Rheumatol Ther (2024) 11:381–395
https://doi.org/10.1007/s40744-024-00643-8

ORIGINAL RESEARCH

Safety and Efficacy of Hybrid Cooperative Complexes of Sodium Hyaluronate and Sodium Chondroitin for the Treatment of Patients with Symptomatic Knee Osteoarthritis

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Received: December 15, 2023 / Accepted: January 18, 2024 / Published online: February 12, 2024

ABSTRACT

Introduction: Knee osteoarthritis (KOA) represents a widespread degenerative disease that causes pain and motor disability. Conservative treatments mainly focus on relieving symptoms, improving joint function, and trying to delay surgery. Safety and efficacy of hybrid cooperative complexes (2.4% sodium hyaluronate and 1.6% sodium chondroitin; HA-SC) for symptomatic KOA were investigated in a single-arm, prospective, pilot study.

Methods: Patients with a visual analogue scale (VAS) pain score ≥ 4 and Kellgren–Lawrence Grade < 4 received a single intraarticular HA-SC injection. Patients with a VAS score change from baseline ≤ 1 received a second injection at day 30. Device-related adverse events (DR-AEs)/adverse events (AEs) were primary endpoints. Secondary endpoints included Western Ontario and McMaster Universities Osteoarthritis Index LK 3.1 (WOMAC LK 3.1), VAS, patient global assessment of disease status (PtGA), and patient proportion needing a second injection.

Results: Of 83 patients with KOA (Kellgren–Lawrence Grade, 2–3), 34.9% had DR-AEs at day 7. No serious DR-AEs/AEs were reported. A significant ($P < 0.0001$) reduction over time in VAS pain score plus WOMAC pain, stiffness, physical function limitation, and total scores was reported. Median PtGA scores indicated a 'slight improvement' at most follow-up visits. Only 18.1% of patients required a second injection.

Conclusions: A single intraarticular HA-SC injection was safe, well-tolerated, and did not

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40744-024-00643-8.

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lead to major deterioration in terms of reducing knee pain, stiffness, and physical function limitation in patients with symptomatic KOA.

Keywords: Conservative therapy; Hyaluronic acid; Injections; Knee; Osteoarthritis; SINOGEL®; Viscosupplementation

Key Summary Points

Why carry out this study?

The number of people affected by symptomatic knee osteoarthritis (KOA) is rising due to an aging population and the increasing rate of obesity or overweight individuals in the general population.

Despite potentially debilitating symptoms, treatments for KOA focus mainly on relieving symptoms instead of symptom reduction or slowing/preventing progressive disease.

In a single-arm, prospective, pilot study, the safety and efficacy of hybrid cooperative complexes (2.4% sodium hyaluronate and 1.6% sodium chondroitin; HA-SC; SINOGEL®) for symptomatic KOA were investigated.

What was learned from the study?

For 83 patients with KOA treated with a single intraarticular HA-SC injection, no serious device-related adverse events/other adverse events were reported and patients had a significant reduction in visual analogue scale pain score, as well as Western Ontario and McMaster Universities Osteoarthritis Index LK 3.1 pain, stiffness, physical function limitation, and total scores over time.

A single intraarticular HA-SC injection was safe, well tolerated, and did not lead to major clinical deterioration in terms of knee pain, stiffness, or physical function limitation in patients with symptomatic KOA.

INTRODUCTION

Knee osteoarthritis (KOA) is a degenerative chronic disease impacting over 650 million individuals worldwide in 2020 [1–3]. By 2050, global cases of KOA are projected to increase by 74.9% [4]. The prevalence of KOA is higher among females compared with males and in individuals with a lower socioeconomic status [5, 6]. Pathological signs of KOA include progressive degeneration and loss of articular cartilage, meniscus, periarticular ligaments, subchondral bone alterations, and synovium [1, 7]. The progression of KOA is typically slow, usually taking decades [8]. Its main symptoms are joint mobility difficulties and stiffness, accompanied by chronic pain [1, 9, 10]. Patients with severe KOA can develop severe progressive motor disability, negatively affecting their quality of life (QoL) and contributing to high healthcare costs [1, 9, 11, 12]. Factors influencing KOA development include joint biomechanical changes (due to aging, trauma, or obesity, etc.), abnormal bone metabolism (caused by metabolic syndrome), the effect of cytokines/related enzymes, or genetic/biochemical abnormalities (e.g., due to plasma adiponectin) [1, 9, 13, 14].

Despite potentially debilitating symptoms, treatments are focused mainly on relieving symptoms rather than reducing symptoms or slowing/stopping disease progression [9, 15]. Several conservative treatment options exist for managing the QoL of patients with KOA [16, 17]. Conservative treatment options include implementing lifestyle changes (e.g., the use of a cane, insoles, patient education, and weight loss), using oral analgesic drugs (e.g., non-steroidal anti-inflammatory drugs [NSAIDs]), physical therapy (e.g., aerobic training, proprioception, strengthening training), and instrumental physical modalities [17]. Total joint arthroplasty is the gold standard treatment for patients with severe osteoarthritis for whom conservative treatment is ineffective or pain severely affects their QoL [9, 18]. Although analgesics, especially nonsteroidal anti-inflammatory drugs, are used to treat osteoarthritis, serious side effects have been reported with

