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Efficacy and safety of a single-injection BDDE-crosslinked hyaluronic acid versus a three-injection hyaluronic acid for knee osteoarthritis: A multicenter, double-blind, randomized, noninferiority study

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Research Article

Keywords: Knee osteoarthritis, Treatment, BDDE-crosslinked, Hyaluronic Acid

Posted Date: August 7th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10419108/v1

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Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Journal of Orthopaedic Surgery and Research on November 22nd, 2026. See the published version at https://doi.org/10.1186/s13018-026-07397-9.

Abstract

Background: LBSA0103 (Synovian®) is a high molecular weight single-injection intra-articular hyaluronic acid product crosslinked by 1,4-butanediol diglycidyl ether (BDDE). This randomized, double-blind, multi-center, non-inferiority study was conducted to evaluate the efficacy and safety of this single-injection intra-articular hyaluronic acid (LBSA0103) compared with a three-injection intra-articular hyaluronic acid (Synvisc®) in patients with knee osteoarthritis (OA).

Methods: 265 patients with knee osteoarthritis were enrolled and randomized to receive three injections of Synvisc®, or three injections of LBSA0103 (including two sham injections), all at weekly intervals. Patients were followed up at 1 week, 6 weeks, 13 weeks, and 26 weeks after the last injection. The main endpoint was the change of WOMAC-Likert pain score from baseline to 13 weeks after the last injection. The noninferiority was assessed with a margin of 1.6. Other outcome measures were the WOMAC-Likert subscale and total scores; global evaluations by both the patient and investigator; physical examinations; proportion of patients taking rescue medicines; and remission rate in accordance with OMERACT-OARSI standards.

Results: The WOMAC-Likert pain scores decreased from baseline to 13 weeks after the last injection with -7.43 and -6.79 respectively for the LBSA0103 and Synvisc groups, indicating a significantly greater decrease in the LBSA0103 group (p=0.039). The upper limit of 97.5% CI was below the margin of 1.6, confirming the noninferiority of LBSA0103 to Synvisc. The changes of all secondary endpoints at the follow-up visits consistently indicated a general improvement in two groups. Most of them were found no significant differences between the groups, except the changes of WOMAC-Likert pain score, investigator's global assessment and range of motion assessment in the knee from baseline to 26 weeks after the last injection. The safety profile of two groups were comparable and no new safety issue was identified.

Conclusions: The single-injection of BDDE-crosslinked LBSA0103 is noninferior to a three injections of Synvisc® at weekly intervals, providing support that LBSA0103 is a safe and effective option in managing Chinese patients with mild to moderate OA of knee.

Trial registration: This study was registered at www.chictr.org.cn with the registration number ChiCTR2400090323 on 27/09/2024.

Background

Osteoarthritis (OA) is a whole-joint disease involving all joint tissues, which contributes to a higher burden of disease in the world [1–3]. It is estimated that over 60 million people suffer from OA in China, with a higher susceptibility among the older population [1,4]. It is mainly characterized by articular cartilage destruction, subchondral bone remodeling, meniscal degeneration, inflammation and fibrosis of both infrapatellar fat pad and synovial membrane [2,5,6]. The common joints of OA involvement are the

hands, knees, hips and spine, which are the main causes of pain and disability, especially symptomatic knee OA [2,7,8]. There are many factors associated with the occurrence of OA, while females, obesity, and joint injuries are related to the development of knee OA [2,9]. The incidence of knee OA increases with age, and higher among women population [2,10].

The primary goals in managing knee OA include relieving pain, avoiding disability, enhancing functionality, and improving the quality of life [2,7,8,11]. Currently recommended treatment strategies include nonpharmacological interventions, pharmacological therapies, and surgical procedures[2,7,8]. Pharmacological therapies primarily include non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular hyaluronic acid (IAHA), etc. For knee OA patients experiencing persistent or moderate to severe pain, IAHA may be considered as a solution for long-term improvement symptoms and delaying joint replacement [2,7,8,11]. Among the various IAHA products marketed globally, the higher molecular weight (MW) of IAHA products by cross-linking can extend the duration of action and require fewer injections [12]. Developing a single-injection product is more attractive, because it can save resources both in terms of time and cost by avoiding multiple hospital visits, and reduce patient discomfort from repeated injections.

LBSA0103 (Synovian®) is a high-MW single-injection IAHA product crosslinked by 1,4-butanediol diglycidyl ether (BDDE). It was first approved for knee OA in South Korea in 2013[13–15], and received approval for the same indication in China in 2023. To date, this product has been registered in more than 16 countries and regions, including Russia, India, Thailand, Malaysia, etc. The efficacy and safety have been well proved in several Korea studies, including a pivotal study, which showed that the single-injection of LBSA0103 was noninferior to the three injections IAHA (Hyruan Plus®) at weekly intervals [12–15]. In order to obtain the approval of LBSA0103 in China, we conducted this study to evaluate the safety and efficacy in Chinese population with the similar design of the Korean pivotal study. However, Hyruan Plus® has not been approved in China. Thus, we compared LBSA0103 with a three injections IAHA (Synvisc®) instead, which has been commercially available in China since 2001. The efficacy and safety of Synvisc® have been reported in multiple clinical trials [16–18].

