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Single intra-articular injection of lightly cross-linked hyaluronic acid reduces knee pain in symptomatic knee osteoarthritis: a multicenter, double-blind, randomized, placebo-controlled trial

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Abstract

Purpose The primary objective was to demonstrate the safety and effectiveness of Monovisc™ in the relief of joint pain in patients with idiopathic knee OA compared to saline injection. It was hypothesized that patient success, defined as ≥ 50% improvement from baseline and ≥ 20 mm absolute improvement from baseline in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) visual analog scale (VAS) pain score, would be greater in the Monovisc™ group compared to the Saline control group.

Methods In this multicenter, double-blind, randomized, placebo-controlled trial, patients with idiopathic, symptomatic, knee OA were randomized to either 4 ml single injection of Monovisc™ or 4 ml injection of 0.9% saline. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used to assess patient outcomes at 2, 4, 8, 12, 20, and 26 weeks post-injection. The primary effectiveness endpoint was a 50% improvement and ≥ 20 mm improvement from baseline in the WOMAC pain through 26 weeks. Secondary outcome measures included a ≥ 20 mm improvement from baseline on the WOMAC physical function, patient global assessment, evaluator global assessment, and knee range of motion.

Results 369 patients (154 male, 215 female) were randomized to either Monovisc™ or saline. The Monovisc™ group had a significantly greater rate of patient success (e.g. ≥ 50% improvement and ≥ 20 mm absolute improvement from baseline in the WOMAC pain through Week 26) compared to saline ($p = 0.043$).

Conclusions Monovisc™, a single-injection intra-articular HA device, is a safe and effective treatment for providing a clinically meaningful reduction in knee pain within 2 weeks. The results of this study support the use of a single injection of hyaluronic acid (Monovisc™) for patients with symptomatic knee OA in patients older than 45 years, as a safe and effective alternative for patients who may want an alternative treatment modality or may not be candidates for partial or total knee replacement.

Level of evidence I, multicenter, double-blind, randomized, placebo-controlled trial.

Keywords Monovisc™ · Hyaluronic acid · Knee osteoarthritis · Intra-articular injection · Knee joint pain

Abbreviations

OA	Osteoarthritis
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
VAS	Visual analog scale
US	United States
NSAIDS	Non-steroidal anti-inflammatory medications
HA	Hyaluronic acid
USD	United States dollar
AAOS	American Academy of Orthopaedics
IRB	Institutional Review Board
GCP	Good clinical practice
ICH	International Conference on Harmonization
BMI	Body mass index

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K–L	Kellgren–Lawrence
MedDRA	Medical Dictionary for Regulatory Activities
ITT	Intent-to-treat
PP	Per protocol
GEE	Generalized estimating equations
MCID	Minimum clinically important differences
ROM	Range of motion
ACR	American College of Rheumatology
OARSI	Osteoarthritis Research Society International

Introduction

Arthritis is the leading cause of disability in the United States among the aging population (US) [11]. It has been estimated that nearly half of the population (46%) will develop knee osteoarthritis (OA) in their lifetime [27]. Of the population currently afflicted with knee OA, one quarter experience pain on walking, have difficulty walking a quarter mile, or have difficulty climbing stairs [24]. Current projections suggest approximately half of the population with knee OA will undergo a total knee replacement [40]. Nearly 5 million Americans are living with a knee replacement and over 620,000 total knee replacement procedures are performed in the US annually, with associated hospital expenditures of $28.5 billion [21, 26].

Current treatments for knee OA focus on symptom and impairment management to enhance quality of life and delay or prevent joint arthroplasty [14, 22, 29, 41]. The benefits of pharmacologic and non-pharmacologic interventions are well-documented, however, prolonged NSAID use carry carries the risk of adverse gastrointestinal side effects [6]. A recent meta-analysis suggests that hyaluronic acid (HA) injections are a safe and effective alternative in treating patients with symptomatic knee OA [25], however, despite these benefits and cost savings compared to total knee replacement, the American Academy of Orthopaedics (AAOS) published clinical practice guidelines in 2013 recommending against the use of hyaluronic acid for patients with symptomatic knee OA. These guidelines as well as other meta-analyses have come under scrutiny, calling into question conclusions based on methodological flaws, potentially limiting patient access to HA injections when they might be of benefit [1, 5].