their long-term use, particularly in older patients [19–22]. Intraarticular corticosteroids can provide short-term pain relief in patients who do not respond to conservative treatment but there are also safety concerns with their long-term use [18, 19, 23]. Symptomatic slow-acting drugs, e.g., hyaluronic acid (hyaluronan) and chondroitin, as well as other innovative injectable and non-injectable substances have been investigated to alleviate symptoms of osteoarthritis [19, 24–27]. The symptomatic benefit of intraarticular hyaluronic acid treatment in patients with osteoarthritis was prolonged rather than immediate, starting at approximately 4 weeks and peaking at around 8 weeks, with some benefit still observed at 24 weeks [19, 28]. Besides pain relief, intraarticular hyaluronic acid may have disease-modifying effects, but confirmation of these effects requires further investigation [29, 30]. Currently, there is a lack of consistency in methods used for intraarticular hyaluronic acid administration and marked variations in the effect size of different hyaluronic acid formulations [19].

A novel hyaluronic acid-based medical device for intraarticular viscosupplementation using hybrid cooperative complexes (HCC) of 2.4% sodium hyaluronate and 1.6% sodium chondroitin of biotechnological origin (HA-SC) was developed (SINOGEL®, IBSA Farmaceutici Italia srl) [19, 31]. This medical device enables intraarticular injection of a high concentration of high molecular weight hyaluronic acid without a marked increase in viscosity [19, 32]. In a prior study, a single intraarticular injection of HA-SC was well tolerated, safe, and efficacious in treating patients with symptomatic hip osteoarthritis [19]. The aim of this single-center, single-arm study was to investigate the safety and efficacy of a single intraarticular injection of HA-SC to treat patients with symptomatic KOA.

METHODS

The single-center study to treat symptomatic KOA in adult patients using HCC of sodium hyaluronate and sodium chondroitin (IBSA Farmaceutici Italia Srl) was performed at the Department of Rehabilitation, Humanitas Research Hospital, Milan, Italy, between November 2021 and February 2023.

Ethics Committee

The study was approved by the Humanitas University Ethical Committee and Institutional Review Board on November 11, 2021 (authorization number 3086). The study was conducted according to the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practices, ISO 14155 (second edition), European Union Council Directive 93/42/EEC amended by 2007/47/EC, MEDDEV 2. 12–1 rev. 6 and amendments, and local legislation on clinical investigations involving medical devices. Patients provided their informed consent before study participation.

Eligibility Criteria

Patients eligible to participate in the study were females or males aged $\geq$ 18 years with unilateral knee osteoarthritis and a visual analogue scale (VAS) pain score of $\geq$ 4 and a standing knee radiograph demonstrating a Kellgren and Lawrence grade of < 4 [33]. Enrolled patients also had $\geq$ 1 prior conservative treatment for osteoarthritis (e.g., physical therapy and simple analgesics), which was unsatisfactory for pain relief.

Exclusion criteria included patients with an active infection, severe inflammation, or skin disease in the index knee joint; a body mass index of $\geq$ 32 kg/m^2; concomitant rheumatic disease; known tumor pathology; or ongoing/planned chemotherapy. Patients were also excluded from the study if they had disease of the spine, hip, or other joints of the lower extremity judged by the investigator as contributing to the index knee pain; untreated symptomatic index knee injury; medium/large surgical hardware or other foreign body for arthritis or cartilage-related pathology in the index knee; or venous/lymphatic stasis in the index leg. Patients with the following prior medications taken within specified timeframes prescreening were also excluded from the study:

intraarticular viscosupplementation or corticosteroids in the knee (≤ 4 months); systemic steroids (≤ 4 weeks), NSAIDs (≤ 48 h), paracetamol (≤ 48 h), opioids/narcotic analgesics (≤ 7 days), or immunosuppressants (≤ 6 weeks); or symptomatic slow-acting drugs for osteoarthritis (≤ 3 months). Patients with a history of allergy; hypersensitivity to hyaluronic acid or paracetamol; planned index knee surgery during the study period; major index knee surgery during ≤ 12 months prescreening; or minor index knee surgery during ≤ 6 months prescreening were also excluded from the study. Pregnant women, nursing mothers, those with pregnancy plans during the study period, patients with drug/alcohol dependency during ≤ 1-year prescreening, or participation in another clinical trial during ≤ 90 days prescreening were also excluded from the study. Finally, although this was not stated specifically in the study protocol, patients with neurological diseases were also excluded from the study as their possible sensory and motor impairments could affect treatment outcome.

Study Design

The study design of the single-arm, prospective, single-center pilot study is shown in Fig. 1. Patient screening assessments included VAS questionnaire for index knee, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) using the Likert (LK) scale version 3.1 questionnaire for index knee, WOMAC LK 3.1 pain scale for non-index knee (if it was unclear whether symptomatic osteoarthritis was present), and an X-ray of the index knee (classified by Kellgren and Lawrence grade by an expert radiologist and confirmed by a central imaging laboratory).

Patients with symptomatic KOA received a single intraarticular injection of HA-SC (SINOGEL®; 72 mg of sodium hyaluronate and 48 mg of sodium chondroitin) via an investigational medical device. The investigational medical device comprised a sterile 3-ml syringe containing high molecular weight sodium hyaluronate (2.4%) and non-sulphated sodium chondroitin (1.6%) for intraarticular administration. Patients with a change in VAS score of ≤ 1 from baseline after the first injection (assessed 30 days after the first injection) could receive a second injection.

