3	1 (0.5%) 1	1 (0.5%) 1
Abscess limb	0 (0.0%) 0	0 (0.0%) 0	1 (0.5%) 1
Arthritis bacterial	0 (0.0%) 0	1 (0.5%) 1	0 (0.0%) 0
COVID−19	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Incision site abscess	0 (0.0%) 0	0 (0.0%) 0	1 (0.5%) 1
Pneumonia	0 (0.0%) 0	0 (0.0%) 0	1 (0.5%) 1
Gastrointestinal disorders	0 (0.0%) 0	1 (0.5%) 1	1 (0.5%) 2
Constipation	0 (0.0%) 0	1 (0.5%) 1	0 (0.0%) 0
Ileus	0 (0.0%) 0	0 (0.0%) 0	1 (0.5%) 1
Incarcerated inguinal hernia	0 (0.0%) 0	0 (0.0%) 0	1 (0.5%) 1
Injury, poisoning and procedural complications	1 (0.3%) 2	2 (1.1%) 2	0 (0.0%) 0
Facial bones fracture	0 (0.0%) 0	1 (0.5%) 1	0 (0.0%) 0
Femoral neck fracture	0 (0.0%) 0	1 (0.5%) 1	0 (0.0%) 0
Patella fracture	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0
Tibia fracture	1 (0.3%) 1	0 (0.0%) 0	0 (0.0%) 0

A: Treatment-emergent adverse events (AEs) reported with at least a frequency of 3 % in any treatment group
B: Treatment-emergent serious adverse events (SAEs) in System Organ Classes with frequency of at least 1%

Table 3 Osteoarthritis and Cartilage

Safety data overview.

Discontinuations – Safety population				
	JTA-004 (N=372)	**Synvisc-One (N=187)**	**Saline solution (N=187)**	**Total (N=746)**
Any discontinuation	30 (8.1%)	16 (8.6%)	13 (7.0%)	59 (7.9%)
Reason for discontinuation				
Withdrawal of consent	9 (2.4%)	12 (6.4%)	3 (1.6%)	24 (3.2%)
Violation of eligibility criteria	1 (0.3%)	0 (0.0%)	1 (0.5%)	2 (0.3%)
Adverse event	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Lost to follow-up	14 (3.8%)	3 (1.6%)	7 (3.7%)	24 (3.2%)
Lack of subject compliance	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Lack of efficacy	1 (0.3%)	0 (0.0%)	1 (0.5%)	2 (0.3%)
Other	3 (0.8%)	1 (0.5%)	1 (0.5%)	5 (0.7%)

Table 4 Osteoarthritis and Cartilage

Overview of study discontinuations.

As illustrated in Fig. 3, post-injection monitoring of changes in vital signs indicated a decrease in both systolic and diastolic blood pressure which was significantly greater in the JTA-004-group as compared to placebo and Synvisc-One®, starting approximately 30 min after injection peaking at approximately 60 min ($p < 0.0001$). No statistically significant differences in heart rate change from

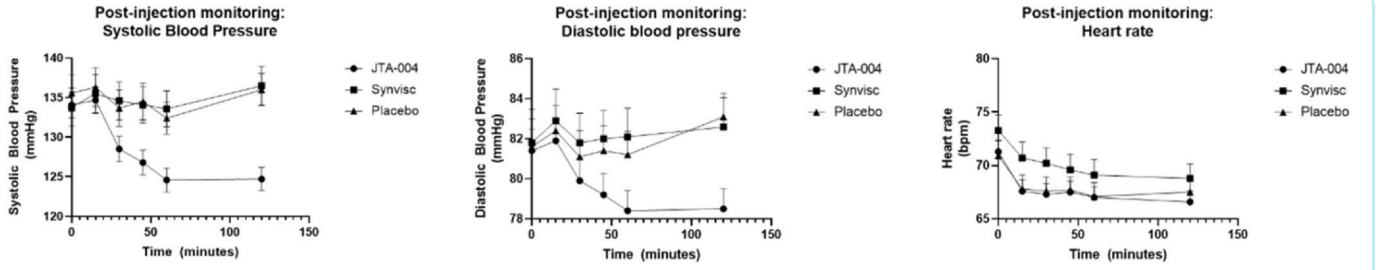

Fig. 3 Osteoarthritis and Cartilage

Post-injection Monitoring of Vital signs. Bpm: Beats per minute.

baseline were observed between treatment groups within two hours of the injection.