Methods

The study was conducted from October 2019 to October 2020 at 11 study centers in China, in compliance with the Declaration of Helsinki, as well as Good Clinical Practice guidelines. The institutional review boards and ethics committees at each participating center reviewed and approved the study protocol. Informed consent was obtained from all patients before any study-related procedure was performed. This study was registered on www.chictr.org.cn (ChiCTR2400090323, 27/09/2024).

Design

This randomized, double-blind, multi-center, noninferiority study was conducted in Chinese knee OA population for evaluating the safety and efficacy, comparing a single-injection of LBSA0103 with a three-injection of Synvisc® at weekly intervals. After a screening period (2 weeks), all eligible patients were randomized in a 1:1 ratio to two groups (LBSA0103 or Synvisc®) and received three weekly treatments. The LBSA0103 group received one actual injection at visit 2, then two sham injections at visit 3 and visit 4 respectively. The Synvisc group received three injections from visit 2 to visit 4. Follow-up was scheduled at 1 week (visit 5), 6 weeks (visit 6), 13 weeks (visit7), and 26 weeks (visit 8) after the last injection (Fig. 1).

Figure 1. Visit flow chart. The bars indicate each visit. The distances between visits are not proportional to the actual times due to the limited space. After screening, participants receive LBSA0103 (one LBSA0103 injection and two sham injections) or Synvisc from visit 2 to visit 4 at weekly interval. Efficacy was assessed at visit 5 to visit 8, with visit 7 evaluation as primary endpoint.

Selection and description of participants

Patients with a confirmed diagnosis of knee OA (mild to moderate), either unilateral or bilateral, according to Chinese Guidelines for the Diagnosis and Treatment of Osteoarthritis (version 2018) were enrolled [7]. The Kellgren–Lawrence grade (I - III) using a standing [19], weight-bearing, semi-flexed, posteroanterior X-ray was required. Inclusion criteria were also including: aged > 40 years, failing to adequately respond to conservative nonpharmacological interventions and/or simple analgesics such as acetaminophen, a baseline Western Ontario and McMaster Universities Osteoarthritis (WOMAC)-Likert pain score [20] between 7 and 17 and a sub-score between 2 and 3 of walking on flat surfaces. Patients with a WOMAC-Likert pain score greater than 3 in the contralateral (non-studied) knee, body mass index (BMI, kg/m^2) > 32 or other conditions that may influence efficacy or safety evaluation were excluded.

Technical information

Patients were randomized using the stratified block randomization method, with the study center and knee OA laterality (bilaterality or unilaterality) as the stratification factors. They were assigned in a 1:1 ratio to the experimental group and the control group, where the experimental group received a single injection of LBSA0103 (3 mL, LG Chem, South Korea) and two sham injections, and the control group received three injections of Synvisc® (2 mL, Genzyme, USA), all at weekly intervals [17].All personnel involved in the study, including subjects and investigators, must be blinded to the treatment assignments. For maintaining blindness, injections were administered only by a designated person and the assessments were conducted independently by another investigator. For each injection, either LBSA0103 or Synvisc was administered following a local anesthetic procedure, using the same needles for the LBSA0103 (including 2 sham injections) or Synvisc with strict aseptic techniques. Sham injections of test group were done subcutaneously and used an empty syringe, and the needle did not enter the joint space. Subcutaneous sham injections were deemed necessary for subjects in the group

of LBSA0103 [21,22]. Furthermore, drapes were used for preventing the subjects from discerning the treatment assignments.

Throughout the study, participants were prohibited from using steroidal medications, analgesics, or NSAIDs (including patches or any topical formulations) to alleviate pain. Physical therapy methods such as electrotherapy, as well as traditional Chinese medical therapies such as acupuncture, were also forbidden. Low-dose aspirin (≤ 325 mg/day) for thrombosis prevention and acetaminophen (≤ 4 g/d) as a rescue medication were permitted.

Outcomes

Primary outcome

The primary endpoint was the change in the WOMAC-Likert pain score from visit 2 to visit 7 [23]. Visit 2 was baseline and visit 7 was 13 weeks after the last injection.

Secondary outcome: The change in the WOMAC-Likert pain score was also evaluated at 1 week (visit 5), 6 weeks (visit 6) and 26 weeks (visit 8) after the last injection as secondary endpoints. Other secondary measures of effectiveness included: 1) changes of WOMAC-Likert stiffness, function, and total scores from baseline to visits 5 ~ 8; 2) changes in the patient's global assessment score (The overall improvement or activity of knee osteoarthritis at present will be self-assessed by the subjects using 100 mm-VAS) and investigator's global assessment score (The overall improvement or activity of knee osteoarthritis of the subject at present will be assessed by the investigators using 100 mm-VAS) from baseline to Visits 5–8; 3) physical assessment at each visit after the last injection, including changes in knee swelling, knee tenderness, and knee range of motion compared to baseline; 4) the proportion of subjects taking rescue medicines at each visit after the last dose; 5) the OMERACT-OARSI remission rate [24] at each visit after the last injection. It was defined in the following ways: first, it could be defined as at least a 50% improvement and 20-point increase (converted to 100 points) in the WOMAC-Likert pain score or functional score 13 weeks after the last injection from baseline. Second, it could also be determined if two out of the following three conditions were met: a) a minimum 20% increase from baseline in the WOMAC-Likert pain score or function score; b) a 10-point increase (after conversion to a 100-point scale) in same; c) a minimum 20% improvement in the patient's global assessment.