Concomitant use of oral NSAIDs/systemic corticosteroids, topical NSAIDs/other pain therapies applied to the index knee, narcotics, and centrally acting medications for analgesia were not permitted during the study until the completion of the 180-day follow-up visit. Concomitant use of intraarticular corticosteroids, hyaluronic acid (other than the study treatment), or other therapy administered to the index knee, as well as any surgery to the index knee were not permitted during the entire study and follow-up periods. During the follow-up period, rescue therapy (1000 mg paracetamol; maximum two tablets per day) was allowed for pain.

Injection Procedure

According to the protocol, the investigator was permitted to choose the position of the knee (e.g., extended or bent) as well as the approach for the injection (e.g., medial or lateral). However, during the study, all patients received the injection using a lateral approach, with the knee extended. The content of the syringe was administered as a single injection into the knee joint. To do this, the injection area was first cleaned using an antiseptic solution, and if desired by the patient, a local, topical anesthetic, such as ethyl chloride, was also applied to the area. A standard ultrasound-guided procedure was used to ensure the correct placement of the injection into the intraarticular space of the knee joint and minimize the risk of adverse events due to the incorrect positioning of the needle. An empty syringe was first attached to the needle to aspirate all available joint fluid. The syringe containing SINOGEL® was then attached to the needle and its contents injected into the synovial space of the joint, taking care to avoid injecting the solution into the extraarticular space of the knee joint, synovial tissues, or joint capsule. Patients were instructed

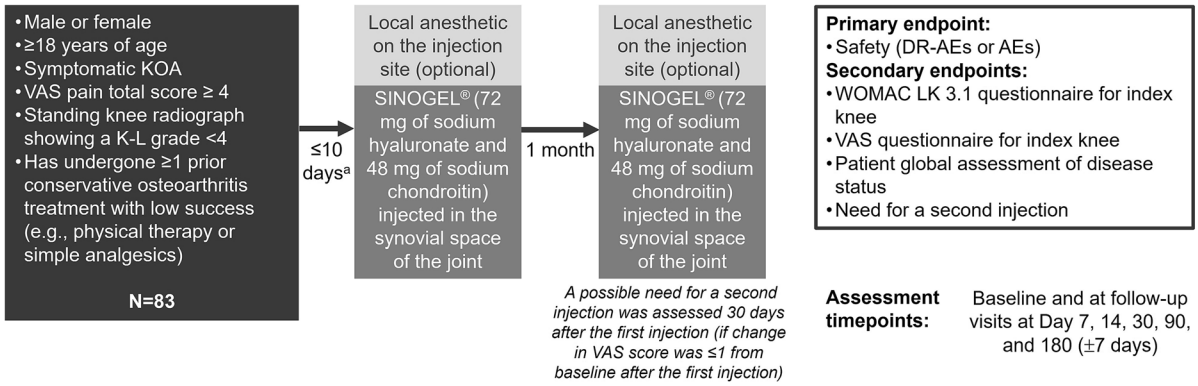


Fig. 1 Study design. [a]The first injection was administered in ≤ 14 days of screening. *AE* adverse events, *DR-AE* device-related adverse events, *K–L* Kellgren and Lawrence, *KOA* knee osteoarthritis, *N* total number of patients, *VAS* visual analogue scale, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

not to exceed their pre-injection physical activity level for 14 days post-injection.

Study Outcomes

The primary endpoint was device-related adverse events (DR-AEs, i.e., any adverse event related to the medical device; Fig. 1) or adverse events (AEs) unrelated to the medical device after a single intraarticular injection of HA-SC. Secondary endpoints are shown in Fig. 1. DR-AEs and AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA®).

WOMAC LK 3.1 consists of 24 items: five items assessing knee pain, two items assessing knee stiffness, and 17 items assessing physical function [34]. Each item of WOMAC LK 3.1 was graded on a five-point LK scale, from 0 (none/never) to 4 (extreme/always) [34]. A higher WOMAC LK 3.1 score indicated worse pain, stiffness, or physical function.

The VAS is a psychometric response scale that can be used in questionnaires and comprises a straight line with its ends defining extreme limits such as "no pain at all" to "pain as bad as it could be" [35]. By completing a daily diary during the first 7 days after treatment administration, patients were asked to mark his or her pain level on a line between the two endpoints of a 10-cm line (a ten-point scale).

Lower WOMAC and VAS scores indicated lower symptom intensity. Patient global assessment of disease activity (PtGA) was assessed according to a five-point qualitative scale where 4 is "very much improved", 3 is "slightly improved", 2 is "no change", 1 is "slightly worsened", and 0 is "very much worsened" [19].

Statistical Analyses

Absolute and relative frequencies were assessed for categorical variables. Means, standard deviations (SD), median values, minimum and maximum, and interquartile range (IQR) were calculated for continuous variables. Additionally, the Kolmogorov–Smirnov normality test was performed for all continuous variables. Variables (that did not have a normal distribution) were assessed using the non-parametric Friedman test. The Friedman test was used to evaluate differences in overall VAS, WOMAC, and PtGA scores between all study timepoints. Statistically significant differences were determined by P values of ≤ 0.05. All statistical analyses were performed using GraphPad Prism software version 9.5.1 (GraphPad Software, San Diego, CA, USA). The planned enrolment number was 80 patients.