Discussion

The main finding of the trial was, that in the overall study population, treatment with a single IA injection of JTA-004 viscosupplement was not different from a single injection of saline solution for the treatment of OA symptoms. A small, statistically insignificant numerical effect compared to placebo was observed both in the JTA-004 and Synvisc-One® groups, but considering the small effect size, despite the consistency of this observation across the outcome measures, the clinical relevance in the broader OA population is likely to be very little, if confirmed to be the true effect of these interventions compared to placebo.

However, this observation may reflect an underlying subgroup of participants who could have derived a higher degree of benefit from JTA-004 and Synvisc-One® as compared to saline, but the pre-planned data analysis did not involve a deeper exploration of such potential subgroups.

The study was not powered to detect superiority of JTA-004 over HA. Despite numerical differences favouring HA in some of the efficacy outcomes such as WOMAC pain and PGA, the magnitude of benefit was very small. Additionally, in other sympotmatic outcomes such as the WOMAC function, stiffness as well as IGA at three months, JTA-004 was numerically better than Synvisc, but similarly the margin of difference was very small and likely not clinically relevant.

Considering the putative mechanism of action of JTA-004 involving an anti-inflammatory effect, it could be considered to evaluate a subgroup of participants with a particular inflammatory biomarker signal. Such subgroups have been defined by Angelini and colleagues [26], but also more straightforward methods involving C-reactive Protein and associated metabolites as markers of systemic inflammation have been associated with a particular beneficial response in OA patients [27,28]. Further post-hoc exploration of the dataset should be considered for the assessment of such subgroups.

While several products containing HA have been approved for the treatment of OA symptoms, other trials have, similar to the current trial, found no significant difference between HA and placebo [29]. Some meta-analyses find a high risk of publication bias for studies evaluating the efficacy of HA and upon adjustment for that, find a modest effect size of HA [7], and in other more recent meta-analyses, finding no significant difference between HA and placebo overall for long-term treatment of OA symptoms [30]. The wide variety of observed levels of efficacy of HA in OA [7] maybe a reflection that certain currently unidentified subpopulations may derive a larger benefit of HA than others. Hence, the results of the current trial indicating a very small and statistically and clinically insignificant effect of HA with or without the human plasma and clonidine, may reflect a very modest effect in a general OA population, which does not exclude more significant effects in selected subpopulations that were not explored in the current analysis.

It is noteworthy that an HA product currently approved for the treatment of OA symptoms fails to outperform saline in this fairly large trial. While not a part of the trial objectives, the results suggest that this type of HA product may not be superior to saline placebo, which should lead to careful considerations regarding its use in a comparable population in clinical practice. Similarly, based on the results of the primary analysis that JTA-004 is not superior to placebo, we can conclude that JTA-004 should not be recommended for use in clinical practice in this population.

The placebo response is a widely known phenomenon with particular importance in clinical trials evaluating pain outcomes. A very high placebo response may limit the capacity for improvement in the comparator group(s), negatively influencing the effect size [31]. Meta-analyses of factors associated with placebo response in OA have found that study drug administration by IA injection is associated with the highest risk of placebo response [1,32,33], and the expected change from baseline in WOMAC pain of an IA placebo has been reported to be in the range of approximately 22 points out of 100 (95%: 17.6–26.4) [33], which in a trial with a mean baseline WOMAC pain score of approximately 50 out of 100 would correspond to a mean placebo response of 44%, with a 95% CI range of 34–54%. The current trial did not include any specific procedures to mitigate the placebo response, besides investigator and study staff training before study start. The observed change from baseline in the placebo group of the current trial was approximately 50%, which is slightly higher than the mean expected placebo response, but within the interval of what could be expected. It has previously been documented in several meta-analyses that the placebo response has been increasing over time [34–36], and as a very recent trial, involving a route of administration associated with the highest expected placebo response (IA injection), during a pandemic with possible impact on the main outcome assessments, this trial may have been particularly prone to placebo response.