Safety was assessed throughout the study as the incidence of adverse effects (AEs), with special attention given to injection site reactions, such as redness, swelling, pain, or heat.

Statistical analysis

Three datasets were defined for analysis. The safety set (SS) included all randomized patients who had received at least one injection. According to the principles of intention-to-treat (ITT), the full analysis set (FAS) included all randomized patients who had received at least one injection and could provide any

follow-up data for primary efficacy assessment after Week 0 (baseline). The per-protocol set (PPS) included all the subjects who were included in the FAS and administered with the investigational product at the protocol defined times and have primary efficacy assessment at Week 15 (13 weeks after final administration). Subjects with major protocol violation which can affect the efficacy assessments from Week 0 to Week 15 would be excluded from the PPS.

The primary objective was to evaluate the noninferior efficacy between LBSA0103 and Synvisc, measured by the change of the WOMAC-Likert pain score. The assumptions related to the WOMAC-Likert pain subscale included a standard deviation of 3.37 for the change, a noninferiority margin of 1.6, a type I error rate of 0.025, and a type II error rate of 0.10. The noninferiority margin was set based on the previous research finding [25]. These assumptions led to the conclusion that 94 participants per arm would be adequate. Considering the minimum clinical trial requirements in China, and a possible 30% drop-out or protocol violation rate, the final sample size was 132 per arm (total 264).

In terms of primary outcome measure, the difference between the two groups (LBSA0103 and Synvisc) was calculated using the one-sided 97.5% confidence interval (CI). If the upper limit of 97.5% CI was below 1.6, LBSA0103 was deemed noninferior to Synvisc. The difference and CI were estimated using an analysis of covariance model that considered baseline values and knee OA laterality. The secondary outcome measures involved analyzing differences between groups and differences from baseline. Based on the data distribution, a Wilcoxon's signed rank or paired t-test was selected within the groups' comparison, and a Wilcoxon's rank-sum or two-sample t-test was selected between the groups' comparison. Data were analyzed using SAS version 9.4.

In this study, no data carried forward is applied to the missing values for the Safety Set (SS). For the Full Analysis Set (FAS), the missing data in the relevant part of the efficacy will be filled using the Last Observation Carried Forward (LOCF) method.

Results

From October 2019 through October 2020, the study was conducted at 11 sites in China. Of the 317 patients screened, 265 (83.6%) were enrolled, and 257 successfully completed their follow-up visits within the 28-week study period. After excluding one participant who withdrew consent prior to the injection, 264 patients accepted the injection and were included for analyzing in the Safety Set (SS). 262 subjects were included in the full analysis set (FAS), and 254 subjects were included in the per-protocol set (PPS) (Fig. 2). The demographics and baseline characteristics were generally comparable between the groups (Table 1).

Figure 2. Allocation of patients and study population.

Table 1
Demographic and baseline disease characteristics

Age, years	**LBSA0103 Group (n = 130)**	**Synvisc Group (n = 132)**	***P* value**
			0.146[a]
Mean (SD)	60.91(7.41)	59.39(8.23)	
Min, Max	43.00,78.00	42.00,77.00	
Sex, n (%)			0.695 [b]
Male	26(20.00%)	29(21.97%)	
Female	104(80.00%)	103(78.03%)	
Ethnicity, n (%)			0.248 [b]
Han	126(96.92%)	124(93.94%)	
Other	4(3.08%)	8(6.06%)	
BMI, kg/m^2			0.869 [c]
Mean (SD)	25.18(3.00)	25.12(2.98)	
Affected knee, n (%)			0.631 [b]
Unilateral	55(42.31%)	52(39.39%)	
Bilateral	75(57.69%)	80(60.61%)	
Duration of knee OA, years			
Left	3.04(3.83)	2.86(3.60)	0.756 [a]
Right	2.97(3.43)	3.13(3.79)	
Studied knee, n (%)			0.901 [b]
Left	64(49.23%)	66(50.00%)	
Right	66(50.77%)	66(50.00%)	
K-L grade, n (%)			0.004 [b]
Grade I	16(12.31%)	25(18.94%)	
Grade II	43(33.08%)	62(46.97%)	
Grade III	71(54.62%)	45(34.09%)	

Age, years	LBSA0103 Group (n = 130)	Synvisc Group (n = 132)	*P* value
			0.146[a]
WOMAC index, Mean (SD)			
Pain subscore	9.63(1.90)	9.59(1.70)	0.771 [a]
Function subscore	26.66(7.91)	26.87(7.26)	0.876 [a]
Stiffness subscore	2.45(1.71)	2.77(1.55)	0.121 [a]
Total score	38.74(10.33)	39.23(9.43)	0.632 [a]

BMI, body mass index; OA, osteoarthritis; K-L, Kellgren–Lawrence grade; and WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

a, the P value was derived using Wilcoxon's rank sum test; b, the P value was derived using the chi-square test; c, the P value was derived using the two-sample t test.

Efficacy

The primary efficacy endpoint was the change in the WOMAC-Likert pain score from visit 2 to visit 7. The scores were − 7.43 and − 6.79 for the LBSA0103 group and the Synvisc group respectively, indicating a significantly greater decrease in the LBSA0103 group ($p = 0.039$). The one-sided 97.5% CI for the difference between the two groups ranged from − 1.30 to 0.02 (PPS). As the upper limit of 97.5% CI was below the prespecified margin (1.6), the noninferiority of LBSA0103 to Synvisc was confirmed. The similar result was observed in FAS, where the 97.5% CI was (-1.24, 0.10).