Minimal Important Change or Difference

Although not part of the study protocol, change in VAS and WOMAC scores were also compared to published minimal important change or difference values. According to a recent systematic literature review [36], the median minimal important change (change in clinical outcome measure within a single group or an individual over time; derived using the anchor method) in VAS score for pain on movement (on a scale where 100 is the worst score) is 19.9 mm (1.99 cm). Similarly, the median minimal important change in WOMAC function score (on a scale where 100 is the worst score) is 17.0. According to the same publication [36], the median minimal important difference (difference between independent groups or between individuals; derived using the anchor method) in WOMAC function, pain, and stiffness scores are 14.5, 8.7, and 20.2, respectively, and the median minimal important difference in WOMAC total score is 6.8. Since a control arm was not available in this study, minimal important change values were used where available, otherwise minimal important difference values (as defined above) were used for comparison with values obtained in our study for the change in median patient reported outcome scores from baseline to day 180.

RESULTS

Baseline Demographic and Clinical Characteristics

Of 83 enrolled patients, 46 (55.4%) were female, and 37 (44.6%) were male (Table 1). The mean age of patients was 66.9 (standard deviation [SD], 10.7; range, 47–87) years. At baseline, the mean duration of pain experienced by patients enrolled in the study was 10.8 months (SD 14.9). More than one-third of patients at baseline (37.3%) had concomitant therapies, and the most common concomitant therapies ($\geq$ 15%) were non-steroid anti-inflammatory drugs (24.1%) and paracetamol (16.9%). Of patients who had comorbidities (42.2%), the most frequent comorbidities ($\geq$ 10%) were anxiety/depression, endocrine disorder, gastrointestinal disease, and renal disease (10.8% each). Most patients (68.7%) had a Kellgren–Lawrence Grade of 2, and 31.3% had a Kellgren–Lawrence Grade of 3.

Safety Findings

A total of 29 patients (34.9%) had DR-AEs at the 7-day follow-up visit, six patients (7.2%) had DR-AEs at the 14-day follow-up visit, and one patient (1.2%) had DR-AEs at 30-, 90-, and 180-day follow-up visits (Table 2). The DR-AEs recorded at the 7-day follow-up visit were pain (18.1%), swelling (16.9%), rigidity (12.0%), and burning (4.8%). The mean duration of DR-AEs from the day of injection (recorded at the 7-day follow-up visit) was 1.0 day (SD 1.5). No serious DR-AEs were reported. None of the patients had adverse events unrelated to the device at any follow-up visit. Rescue therapy (paracetamol) was required for pain relief by 21.7, 15.7, 21.7, 22.9, and 22.7% of patients at respective follow-up visits (Table 2).

Self-reported Pain, Stiffness, and Physical Function

A reduced median WOMAC score for pain (from 7 at baseline to 4 at the 180-day follow-up visit) post-treatment was reported (Fig. 2 and Table 3). The median WOMAC score for stiffness was reduced from 3 at baseline to 2 at the 180-day follow-up visit. The intraarticular injection of HA-SC also led to an improvement in the physical function of patients; median WOMAC domain score for limitation in physical function decreased from 26 at baseline to 13 at the 180-day follow-up visit. Median total WOMAC scores decreased from 37 at baseline to 18 at the 180-day follow-up visit. The reduction in symptom intensity according to the WOMAC domain scores over time was statistically significant for pain, stiffness, and physical function limitation, as well as for the total WOMAC score (Table 3; $P < 0.0001$ each).

A single intraarticular injection of HA-SC also led to a significant reduction ($P < 0.0001$) in median VAS score for pain from 6 at baseline

Table 1 Baseline demographic and clinical characteristics

Characteristic	*N* = 83	Characteristic	*N* = 83
Mean (SD) age, years	66.9 (10.7)	Concomitant therapies, *n* (%)[a]	31 (37.3)
Median (range) age, years	67 (47 − 87)	NSAID	20 (24.1)
Females, *n* (%)	46 (55.4)	Paracetamol	14 (16.9)
Males, *n* (%)	37 (44.6)	Opioid	8 (9.6)
Married, *n* (%)	59 (71.1)	Muscle relaxant	1 (1.2)
Weight, kg, mean (SD)	72.0 (13.2)	Steroid	1 (1.2)
Height, m, mean (SD)	1.7 (0.1)	Comorbidities, *n* (%)[b]	35 (42.2)
BMI, kg/m^2, mean (SD)	25.1 (3.4)	Anxiety/depression	9 (10.8)
Mean (SD) pain duration, months	10.8 (14.9)	Endocrine disorder	9 (10.8)
Median (range) pain duration, months	6 (0 − 72)	GI disease	9 (10.8)
K–L grade 2 (mild), *n* (%)	57 (68.7)	Renal disease	9 (10.8)
K–L grade 3 (moderate), *n* (%)	26 (31.3)	Other musculoskeletal pathologies[c]	7 (8.4)
		Respiratory disease	6 (7.2)
		Other[d]	7 (8.4)

BMI body mass index, *GI* gastrointestinal, *K–L* Kellgren–Lawrence, *n* number of patients, *N* total number of patients, *N/A* not available, *NSAID* non-steroid anti-inflammatory drug, *SD* standard deviation

[a]Patients could have more than one concomitant therapy

[b]Patients could have more comorbidity

[c]Aside from knee arthrosis

[d]Six patients with ischemic heart disease and one patient with a cardiac pacemaker

to 4 at the 180-day follow-up visit (Fig. 3 and Table 3). However, in terms of the minimal important clinical change or difference for knee osteoarthritis using median values previously reported [36], there was only a clinically meaningful change in WOMAC total score and VAS pain score from baseline to day 180 (Table 3).