As discussed above, the observed effects of IA isotonic saline injections in knee OA are known to be substantial. Discussions have emerged regarding whether joint lavage and saline injections may have a direct therapeutic effect beyond an unspecific placebo effect. The hypothetical mechanism of action could involve removal/extraction of synovial fluid with a high concentration of inflammatory cytokines and subsequent dilution or washing of the joint cavity with saline solution [37,38]. A few reports have described that joint lavage was associated with a reduction in OA symptoms [37,38] and synovial fluid inflammatory markers [37]. However, the study

designs, which do not involve a sham or no treatment group, and the retrospective nature of the analyses, do not allow for a clear understanding of the implications of the data. Another recent large randomized controlled clinical trial in knee OA included both an IA saline solution and a sham injection treatment group, hence allowing for analysis of what the injection of saline means for symptom changes as compared to the knee puncture with no saline injection [39]. While no assessments of changes in synovial fluid components and cytokine profiles were performed, the results were striking as there was no observed difference in the change from baseline in any of the symptomatic outcomes, which does not indicate a therapeutic effect of a single saline injection beyond the contextual effects of joint puncture. Similarly, a meta-analysis of placebo effects in OA trials also found that the proportion of the observed effects of joint lavage treatment attributable to contextual rather than specific effects to be close to 100% [40]. Based on these reports it remains unclear whether the observed effects of saline injections in knee OA can be attributed to relevant changes in joint inflammation due to injection of saline or not.

Due to the hypothetical risks of hypotensive effects of systemic exposure to clonidine, the trial involved monitoring vital signs for two hours following the IMP injection. The results indicate a clear hypotensive effect, with a peak mean reduction of approximately 10 mmHg in systolic blood pressure and approximately three mmHg in diastolic blood pressure. However, the clinical implications of this observation are likely negligible, as during the entire trial, only two, non-serious, mild AEs concerning hypotension were reported, both occurring on the day of IMP injection in the JTA-004 group. The results document the level of hypotensive effects of clonidine when delivered intra-articularly. While several reports have documented AEs of hypotension with IA clonidine administration, they have not assessed the magnitude of changes in systemic blood pressure [17–19,41], so the current report is, to the authors' knowledge, the first to report detailed quantitative data on the systemic hypotensive effects of IA clonidine.

Limitations

The trial did not involve any assessment of the distribution, pharmacokinetics, or pharmacodynamic activity of JTA-004 in the target tissues. As such, it is impossible to ascertain whether the observed results were either fully or partly caused by insufficient or absent target engagement or due to adequate engagement but insufficient clinical relevance of such engagement.

The trial did not involve specific biomarker assessments from serum beyond regular clinical chemistry, or from urine or synovial fluid which limits the ability to describe the pharmacodynamics of the treatment interventions.

The inclusion of participants with bilateral OA may be regarded as a limitation. Some studies have found that bilateral OA could lead to confounding of pain reporting [42,43], and consequently, restrictions in terms of the level of symptoms of the contralateral (non-target) knee could be utilized to ensure accuracy of target knee pain reporting.

The tested dose of JTA-004 was based on experience from the former phase 2/3 trial in knee OA [20]. The former trial evaluated three different dose combinations, including the dose combination used in the current trial. In the earlier trial, the observed beneficial effects of JTA-004 appeared similar in all three dose combinations, based on which the dose combination of JTA-004 used in the current trial was selected as the formulation with the lowest injection volume to reduce the risk of local irritation. However, due to the smaller size of the former trial, it is possible that limited study power and hence data variability may have clouded the "true" beneficial effects of higher dose formulations and thereby overestimated the potential beneficial effects of the dose selected for the current trial, and as the trial tested only one dose of JTA-004, no such evaluation of dose-dependency could be made.

The accuracy of IA injections is an important element in trials evaluating investigational products delivered by the IA route. One report evaluating the accuracy of corticosteroid injections to the knee found that approximately 70 % of injections were accurately delivered, but also found that the failure to accurately inject into the joint space did not appear to influence the efficacy results [44]. A systematic review assessing the accuracy of ultrasound vs. landmark guided arthrocentesis found that ultrasound guidance was more successful, indicating higher accuracy of the needle insertion to the joint space [45]. The trial protocol for the current trial did not require the use of ultrasound guidance when injecting the investigational product, and hence the accuracy of the injection cannot be verified, which is a limitation of the study.

Another limitation of the trial is the heterogeneity of the enrolled population. Patients with both moderate (Kellgren–Lawrence grade 2) and more advanced (grade 3) radiographic OA were included, as were individuals with widely varying baseline pain levels and inflammatory phenotypes. Such variability may dilute potential signals of efficacy in more narrowly defined subgroups, although this was not evaluated further in this report. Conversely, based on the regulatory guidance for pivotal OA trials, the trial excluded participants with very early and very late OA (KL grades 1 and 4, respectively), which limits the applicability of the results in this population.