The changes in the WOMAC-Likert pain, stiffness, function, and total scores from baseline to follow-up visits are shown in Fig. 3 (PPS). At one week after the last injection, a substantial decrease in the pain score was observed, and maintained to visit 8 (26 weeks after the last injection) in two groups. The score was decreased more significantly in the LBSA0103 group at 13 and 26 weeks after the last injection. The same trends were found in the stiffness, function, and total scores.

Figure 3. Mean change in WOMAC-Likert scores from Baseline: (a) pain score; (b) function score; (c) stiffness score; (d) total score;

Changes in the secondary endpoints at the follow-up visits consistently indicated a general improvement in both groups. Main outcome measures in the secondary endpoints, changed from baseline to visit 7 and 8, are listed in Table 2 (PPS). Most of these changes were found no significant differences between the groups, except the following ones: the WOMAC-Likert pain score at week 26 after the last injection

showed improvements of -7.67 and − 6.91 (p = 0.009) in the LBSA0103 and Synvisc groups respectively, the investigator's global assessment and range of motion assessment in the knee at Visit 8 were greater in the LBSA0103 group than in the Synvisc group.

Table 2
Changes of outcome variables from baseline to visit 7 and visit 8

WOMAC index, Mean (SD)	**LBSA0103 Group (n = 126)**	**Synvisc Group (n = 128)**	***P* value**
Pain subscore			
Changes from baseline to visit 7	-7.43(2.60)	-6.79(2.72)	0.039[a]
Changes from baseline to visit 8	-7.67(2.39)	-6.91(2.65)	0.009[a]
Total score			
Changes from baseline to visit 7	-28.26(12.10)	-26.50(12.27)	0.117[a]
Changes from baseline to visit 8	-29.39(10.97)	-26.47(12.82)	0.058[a]
Patient's global assessment			
Changes from baseline to visit 7	-38.15(17.21)	-34.34(18.28)	0.092[a]
Changes from baseline to visit 8	-40.34(17.71)	-36.23(18.85)	0.060[a]
Investigator's global assessment			
Changes from baseline to visit 7	-38.29(15.20)	-34.89(16.13)	0.073[a]
Changes from baseline to visit 8	-40.67(16.25)	-35.48(17.60)	0.022[a]
Physical assessment			
knee range of motion			
Changes from baseline to visit 7	5.29(11.39)	3.77(10.15)	0.858[a]
Changes from baseline to visit 8	8.52(11.57)	4.84(10.11)	0.034[a]
OMERACT-OARSI remission			
Changes from baseline to visit 7	117(92.86%)	121(94.53%)	0.583[d]
Changes from baseline to visit 8	123(97.62%)	120(93.75%)	0.130[d]

WOMAC: Western Ontario and McMaster Universities Osteoarthritis; *OMERACT-OARSI*: Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative.

a, P value was derived using Wilcoxon's rank sum test; b, P value was derived using two-sample t test; c, P value was derived using Fisher's exact test; d, P value was derived using chi-square test.

Safety

Patients in both LBSA0103 and Synvisc groups were well tolerated. In the LBSA0103 group, 103 AEs were reported by 54 subjects (41.22%), whereas in the Synvisc group, 138 AEs were reported by 53 subjects (39.85%) throughout the study (p = 0.900). Most events were mild to moderate. In the LBSA0103 group, 3 serious AEs were reported in 3 participants (2.29%). In the Synvisc group, 8 serious AEs were reported in 6 participants (4.51%). Importantly, no serious AEs were judged as study drug related. The frequency and severity of AEs were comparable between the two groups. No deaths occurred in this study.

Among the AEs with incidence ≥ 1%: In the LBSA0103 group, the most common AEs were injection site pain (5.34%), upper respiratory infection (3.82%), joint pain (3.82%); in the Synvisc group, the most common AEs were arthralgia (8.27%), injection site pain (5.26%), joint swelling (4.51%). The incidence of arthralgia and joint swelling in the Synvisc group were higher than that in the test group, and the incidence of injection site pain was similar between two groups (Fig. 4).

Figure 4. The incidence of arthralgia and joint swelling between the two groups.

A total of 8.4% of patients reported local injection site reactions after LBSA0103 administration, including 12 pain reactions in 8 subjects (6.11%) and 5 swelling reactions in 4 subjects (3.05%). In the Synvisc group, symptoms were reported in 7.52% of the patients, with 1 subject (0.75%) experiencing 1 erythema reaction, 9 subjects (6.77%) experiencing 12 pain reactions, and 4 subjects (3.01%) experiencing 4 swelling reactions. Local injection site reactions were reported by patients and assessed by investigators. The incidence was similar between the two groups (Table 3). Overall, the safety profile of two groups were comparable and no new safety issue was identified.

Table 3
Summary of patients experiencing adverse events (SS)

AE	LBSA0103 Group (n = 131)	Synvisc Group (n = 133)
	No. of patients (%)	No. of patients (%)
AEs	54(41.22%)	53(39.85%)
Mild	47(35.88%)	43(32.33%)
Moderate	11(8.40%)	21(15.79%)
Severe	5(3.82%)	4(3.01%)
AEs associated with the study drug	7(5.34%)	10(7.52%)
Serious AEs	3(2.29%)	6(4.51%)
Serious AEs associated with the study drug	0(0.00%)	0(0.00%)
Local reaction at the injection site	11(8.40%)	10(7.52%)

AE, adverse event; SS, safety set.