Patient Global Assessment of Disease Activity

Median PtGA, assessed at follow-up visits only, was 3 (indicating that patients assessed their disease activity as "slightly improved") at the 7-, 14-, 90-, and 180-day follow-up visits, and 4 ("very much improved") at the 30-day follow-up visit; median PtGA scores were significantly different between follow-up visits ($P = 0.0116$; Fig. 3 and Table 3).

Outcomes for Patients Who Needed Two Injections at the 30-Day Follow-Up Visit

A total of 15 of 83 patients (18.1%) required a second injection at the 30-day follow-up visit as their change from baseline in VAS score was ≤ 1 after their first injection. There was a statistically significant reduction in median WOMAC total and domain scores for physical function and pain over time (see Table S1 in the electronic supplementary material for details). However, there was no significant change in median values for WOMAC stiffness score, VAS pain score, or PtGA over time for this small group of patients who had a second injection

Table 2 Safety findings ($N = 83$)

	7-day f/u	14-day f/u	30-day f/u	90-day f/u	180-day f/u
DR-AEs[a], *n* (%)	29 (34.9)	6 (7.2)	1 (1.2)	1 (1.2)	1 (1.2)
Pain	15 (18.1)	N/A	N/A	N/A	N/A
Swelling	14 (16.9)	N/A	N/A	N/A	N/A
Rigidity	10 (12.0)	N/A	N/A	N/A	N/A
Burning	4 (4.8)	N/A	N/A	N/A	N/A
AEs unrelated to use of the device, *n* (%)	0	0	0	0	0
DR-AE duration from the day of injection, days					
Mean (SD)	1.0 (1.5)	N/A	N/A	N/A	N/A
Median (range)	0.0 (0.0, 6.0)	N/A	N/A	N/A	
Patients who required rescue therapy, *n* (%)	18 (21.7)	13 (15.7)	18 (21.7)	19 (22.9)	23 (22.7)

AE adverse event, *DR-AE* device-related adverse events, *F/u*, follow-up, *N* number of patients, *N/A* not available, *SD* standard deviation

[a]DR-AE related to the use of an investigational medical device. Individual patients could have more than one device-related adverse event

(see Tables S1 and S2 in the electronic supplementary material for details). In terms of the minimal important clinical change or difference for knee osteoarthritis using median values previously reported [36], there was only a clinically meaningful change in WOMAC total score from baseline to day 180 (Tables S1, S2).

Seven of 15 patients who had a second injection (46.7%) had device-related adverse events that were mainly swelling (five patients) and rigidity (three patients; see Table S3 in the electronic supplementary material for details). In addition, one patient had a burning sensation, and one patient had pain. However, the median duration of these symptoms was 0 days (i.e., the median time to symptom resolution was within a day). Seven (46.7%) of patients who eventually had a second injection at the 30-day follow-up visit needed rescue medication at the 7-day follow-up visit, nine (60.0%) patients who had a second injection needed rescue medication at the 30-day follow-up visit, and six (40.0%) patients who had a second injection needed rescue medication at the 180-day follow-up visit.

DISCUSSION

Several types of HA comprising different molecular weights are commercially available, and it has been reported that higher molecular weight HA provides greater anti-inflammatory and proteoglycan synthesis effects, as well as improved joint lubrication and viscoelasticity maintenance [18]. However, characteristics of intraarticular HA, including its molecular weight and structure, and the manufacturing process for developing these products result in differences in the reported clinical outcomes (effectiveness and safety) for KOA treatment [26, 37]. Safety outcomes (DR-AEs and adverse events AEs unrelated to use of the device) were the primary endpoint of the present pilot study. At data cutoff, following treatment with a single intraarticular injection of HA-SC (SINOGEL®), about a third of patients had DR-AEs (low-grade pain, swelling, rigidity, or burning, lasting for a day, on average) at the 7-day follow-up visit, and fewer patients had these DR-AEs over time (only 1.2% of patients at the 30-, 90-, and 180-day follow-up visit). Importantly, no patients had serious DR-AEs or adverse events unrelated to the device. Rescue therapy