While the majority of HA products involve a series of 3–5 injections, lightly cross-linked intra-articular hyaluronic acid (Monovisc™) is a single-injection device formulated to deliver the same HA dose (88 mg) as 3 injections of Orthovisc™, a US-approved, multi-injection viscosupplement. Lightly cross-linked intra-articular hyaluronic acid (Monovisc™) is composed of cross-linked sodium hyaluronate that is made from ultra-pure, natural hyaluronan. Cross-linking increases the time the substance stays in the joint synovial fluid, potentially increasing the efficacy and the duration of the treatment effect [3, 20]. Monovisc™ is the first single-injection treatment in the US market formulated from an animal-free HA source. A single-injection treatment is more convenient for patients and decreases the risk of noncompliance associated with other devices (e.g. patients not returning to complete the injection series) [20].

The purpose of this clinical trial was to demonstrate the safety and effectiveness of Monovisc™ in the relief of joint pain in patients with idiopathic knee OA. It was hypothesized that patient success, defined as $\geq 50\%$ improvement from baseline and ≥ 20 mm absolute improvement from baseline in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) visual analog scale (VAS) pain score, would be greater in the Monovisc™ group compared to the Saline control group.

Materials and methods

This study was a multicenter, double-blinded, randomized clinical trial examining the safety and effectiveness of Monovisc™, a single intra-articular HA injection for the treatment of idiopathic, symptomatic knee OA. The study was conducted at 31 sites across the US between January 2008 and December 2009. All subjects provided written informed consent prior to enrollment. The study was approved by the Food and Drug Administration (FDA) under IDE G070196 and a Central Institutional Review Board (IRB). The study was conducted in accordance with Good Clinical Practice (GCP) principles, as required by the International Conference on Harmonization (ICH) and the Declaration of Helsinki. The study was registered with Clinicaltrials.gov, a National Institute of Health trial registry, under identification number NCT00653432.

Patient selection

Eligible participants were between 35 and 75 years old, had a body mass index (BMI) between 20 and 40 kg/m^2, and had a diagnosis of idiopathic knee OA as defined by the American College of Rheumatology [2]. Additional inclusion criteria were symptom duration of at least 6 months, confirmed radiographic evidence of OA within 6 months of study enrollment, KellgrenLawrence (K–L) grade II or III OA in the index knee [19], and a baseline summed WOMAC VAS pain score greater than 200 mm and less than 400 mm out of a maximum 500 mm scoring system.

Exclusion criteria included intra-articular crystals, neoplasms, rheumatoid arthritis, fibromyalgia, peripheral neuropathy, vascular insufficiency, immunocompromised or immunosuppressive disorder, systemic bleeding disorder, symptomatic pes anserine bursitis, clinically significant knee

deformity that could interfere with the ability to evaluate the effectiveness of the treatment on pain and function, intra-articular HA injection in the index knee within 6 months, intra-articular steroid injection or knee arthroscopy in the index knee within 3 months, open surgical procedure in the index knee within 12 months, synovial fluid aspirate greater than 20 ml, and range of motion less than 90° in the index knee. Patients with K–L grade III or IV OA in the contralateral knee, a baseline summed WOMAC VAS pain score greater than 150 mm in the contralateral knee, and patients who underwent an open surgical procedure within 3 months in the contralateral knee were excluded.

Treatment

Eligible participants were randomized to either the lightly cross-linked, single-injection intra-articular hyaluronic acid (Monovisc™) group or the Saline control group approximately 1 week after the screening visit and following a 7-day analgesic/NSAID washout period. The Monovisc™ group received a 4 ml dose of Monovisc™, and the Saline control group received 4 ml of 0.9% saline. All intra-articular injections were administered with a 5 ml syringe using either a medial or lateral approach. Prior to the administration of the injection, an 18–21 gauge needle was used to aspirate the knee if effusion was present. The blinded injector inspected the synovial fluid prior to the injection for visual signs of infection, crystals, or any other contraindications to proceed. Regardless of fluid appearance, the aspirated synovial fluid was sent to the lab for microscopic evaluation to rule out inflammatory or crystalline arthropathies.

Oral glucosamine and chondroitin sulphate were permitted if subjects maintained a constant dosage throughout the duration of the study. Daily acetaminophen consumption of up to 4 g (8–500 mg tablets) was permitted as rescue medication starting 7 days prior to the randomization visit. Subjects were not allowed to take acetaminophen 24 h prior to each follow-up appointment.