Discussion

To our knowledge, the single injection of IAHA products has not been approved in China yet, and no comparison results have been reported between the one injection and three injections products in Chinese population. In this multicenter, double-blind, active-controlled study, the safety and efficacy of single-injection of LBSA0103 were not inferior to three injections of Synvisc at weekly intervals in Chinese patients with mild to moderate OA of knee. From baseline to 26 weeks after the last injection, significant improvements were shown in the WOMAC-Likert subscale score, global assessments by the investigator, and the physical assessments.

The scores of primary efficacy endpoint were − 7.43 and − 6.79 respectively, indicating a significantly greater decrease in the LBSA0103 group compared with Synvisc group (p = 0.039). As the upper limit of 97.5% CI for the difference between groups was below the prespecified margin (1.6), the noninferiority of LBSA0103 to Synvisc was confirmed. The WOMAC-Likert pain score at visit 8 in the two groups decreased by -7.67 and − 6.91 respectively, being significantly greater in the LBSA0103 group than in the Synvisc group (p = 0.009). At one week after the last injection, a substantial decrease both in the WOMAC-Likert subscale and total scores was demonstrated, and maintained at 26 weeks, indicating the rapid and long-lasting effect. This was slightly different from a meta-analysis, which showed that the efficacy of IAHA was sustained for 4 weeks and maintained for up to 24 weeks [26].

In addition, the change in the WOMAC-Likert pain score observed in the present study (-7.43 at 13 weeks after the last injection of LBSA0103 was higher than that in a previous trial of Korean reported by Chul-Won Ha (-3.96 at 12 weeks after the last injection of LBSA0103) [12]. Although the two studies are both LBSA0103 administered to Asian patients, the administration methods and evaluation time points were different. In the Korean trial, the LBSA0103 group received sham injections at week 0 and week 1, then received LBSA0103 injection at week 2; the primary endpoint was evaluated at week 12 after the last injection of LBSA0103. In this study, the LBSA0103 group received LBSA0103 injection at week 0, then received sham injections at weeks 1 and 2; the primary endpoint was evaluated at week 13 after the last injection (15 weeks after the last injection of LBSA0103). Other factors, such as baseline variables, pain sensitivity, and seasonal weather, may also influence the results of different studies. In a multicenter, randomized, double-blind trial, the WOMAC-Likert pain score decreased by 5.97 at week 18 after a BDDE cross-linked HA (Dulorane®) injection in patients with mild to moderate OA [27]. Although the above studies had different absolute pain score reduction, all of them achieved the primary endpoint which was demonstrated non-inferiority in efficacy comparing to the 3 or 5-shot HA preparation.

Currently, the efficacy of IAHA remains controversial, as contradictory results have been found comparing with placebo in some studies [28–32]. As a result, the recommendations of IAHA injections for the treatment of knee OA provided by clinical practice guidelines are not consistent in different countries [33–35]. In this study, the single-injection of LBSA0103 could achieve the noninferiority efficacy which was measured as decrease of WOMAC-Likert pain sub-score, comparing with three injections of Synvisc. For the subjects in this study, pain was effectively relieved at 13 weeks after the last injection and maintained to 26 weeks.

The incidence of adverse reactions was 5.34% in the LBSA0103 administered group and 7.52% in the Synvisc administered group. This safety result was consistent with that of other IAHA injections [36]. The incidence of arthralgia and joint swelling in the Synvisc group were higher than that in the LBSA0103 group(3.82% and 2.29% respectively in the LBSA0103 group, 8.27% and 4.51% respectively in the Synvisc group). The incidence of local reactions at the injection site was similar in both groups, at 8.40% in the LBSA0103 group and 7.52% in the Synvisc group. The incidence of local injection reactions was as high as 58.05% after a single injection of LBSA0103 in a previous Korean trial [12,14]. The difference between these findings may be due to differences in clinical practice in different regions. According to the current expert consensus in China and abundant treatment experience with IAHA injection in the joint cavity, the very slight local reactions are not clinically significant. In addition, subcutaneous local anesthesia before each injection in this study may have reduced subjects' sensitivity to pain.

LBSA0103 is formed by the cross-linking gelation reaction of hyaluronic acid(HA) and 1,4-butanediol diglycidyl ether (BDDE). The cross-linking reaction maximizes the molecular weight of sodium hyaluronate. The cross-linking structure gives LBSA0103 certain unique physical and chemical stabilities and viscoelastic properties. It can better resist degradation and maintain its function in the joint cavity for a long time, which is why it can achieve long-acting effects with a single injection. Synvisc is

composed of hylan A and hylan B, which are two types of chemically modified hyaluronic acids. The modification method and resulting molecular weight characteristics are different from those of LBSA0103, which has the same high molecular weight but results in shorter durability. In addition, the HA in LBSA0103 is produced by microbial fermentation using genetic engineering technology. Unlike regular HA extracted from chicken crowns (Synvisc), it contains no algal proteins, which could decrease the incidence of adverse events.