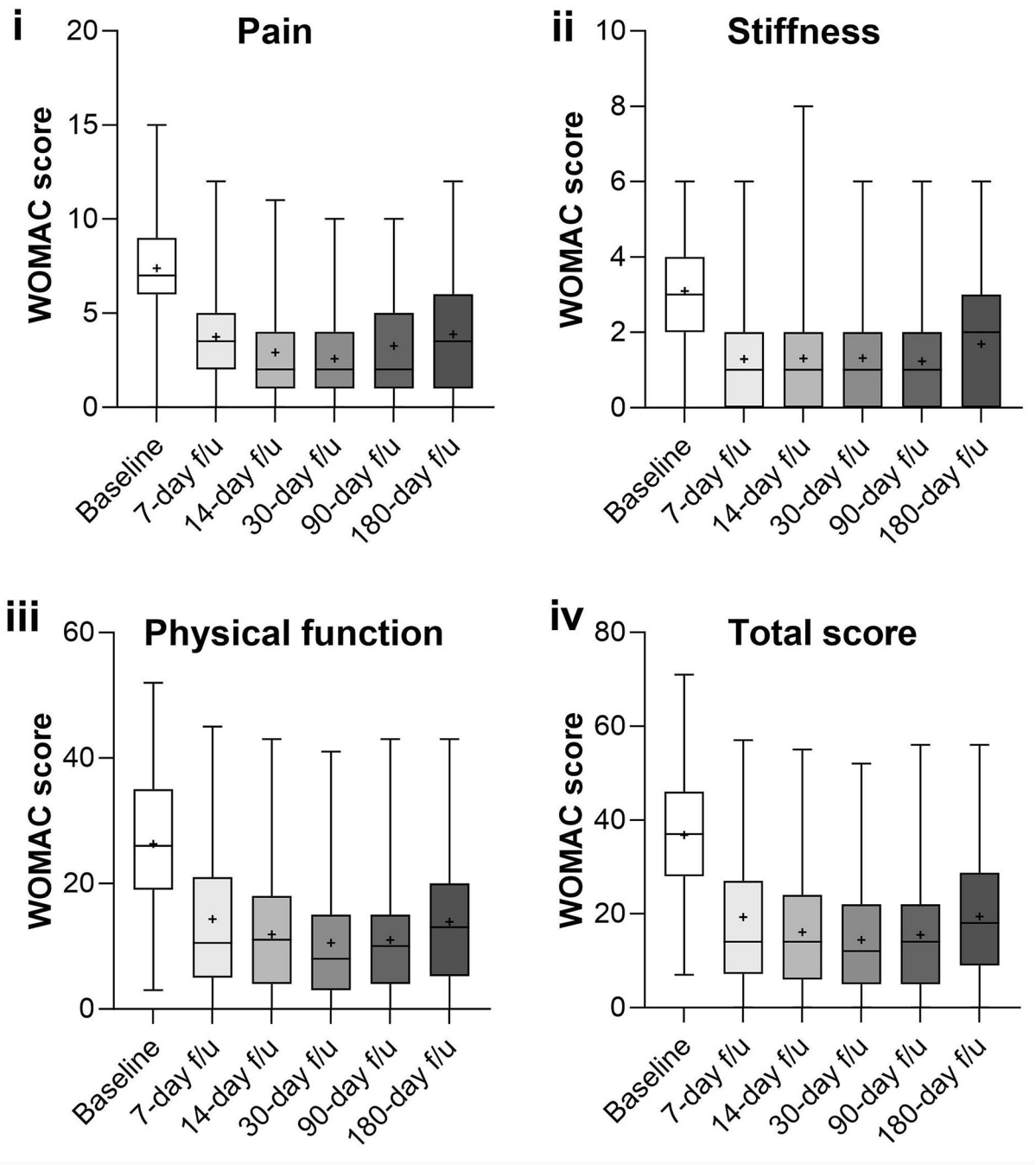


Fig. 2 WOMAC domain scores for pain (**A**), stiffness (**B**), and physical function (**C**), and WOMAC total score (**D**). *Lines within the box plots* represent median values, *upper and lower whiskers* represent maximum and minimum values, respectively, *the top and end of each box* represent upper quartile range (Q3) and lower quartile range (Q1), respectively, and *crosses* represent mean values. Statistical analysis results are shown in Table 3. *F/u* follow-up, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

Table 3 Statistical analysis of WOMAC domain scores (pain, stiffness, and physical function), WOMAC total score, VAS pain score, and PtGA score over time

	Median (IQR)							
	Baseline	**7-day f/u**	**14-day f/u**	**30-day f/u**	**90-day f/u**	**180-day f/u**	**Change from baseline to day 180**	**Friedman test *P* value**
N	83	80	79	79	79	76		
WOMAC score								
Pain	7 (6, 9)	4 (2, 5)	2 (1, 4)	2 (1, 4)	2 (1, 5)	4 (1, 6)	3	**< 0.0001***
Stiffness	3 (2, 4)	1 (0, 2)	1 (0, 2)	1 (0, 2)	1 (0, 2)	2 (0, 3)	1	**< 0.0001***
Physical function	26 (19, 35)	11 (5, 21)	11 (4, 18)	8 (3, 15)	10 (4, 15)	13 (5, 20)	13	**< 0.0001***
Total score	37 (28, 46)	14 (7, 27)	14 (6, 24)	12 (5, 22)	14 (5, 22)	18 (9, 29)	19	**< 0.0001***
VAS pain score	6 (5, 7)	3 (2, 5)	2 (1, 4)	2 (1, 4)	3 (1, 5)	4 (2, 5)	2	**< 0.0001***
PtGA score[a]	N/A	3 (3, 4)	3 (3, 4)	4 (3, 4)	3 (2, 4)	3 (2, 4)		**0.0116***

A lower WOMAC score indicates lower symptom intensity. Descriptive statistics were used to establish median (IQR) values for all patients ($N = 83$). Four patients with missing WOMAC, VAS, and PtGA scores for all f/u timepoints and three patients with missing WOMAC, VAS, and PtGA scores for the 180-day f/u visit (due to dropping out of the study) were excluded from the Friedman's test as this statistical test cannot compute missing values