Randomization

A third party vendor generated and maintained the 1:1 randomization schedule and supplied the sites with the blinded study treatment devices. A "blinded evaluator" at each site conducted all study pre- and post-injection evaluations and was blinded to the study treatment group. The "treating physician" only performed the knee aspirations and was responsible for administering the study treatment to the subjects. The "treating physician" never evaluated the clinical status of the patient. Patients were blinded to the study treatment group throughout the duration of the study.

Outcomes

Subjects were evaluated at the following intervals: 2 weeks ± 2 days, 4 weeks ± 3 days, 8 weeks ± 6 days, 12 weeks ± 9 days, 20 weeks ± 14 days, and 26 weeks ± 14 days. WOMAC VAS pain subscore was used as the primary outcome measure. The primary effectiveness endpoint was ≥ 50% improvement from baseline and ≥ 20 mm absolute improvement from baseline in the WOMAC VAS pain score through week 26 as defined by OMERACT-OARSI [31]. Secondary outcome measures included the percentage of patients that demonstrated a ≥ 20 mm improvement from baseline on the WOMAC physical function subscore, patient global assessment VAS, evaluator global assessment VAS, and knee flexion and extension range of motion. The WOMAC is a reliable and validated, disease-specific questionnaire that quantifies pain, stiffness and physical function in patients with knee OA [7, 23]. The WOMAC includes 5 items that measure pain, 2 items that measure stiffness and 17 items that measure physical function on a VAS ranging from 0 to 100 mm with higher scores representing worse status. The patient global and evaluator global assessments were graded on a similar VAS scale ranging from 0 to 100 mm.

Safety was assessed at each study interval by the "blinded evaluator". Adverse events included any illness, sign, symptom, or clinically significant laboratory abnormality that worsened during the clinical trial regardless of the relationship to the study device, as defined by the Medical Dictionary for Regulatory Activities (MedDRA version 8.0 or higher). The severity and causality of adverse events were determined by the blinded evaluator. The index knee was also assessed for pain, redness, and swelling at each interval and coded as an adverse event if the severity was greater than the baseline evaluation.

Statistical analysis

Sample size calculations

A priori sample size calculations were conducted to determine the size of the study population using the following assumptions: (1) 2-sided Fisher exact test, (2) significance level of 0.05, (3) 1:1 randomization allocation, (4) 90% power, (5) 5% dropout rate, (6) 40% improvement in baseline WOMAC VAS pain subscore, and (7) a ≥ 15 mm improvement from baseline in the WOMAC VAS pain subscore. Based on these criteria, a total of 350 patients were required for the primary and secondary effectiveness endpoint analyses.

Effectiveness analysis

Effectiveness was assessed using the intent-to-treat (ITT) and per protocol (PP) analyses. The ITT population included all randomized patients that received the study treatment injection and had at least one post-injection visit. The PP population included all randomized patients that received the study treatment injection, had at least one post-injection visit, and experienced no other major protocol deviations.

Patients were classified into a responder category (yes/no) based on the achievement of the patient success criteria (e.g. $\geq 50\%$ improvement from baseline and ≥ 20 mm absolute improvement from baseline in the WOMAC VAS pain score). Primary and secondary outcome measures were analyzed using generalized estimating equations (GEE) for proportional odds logistic regression. The GEE model was fit to the observed data using baseline measure, site, visit, treatment group, and visit-by-treatment group interaction with covariates of contralateral knee pain, K–L grade, age, and site. Assuming the primary endpoint met significance, secondary effectiveness endpoints were to be assessed in a predefined sequential order until statistical significance was no longer achieved.

Safety analysis

The safety analysis was conducted using all randomized patients that received the study treatment injection. Patient-level incidence of adverse events was analyzed using a 2-sided Fisher exact test, and event-level incidence of adverse events was analyzed using a Wilcoxon rank sum test.