There may be some limitations in this study, which have to be noted. First, considering the benefit for patients, we used an active-controlled therapy (Synvisc®) instead of placebo, which have been approved both in the United States and China. Several studies have shown that Synvisc® can significantly relieve the pain of knee OA [16–18]. Second, to maintain the double-blindness of the study, we administered two sham injections to the test group; therefore, it is not known how much of the observed pain-relief effectiveness can be attributed to a placebo response. Another BDDE-crosslinked HA product (Dulorane®) was evaluated with the same trial design (IA injection plus sham injection for the test group) and had approved by the FDA. We believe that the sham injection design in this study was an acceptable measure for comparing the two groups while maximizing the subjects' benefit. In addition, the follow-up visit was only up to 26 weeks after the last injection, and further studies are needed in the future, such as a prospective cohort study with follow-up of 52 weeks.

Conclusions

The present study showed that the single-injection of BDDE-crosslinked IAHA (LBSA0103) was noninferior to a three injections of IAHA (Synvisc®) at weekly intervals, and provided supports of LBSA0103 as a safe and effective option in maginging Chinese patients with mild to moderate OA of knee.

Abbreviations

AEs: Adverse effects

BDDE: Butanediol diglycidyl ether

BMI: Body mass index

CI: Confidence interval

FAS: Full analysis set

FDA: Food and Drug Administration

IAHA: Intra-articular hyaluronic acid

IRBs: Institutional review boards

ITT: Intention-to-treat

K-L: Kellgren–Lawrence grade

LOCF: Last observation carried forward

MW: Molecular weight

NSAIDs: Non-steroidal anti-inflammatory drugs

OA: Osteoarthritis

OMERACT-OARSI: Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials

PPS: Per-protocol set

Response Criteria Initiative.

SS: Safety set

WOMAC: Western Ontario and McMaster Universities Osteoarthritis

Declarations

Ethics approval and consent to participate

The government regulatory authority and the institutional review boards (IRBs) of each study center granted approval for the study at Peking University Third Hospital (Review ID: 2019-017-01; Approval date: 11 March 2019), Beijing Hospital (Review ID: 2019BJYYEC-108-01; Approval date: 6 August 2019), Peking University Shougang Hospital (Review ID: 2019-26; Approval date: 6 August 2019), Rui Jin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (Review ID: 2019-58; Approval date: 24 June 2019), Beijing Luhe Hospital, Capital Medical University (Review ID: 2019-LHYW-017-01; Approval date: 29 May 2019), Guangzhou First People's Hospital (Review ID: A-2019-016-01; Approval date: 10 June 2019), Zhengzhou Central Hospital, China (Review ID: 2019-026-01; Approval date: 24 May 2019), The Second Affiliated Hospital of Nanchang University (Review ID: 2019-25; Approval date: 31 May 2019), Jilin Province FAW General Hospital (Review ID: 2019-004-01; Approval date: 31 May 2019), Central Hospital Affiliated to Shandong First Medical University (Review ID: 2019-045-01; Approval date: 7 May 2019), Heping Hospital Affiliated to Changzhi Medical College (Review ID: 2019-13; Approval date: 9 May 2019). Each informed consent was signed and obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets from the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

No external funding was received for this study.

Authors' contributions

Hong Cai was the coordinating principal investigator of the study and involved in the development of the study protocol, study execution, and evaluation of the study results. Hui Feng and Zhenpeng Guan were involved in the study design, data collection, data analysis, and manuscript drafting, they contributed equally to this work. Qingyun Xue, Weibin Zhang, Liang Liu, Yunfa Yang, Zhi Zhu, Guicheng Gao, Bin Dai, Shuya Guo, Yuan Li were involved in the study preparation, evaluation of the trial and drafting the manuscript. All the authors were involved in the review and approval of the manuscript and contributed to this work.

Acknowledgements

Not applicable.

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Figures

Figure 1

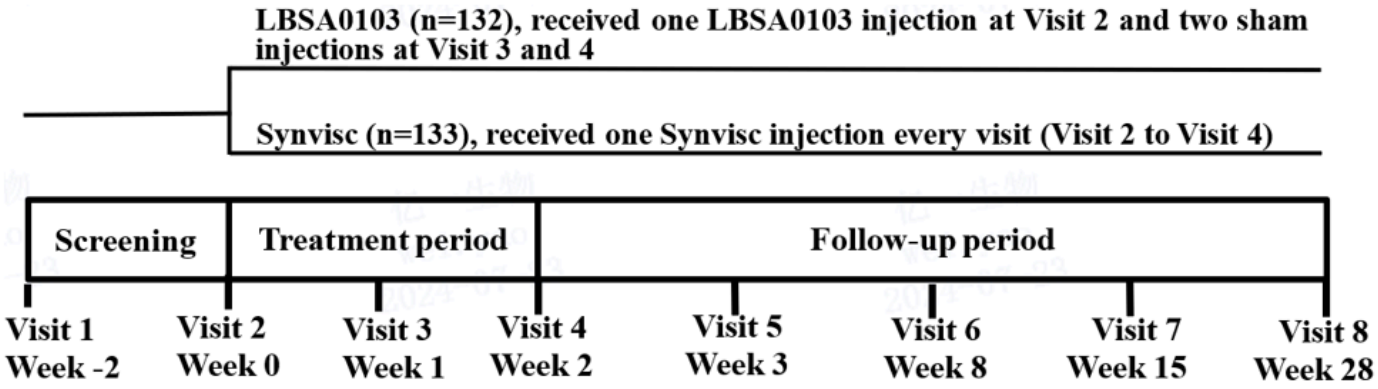

Figure 1

Visit flow chart. The bars indicate each visit. The distances between visits are not proportional to the actual times due to the limited space. After screening, participants receive LBSA0103 (one LBSA0103

injection and two sham injections) or Synvisc from visit 2 to visit 4 at weekly interval. Efficacy was assessed at visit 5 to visit 8, with visit 7 evaluation as primary endpoint.