F/u follow-up, *IQR* interquartile range, *N/A* not available, *PtGA* patient global assessment of disease activity, *VAS* visual analogue scale, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

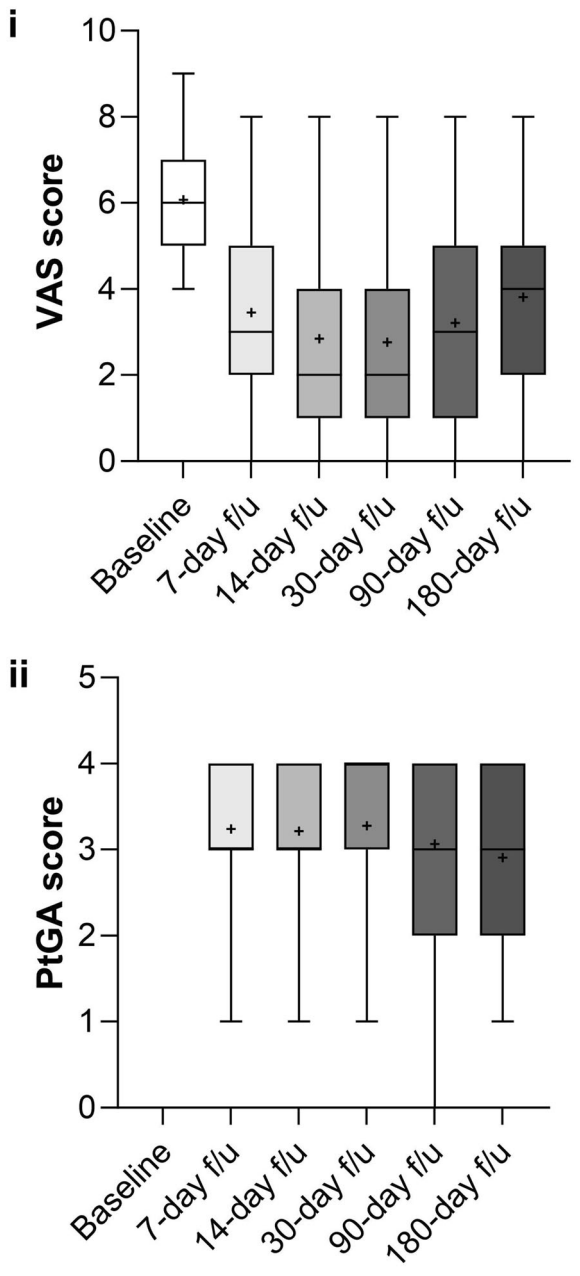
*Statistically significant *P* values (< 0.05)

[a]PtGA scores: 4 = much improved, 3 = slightly improved, 2 = no change, 1 = slightly worsened, 0 = much worse

(paracetamol) for pain relief was required by a small proportion of patients (15.7–22.9%) at the follow-up visits.

As well as the device being well-tolerated without producing unexpected DR-AEs, the treatment led to statistically significant reduction ($P < 0.0001$) in the median WOMAC scores for pain, stiffness, and limitation in physical function, as well as WOMAC total score over time. The reduction post-treatment in median VAS score for pain over time was also significant ($P < 0.0001$). Median PtGA scores (rated by patients and assessed at follow-up visits only) indicated a 'slight improvement' in disease activity (median score of 3) at most follow-up visits.

Per the study design, only 18.1% of patients required a second injection at the 30-day follow-up visit as their change in VAS score from baseline was ≤ 1 after the first injection; for these patients, treatment led to a statistically significant reduction in median WOMAC total score and WOMAC domain scores for physical function and pain over time but no significant change in median WOMAC stiffness score, VAS pain score, or PtGA over time. With regards to the minimal important clinical change or difference for knee osteoarthritis using median values previously reported [36], there was only a clinically meaningful change in WOMAC total score from baseline to day 180 for patients who had one or two injections of SINOGEL®. For patients who had a second injection, 46.7% had DR-AEs (mainly swelling or rigidity; median duration of symptoms, 0 days); rescue medication was needed by 46.7% of patients at the 7-day follow-up visit and 60.0% of patients at the 30-day follow-up visit.



◀**Fig. 3** VAS domain scores for pain (**A**) and patient's global assessment of disease status scores* (**B**). *As measured by the WOMAC scale. *Lines within the box plots* represent median values, *upper and lower whiskers* represent maximum and minimum values, respectively, *the top and end of each box represent* upper quartile range (Q3) and lower quartile range (Q1), respectively, and *crosses* represent mean values. Statistical analysis results are shown in Table 3. *F/u* follow-up, *PtGA* patient global assessment of disease activity, *VAS* Visual Analogue Scale, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