Non-inferiority analysis

To determine the non-inferiority and/or superiority of Monovisc™ to Orthovisc™, the Monovisc™ group was compared to previously published, comparable studies of patients receiving Orthovisc™ [8, 28]. Brandt et al. compared 3 injections of Orthovisc™ (O3) to a Saline control group (S3). Neustadt et al. compared 4 injections of Orthovisc™ (O4) to 3 injections of Monovisc™ followed by 1 arthrocentesis (O3A1) and 4 arthrocenteses (A4). The proportion of responders with 20, 40 and 50% improvements from baseline WOMAC VAS pain score were the primary endpoints in the GEE model for both the ITT and PP populations. Additionally, change from baseline on WOMAC VAS total score (mm), pain on standing (mm), investigator global score (mm), and patient global score (mm) were used as secondary endpoints. Conservative, non-inferiority margins were derived from established minimum clinically important differences (MCID) for the primary and secondary endpoints. The MCID for changes in baseline pain scores have been reported between 12 and 20% [4, 35, 39]. A conservative non-inferiority margin of 5% was chosen for the primary endpoint of change in WOMAC VAS pain score. Similarly for the secondary endpoints, a conservative non-inferiority margin of 5 mm was chosen based on previously accepted margins of 8–11 mm on a 100 mm scale [17, 39]. Mean differences and confidence intervals were calculated between the Monovisc™ group and each Orthovisc™ treatment group. Non-inferiority of Monovisc™ was achieved if the lower bound confidence interval was greater than -5. If the lower bound confidence interval was above 0, Monovisc™ was considered to be non-inferior and superior to Orthovisc™.

Results

Patient population

Seven hundred and eighty-three patients were screened with 369 patients meeting eligibility criteria (47%) (154 male, 215 female) and randomized (184 in the Monovisc™ group, 185 patients in the Saline group). Three hundred and sixty-five patients were included in the ITT population: 181 patients in the Monovisc™ group and 184 patients in the Saline group (Fig. 1). Three hundred and thirty-four patients were included in the PP population: 164 patients in the Monovisc™ group and 170 patients in the Saline group. Patient demographics and baseline characteristics are presented in Table 1. There were no significant differences between the Monovisc™ group and the Saline group on any of these baseline measures or patient demographics (n.s.). A total of 331 patients (90%) completed the study.

Effectiveness measures

The Monovisc™ group demonstrated a significant improvement from baseline WOMAC VAS pain score at all follow-up intervals ($p < 0.001$). Patient success was significantly higher in the Monovisc™ group compared to the Saline group in the ITT population ($p = 0.043$) and the PP population ($p = 0.038$) (Table 2). Pain reduction of at least 50% and ≥ 20 mm absolute improvement from baseline in the WOMAC VAS pain score was achieved by 44.4% of patients in the Monovisc™ group at the first post-injection follow-up 2 weeks after the injection compared to only 34.1% in the Saline group. More than 55% of patients in the Monovisc™ group demonstrated continued pain relief above the 50% threshold at all subsequent follow-up visits past 8 weeks. For all secondary effectiveness variables, the Monovisc group demonstrated significant improvements over baseline values (Table 3).