Figure 2

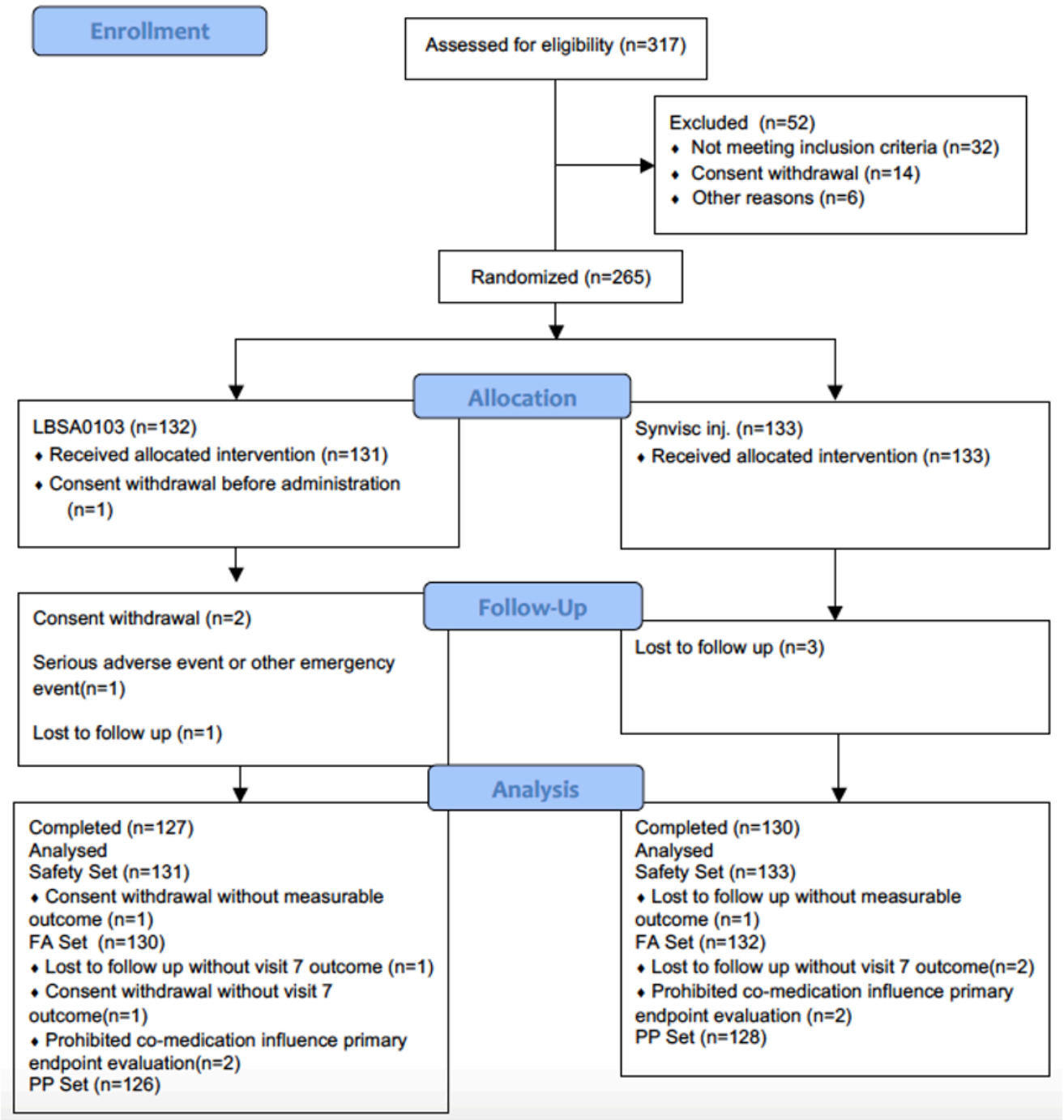

Figure 2

Allocation of patients and study population.