As a statistical limitation, the main the statistical analyses of the trial were performed on the full analysis set, rather than the ITT population. As a common principle in randomized controlled trials, the treatment policy estimand is best assessed by evaluating participants based on the treatment they were originally assigned to receive, rather than the treatment they actually received. This means that participants will be followed, assessed, and analyzed according to their assigned treatment group, regardless of adherence to the planned regimen or initiation of rescue interventions. In the current trial, the main efficacy analysis was performed while excluding participants who did not have a WOMAC pain assessment within the specified range at the baseline visit, but no other restrictions comparing to an ITT principle. The observation of participants who did not have a WOMAC pain assessment within the specified range at the baseline visit, and the resulting decision to analyse as the FAS rather than the ITT was made prior to unblinding, it is the opinion of the authors that this does not lead to relevant confounding in the analysis. While not reported here, there were no relevant differences the trial results with regards to the efficacy of JTA-004 between the FAS and the ITT, indicating that any potential confounding caused by this is likely irrelevant to the reported conclusions of the trial.A further consideration is the impact of the dosing regimen on clinical outcomes. The JTA-004 trial employed a single IA injection, which may have constrained its therapeutic potential. Evidence from hyaluronic acid (HA) treatments—the most commonly used IA viscosupplement—indicates that multiple injection regimens tend to yield more consistent and sustained symptom relief compared to single injections. For instance, a meta-analysis by Rutjes et al. demonstrated that repeated HA injections were associated with greater pain reduction and functional improvement over placebo, effects that often persisted for 6 months or more. In contrast, Raynauld and colleagues found no apparent additional benefit from repeat injections of hylan G-F 20 [46]. Given these findings, the single-injection approach in the JTA-004 trial may or may not have limited the magnitude and durability of pain relief achievable with this investigational product. Ideally, future studies could explore multiple or repeated dosing schedules of JTA-004, which might improve IA drug levels and therapeutic effects.

The trial was conducted during the COVID-19 pandemic, the impact of which is uncertain. Two reports describing changes observed in OA symptoms after a period of quarantine due to COVID-19 describe conflicting results, one suggesting improved symptoms

associated with reduced physical activity [47], and one describing a worsening of symptoms for OA patients waiting for arthroplasty [48]. The conflicting results of these small studies indicate that increased variability in OA symptomatic assessments may be expected due to unexpected changes in behavior and daily activities. Based on this, it is possible that the outcome of the trial could have been influenced by different types of restrictions in different participating countries, with varying durations.

In conclusion, the results indicate that a single intra-articular injection of JTA-004 viscosupplement was not superior to placebo or Synvisc-One® for treating OA symptoms in the overall study population.

The patient and public involvement statement

Patients or members of the public were not involved in the design of the trial.

Author contributions

EL, PA and HR were the main investigators of the study. ARB and OG contributed to trial design. ARB and OG were responsible for study implementation and data acquisition, and together with YH, provided the first draft of the manuscript. All authors critically revised the manuscript. CN had final responsibility for the decision to submit for publication. CN, FR, and ARB had full access to and verified all study data.

Patient consent for publication

Consent obtained directly from subjects.

Ethics approval

This study was approved by the relevant competent and local Ethics Committees in Denmark, Belgium, Czech Republic, Poland, Moldova, and the United Kingdom. All participants gave informed consent to participate in the study before taking part.

Funding

The study was sponsored by Bone Therapeutics, later BioSenic.

Data availability

Data and study protocol are available upon reasonable request to the corresponding author.

Declaration of Competing Interest

The study was sponsored by BioSenic SA (Formerly Bone Therapeutics).

YH is a scientific advisor for Artialis SA, Nestlé SA, Wobenzym, Allegro, Expanscience, Tilman, Grunenthal, LABRHA, Kiomed Pharma, and Genequine. Asger R. Bihlet is a full-time employee of NBCD A/S. Helene Rovsing, and Peter Alexandersen are full-time employees of Sanos Clinic A/S, Denmark. Yves Henrotin is a full-time employee of the University of Liège. Carole Nicco and François Rieger are full-time employees of Medsenic SA and Carole Nicco is on secondment from Université Paris Cité. Edith Lau Ming is a full-time employee of CCR Hong Kong. At the time of planning and conduct of the trial, Olivier Godeaux was a full-time employee of Bone Therapeutics, which sponsored the trial.

Acknowledgements

We thank all the subjects and study staff who participated in this clinical study.

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