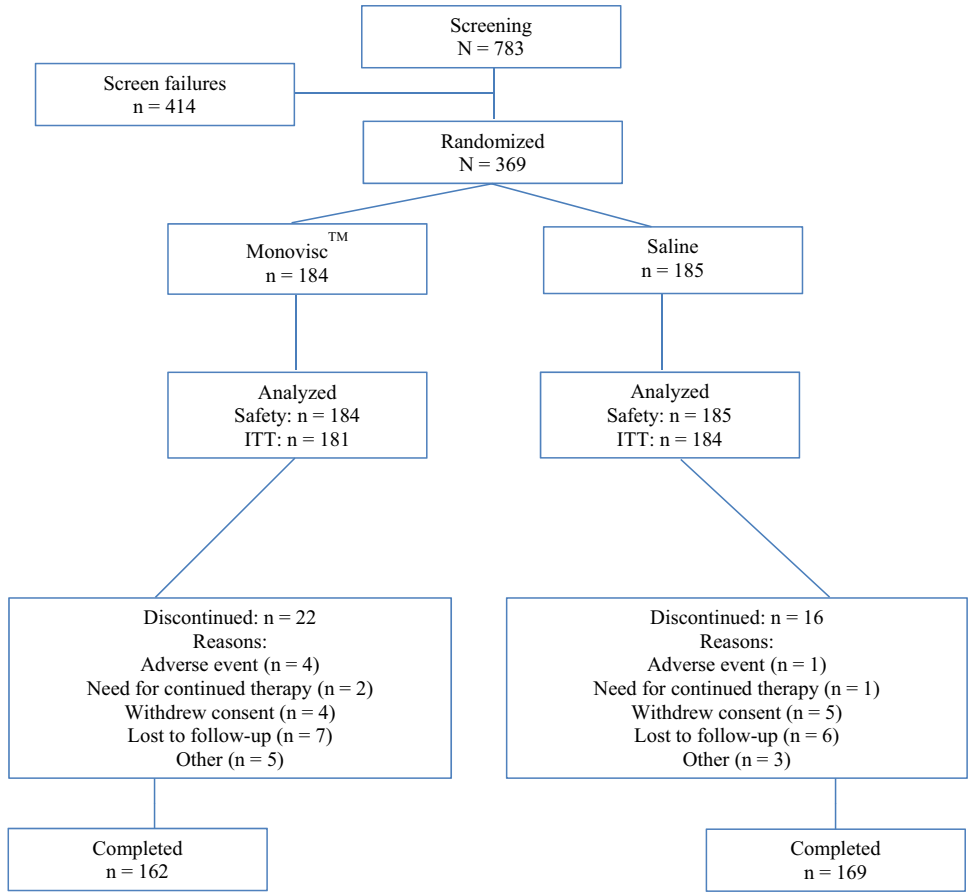

Fig. 1 Consolidated standards of reporting trials flow diagram. *ITT* intent-to-treat

Table 1 Patient demographics and baseline characteristics by treatment group

Characteristic	Monovisc™ group	Saline group
Gender, male/female (*n*)	75/109	79/106
Age, mean ± SD years	59.5 ± 8.0	58.7 ± 9.2
Body mass index (mean ± SD kg/m^2)	29.9 ± 4.3	30.4 ± 4.6
Index knee, right/left, (*n*)	104/80	92/93
K–L grade, grade II/grade III (*n*)	105/79	97/88
Baseline WOMAC pain (mean ± SD)	58.8 ± 12.0	58.5 ± 12.0
Baseline WOMAC physical function (mean ± SD)	55.7 ± 15.9	54.1 ± 17.3
Baseline evaluator global assessment (mean ± SD)	59.1 ± 15.5	58.9 ± 14.6
Baseline patient global assessment (mean ± SD)	63.1 ± 17.5	61.7 ± 16.7
Total knee range of motion, degrees (mean ± SD)	116 ± 16	115 ± 16

There were no significant differences in patient demographics or baseline measures between treatment groups, ns

SD standard deviation, *K–L* Kellgren–Lawrence, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index.

Safety measures

Adverse events are reported in Table 4. The incidence of serious adverse events was less than 5% in both the Monovisc™ and Saline groups. No serious adverse events were related to the study device. The most common device- or procedure-related adverse events were arthralgia (n.s.) and joint swelling (n.s.) which did not differ significantly between groups.

Table 2 Primary outcome measure of patient success defined as 50% Improvement from baseline and ≥ 20 mm absolute improvement from baseline on WOMAC pain score

	Patient success (% Patients)		
	Monovisc™ group	Saline group	*p* value
Week 2	44.38	34.12	< 0.001*
Week 4	49.11	45.29	0.003*
Week 8	55.03	50.00	0.090
Week 12	52.53	52.63	0.333
Week 20	54.27	55.36	0.835
Overall	51.14	48.97	0.043*

*Denotes significance of $p < 0.05$

Non-inferiority to Orthovisc™

Patient demographic data were similar between the Monovisc™ group and the Orthovisc groups™ (Table 5). For the primary endpoint of the proportion of responders reporting 20, 40 and 50% improvement from baseline WOMAC VAS pain score, Monovisc™ was non-inferior to Orthovisc™ (O3A1) in both the ITT and PP populations with the exception of the Orthovisc™ group (O3) in the Brandt et al. study (Table 6). The reason for not achieving non-inferiority against this population was likely due to the small sample size of the Orthovisc™ (O3) group. Monovisc™ was also shown to be non-inferior and superior to both the Arthrocentesis control group (A4) and the Saline control group (S3). In the secondary analysis, Monovisc™ was non-inferior or non-inferior and superior to 3 injections of Orthovisc™ (O3 and O3A1), the Arthrocentesis control group (A4), and the Saline control group (S3) on change in WOMAC VAS pain, change in pain on standing, change in investigator global score, and change in patient global score with the exception of pain on standing compared to 3 injections of Orthovisc™ followed by arthrocentesis (O3A1) (Table 6).