Figure 3

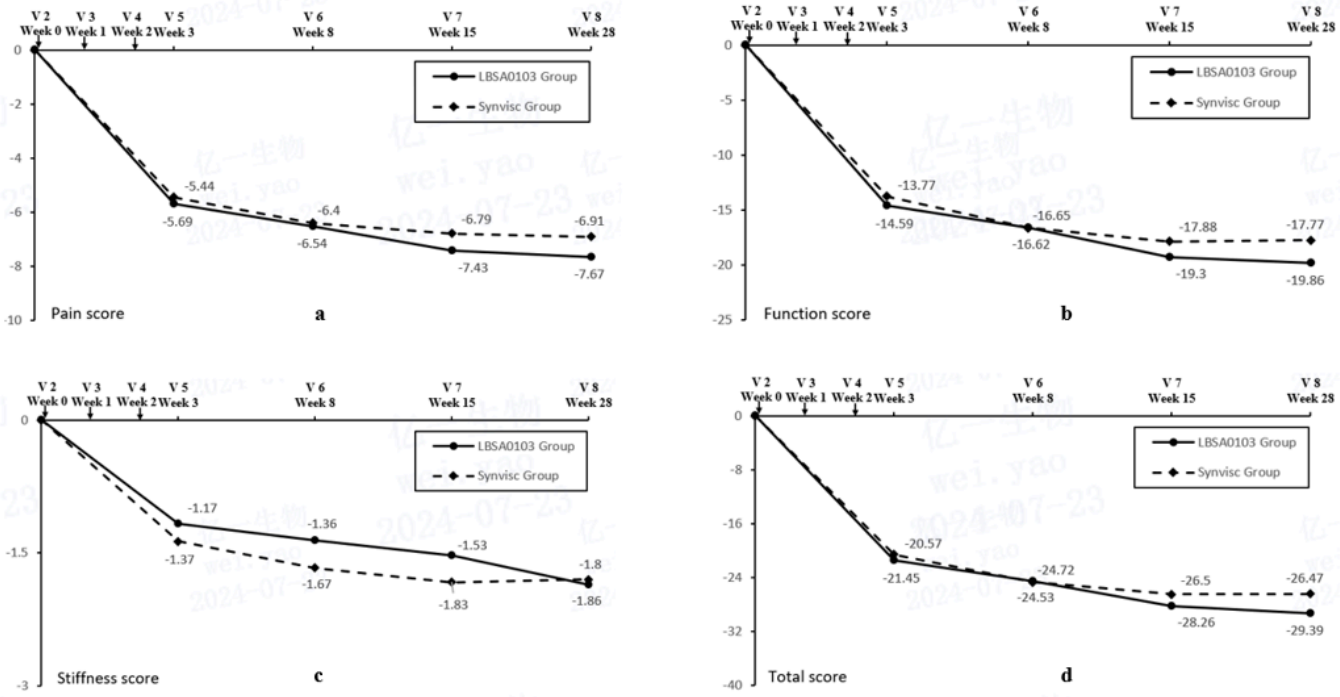

Figure 3

Mean change in WOMAC-Likert scores from Baseline: (a) pain score; (b) function score; (c) stiffness score; (d) total score;

Figure 4

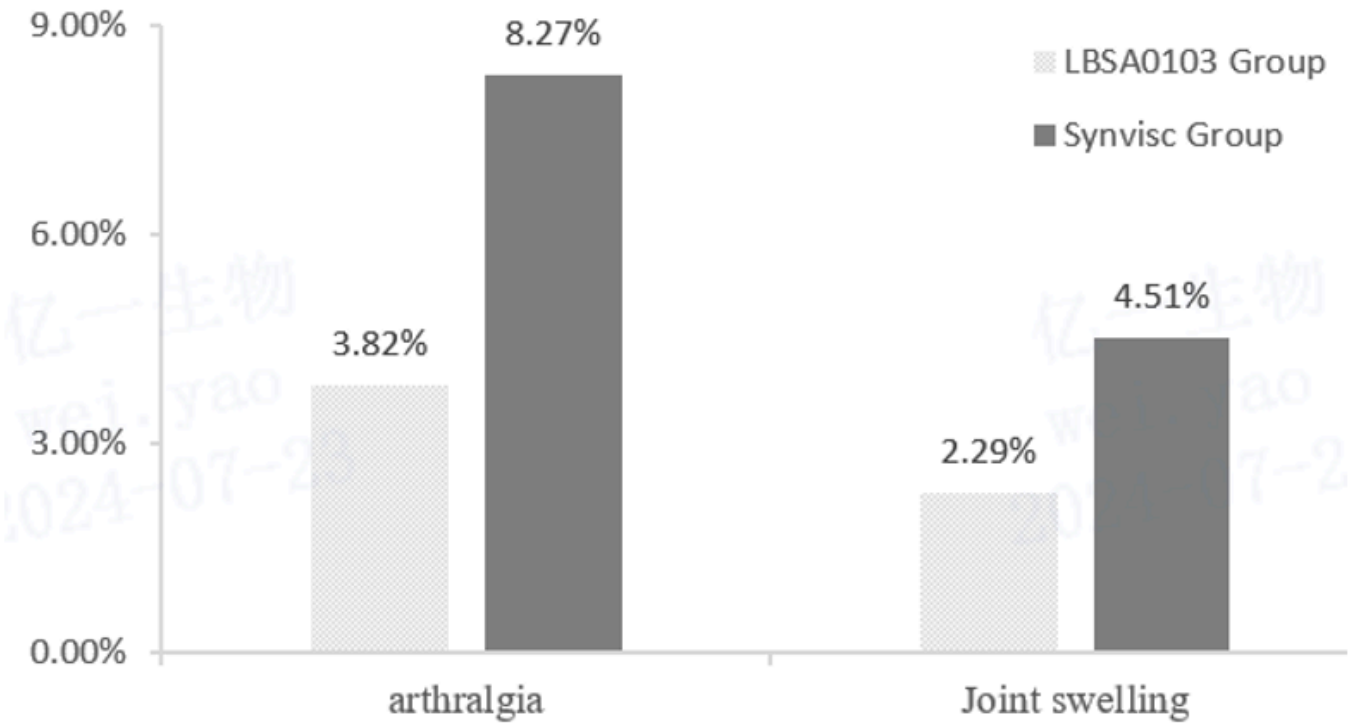

Figure 4

The incidence of arthralgia and joint swelling between the two groups.