In-line with prior findings for HA-SC (SINOGEL®), our study shows that a single intraarticular injection of HA-SC is safe and does not lead to major clinical deterioration in patients with KOA of minimal to moderate severity. In a prospective, open-label, pilot study conducted at six clinical sites in Italy, 48 patients (mean age, 61.2 years) with radiographically confirmed symptomatic hip osteoarthritis (94% with Kellgren–Lawrence Grade 2 or 3) and moderate-to-severe pain received a single intraarticular injection of HA-SC (SINOGEL®) [19]. In that study, 20.8% had DR-AEs of moderate-to-severe intensity (most commonly, injection site pain or localized arthralgia), and global evaluation of tolerability was rated as excellent or good by 75.0% of patients and 77.1% of investigators. Patients in that study experienced a rapid and significant decrease in mean VAS score for pain post-treatment (67.5 at baseline to 29.3 on day 7; $P < 0.0001$), and the effects were sustained during the 6-month follow-up period [19]. In addition, patients had a significant improvement in Lequesne's Index for hip osteoarthritis total score (mean 10.4 at baseline to 5.1 at the 6-month follow-up visit; $P < 0.0001$) and, regarding global improvement, most patients reported that their hip osteoarthritis had "very much improved" or "slightly improved" post-treatment [19]. Furthermore, although 75.0% of patients required rescue medication (paracetamol) during the study, the mean number of daily tablets for these patients was generally low and decreased over time [19].

For 692 patients with moderate-to-severe KOA (Kellgren and Lawrence Grade 2 or 3) randomized to a single intraarticular injection of a different formulation, intraarticular injection of high and low molecular weight hyaluronic acid (HA-HL) versus placebo in a prospective, double-blind study, a rapid decrease in mean VAS pain score from baseline to the 1-week follow-up visit was observed with HA-HL (26 [SD, 24]) versus placebo (23 [SD, 23]; $P = 0.008$), and this effect was sustained at the 24-week follow-up visit [38]. In that study, the use of rescue medication (paracetamol) was lower for patients in the HA-HL arm, and both HA-HL and placebo were well tolerated [38].

Several studies have investigated the safety and efficacy of intraarticular hyaluronic acid for KOA [39, 40]. In a clinical trial, 238 patients with mild-to-moderate KOA were randomized to hyaluronic acid (three doses weekly), platelet-rich plasma, plasma rich in growth factors, or ozone therapy [40]. Although the best therapeutic effect was seen in that study with ozone therapy versus the other treatment arms at the 2-month follow-up visit, hyaluronic acid, platelet-rich plasma, or plasma rich in growth factors showed better therapeutic effect versus ozone therapy at the 6-month follow-up visit [40]. In a systematic review and meta-analysis of 18 randomized controlled trials on intraarticular injections of platelet-rich plasma and hyaluronic acid for KOA, clinical outcomes were better with platelet-rich plasma versus hyaluronic acid at short-term follow-up; however, limitations of this systematic review included the fact that the studies used different treatment administration techniques, product compositions, patient-reported outcomes, and follow-up times [41].

Our study is limited, since it was an open-label, single-arm pilot study rather than a definitive trial, and the study did not include a control arm. In addition, the sample size of patients was small, particularly for those who needed a second injection.

CONCLUSIONS

Despite the limitations of the study, the present findings are promising and indicate that a single intraarticular injection of HA-SC (SINOGEL®) is safe, well-tolerated, and did not lead to major deterioration in terms of knee pain, stiffness, or limitations in physical function in patients with symptomatic KOA. Encouragingly, a low proportion of patients required a second intraarticular injection of HA-SC at the 30-day follow-up visit or paracetamol as rescue therapy for pain relief at the follow-up visits.

Medical Writing. The authors are grateful to Sally Hassan, PhD, an employee of Papyrus Medical Communications Ltd, for medical writing support in developing the first draft of the manuscript. Medical writing support was funded by IBSA Farmaceutici Italia Srl.

Author Contributions. Conceptualization: Cristiano Sconza, Dario Romano, and Stefano Respizzi; Methodology: Berardo Di Matteo and Elizaveta Kon; Validation: Cristiano Sconza and Berardo Di Matteo; Investigation: Cristiano Sconza and Dario Romano; Data curation: Dario Romano and Stefano Respizzi; Writing—original draft preparation: Cristiano Sconza and Berardo Di Matteo; Writing—review and editing: Dalila Scaturro, Angelo Alito, Giulia Leonardi, and Giulia Letizia Mauro; Visualization: Cristiano Sconza, Dalila Scaturro, and Giulia Letizia Mauro; Supervision: Angelo Alito, Giulia Leonardi, Elizaveta Kon, and Berardo Di Matteo. All authors have read and agreed to the published version of the manuscript.

Funding. This study was an Investigator Initiated Trial, which was partially supported by IBSA Farmaceutici Italia Srl. Medical writing support in developing this manuscript and the journal's Rapid Service Fee were funded by IBSA Farmaceutici Italia Srl.

Data Availability. The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request. These data are not publicly available due to privacy or ethical restrictions.

Declarations

Conflict of Interest. Cristiano Sconza, Dario Romano, Dalila Scaturro, Giulia Letizia Mauro, Giulia Leonardi, Angelo Alito, Stefano Respizzi, Elizaveta Kon, and Berardo Di Matteo declare no conflict of interest.

Ethical Approval. The study was approved by the Humanitas University Ethical Committee and Institutional Review Board on 11 November 2021 (authorization number 3086). The study was conducted according to the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practices, ISO 14155 (second edition), European Union Council Directive 93/42/EEC amended by 2007/47/EC, MEDDEV 2. 12–1 rev. 6 and amendments, and local legislation on clinical investigations involving medical devices. Patients provided their informed consent before study participation.

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