Discussion

The clinical significance of this level 1 study is that a single-injection intra-articular HA device is a safe and effective treatment for symptomatic knee OA eliciting a clinically meaningful reduction in knee pain within 2 weeks of the injection, with subsequent pain relief persisting for at least 6 months. The majority of patients receiving Monovisc™ demonstrated a > 50% reduction in WOMAC pain and > 20 mm reduction in WOMAC VAS pain subscore as well as improvements in WOMAC function, patient global and physician global assessment, and knee range of motion (ROM). Patients receiving a single injection of Monovisc™

Table 3 Secondary endpoint measures from the intention to treat analysis

	WOMAC physical function			Patient global assessment VAS			Evaluator global assessment VAS			Knee range of motion		
	Monovisc™ group	Saline group	*p* value	Monovisc™ group	Saline group	*p* value	Monovisc™ group	Saline group	*p* value	Monovisc™ group	Saline group	*p* value
Week 0	55.8 ± 15.9	54.1 ± 17.3	n.s	62.9 ± 17.5	61.6 ± 16.7	n.s	59.1 ± 15.5	58.9 ± 14.6	n.s	116.3 ± 16.4	114.5 ± 16.0	n.s
Week 2	35.9 ± 24.3	37.2 ± 22.7	n.s	40.3 ± 26.4	39.8 ± 23.4	n.s	36.8 ± 21.6	37.5 ± 20.9	n.s	118.0 ± 13.5	117.4 ± 15.2	n.s
Week 4	34.7 ± 24.4	36.3 ± 24.9	n.s	36.1 ± 25.9	38.1 ± 26.8	n.s	34.0 ± 21.9	35.1 ± 23.2	n.s	119.0 ± 16.2	117.8 ± 13.1	n.s
Week 8	33.1 ± 25.5	31.9 ± 24.1	n.s	33.4 ± 26.3	34.6 ± 26.2	n.s	30.2 ± 21.6	32.8 ± 22.5	n.s	117.3 ± 14.7	118.7 ± 14.5	n.s
Week 12	24.7 ± 26.2	31.7 ± 25.3	n.s	33.7 ± 27.5	33.2 ± 26.9	n.s	30.4 ± 23.5	32.1 ± 23.2	n.s	117.8 ± 14.4	119.3 ± 15.2	n.s
Week 20	30.3 ± 25.5	22.7 ± 26.0	n.s	31.1 ± 26.2	32.4 ± 27.1	n.s	28.2 ± 21.38	30.6 ± 22.7	n.s	118.4 ± 14.7	118.3 ± 14.7	n.s
Week 26	32.5 ± 24.8	33.1 ± 25.2	n.s	33.7 ± 26.0	33.4 ± 26.2	n.s	31.9 ± 22.0	30.9 ± 22.9	n.s	117.2 ± 13.9	118.8 ± 14.2	n.s

Table 4 Safety measures

Safety measure	Monovisc™ group		Saline group	
	Patients *n* (%)	Events *n*	Patients *n* (%)	Events *n*
Total adverse events	121 (65.8%)	388	123 (66.5%)	398
Total serious adverse events	8 (4.3%)	9	5 (2.7%)	5
Unexpected adverse device effects	0 (0.0%)	0	0 (0.0%)	0
Device-related adverse events	13 (7.1%)	24	10 (5.4%)	14
Related adverse events occurring in ≥ 1.0%				
Arthralgia	7 (3.8%)	11	7 (3.8%)	8
Joint swelling	2 (1.1%)	2	1 (0.5%)	2
Joint stiffness	1 (0.5%)	1	2 (1.1%)	2

There were no significant differences in incidence of adverse events between treatment groups

Table 5 Patient demographics and baseline data for the non-inferiority analysis

Variable	03 *N* = 83 *N* (%) Mean ± SD	Saline (9501) *N* = 81 *N* (%) Mean ± SD	04 *N* = 104 *N* (%) Mean ± SD	03Al *N* = 90 *N* (%) Mean ± SD	A4 *N* = I00 *N* (%) Mean ± SD	M1 (ITT) *N* = 181 *N* (%) Mean ± SD	Saline (0702 ITT) *N* = 184 *N* (%) Mean ± SD
Gender (% male)	32 (38.6)	32 (39.5)	58 (55.8)	45 (50.0)	50 (50.0)	74 (40.9)	78 (42.4)
Age (years)	64.6 ± 8.2	67.7 ± 8.5	58.6 ± 8.9	59.2 ± 8.6	59.0 ± 8.1	59.7 ± 7.9	58.7 ± 9.2
BMI (kg/m^2)	32.0 ± 6.5	29.7 ± 6.2	29.0 ± 4.2	29.9 ± 4.3	29.6 ± 3.9	29.8 ± 4.7	30.4 ± 4.6
Radiographic evaluation							
K–L grade II	37 (44.6)	32 (39.5)	56 (53.8)	58 (64.4)	53 (53.0)	103 (56.9)	97 (52.7)
K–L grade III	46 (55.4)	49 (60.5)	48 (46.2)	32 (35.6)	47 (47.0)	78 (43.1)	87 (47.3)
WOMAC pain score—index knee (mm)	274.1 ± 64.9	268.2 ± 69.3	288.2 ± 59.8	289.7 ± 49.5	293.4 ± 58.7	294.0 ± 60.0	291.6 ± 60.7
WOMAC pain score—contralateral knee (mm)	83.1 ± 57.0	87.0 ± 54.2	68.7 ± 47.1	69.7 ± 47.0	67.8 ± 48.3	59.5 ± 48.0	65.5 ± 48.4
Pain on standing score (mm)	51.2 ± 24.7	46.9 ± 23.2	64.8 ± 18.4	65.4 ± 16.9	65.9 ± 15.8	59.4 ± 17.6	58.6 ± 17.5
Investigator global score (mm)	53.3 ± 19.0	50.6 ± 19.4	58.8 ± 14.3	58.2 ± 14.3	57.8 ± 14.7	59.1 ± 15.5	58.9 ± 14.6
Patient global score (mm)	55.7 ± 20.4	53.4 ± 21.6	67.3 ± 14.9	62.4 ± 16.5	64.3 ± 14.9	62.9 ± 17.5	61.6 ± 16.7

O3—Patients receiving 3 injections of Orthovisc™ in the study by Brandt et al., Saline (9501)—Patients receiving 3 injections of Saline in the study by Brandt et al., O4—Patients receiving 4 injections of Orthovisc™ in the study by Neustadt et al., O3A1—Patients receiving 3 injections of Monovisc™ followed by 1 arthrocentesis in the study by Neustadt et al., A4—Patients undergoing 4 arthrocenteses in the study by Neustadt et al., M1—Patients receiving 1 injection of Monovisc in the present study from the Intention to Treat (ITT) arm, Saline (0702)—Patients in the Saline control group in the present study

also performed similar to or better than patients receiving 3 injections of Orthovisc™, further supporting its efficacy in patients with KL grade II or III knee OA.

Clinical practice guidelines on the use of HA for knee OA are conflicting with AAOS guidelines reporting strong evidence against the use of intra-articular HA, American College of Rheumatology (ACR) guidelines indicating they cannot recommend the use of intra-articular HA except in select cases, and Osteoarthritis Research Society International (OARSI) guidelines indicating there is uncertain evidence for the use of intra-articular HA in knee OA [9, 18, 22]. Clinical practice guidelines have been called into question due to methodological flaws [5]. For example, the AAOS guidelines, while demonstrating significant treatment effects of HA, used only a small subset of studies in their meta-analysis and solely used minimally clinical important improvement of primary outcome measures to derive their recommendations of which the inherent limitations of this method have previously been discussed [5].

Recent meta-analyses, however, have demonstrated the positive benefit of intra-articular HA. Strand et al conducted a systematic review and meta-analysis of 29 randomized, saline-controlled trials of US-approved HA products including 4866 unique patients [38]. They demonstrated a large treatment effect of HA in reducing pain and improving function from post-injection week 4 through week 26. Another systematic review of meta-analyses by Cambell et al. found that 5 of 10 meta-analyses demonstrated the benefit of HA in improving pain and 4 of 10 meta-analyses demonstrated the benefit of HA in improving function through 26 weeks, suggesting intra-articular HA has a viable treatment option for knee OA using the best available evidence [10].

Table 6 Non-inferiority analysis of primary and secondary endpoints using GEE Model

Variable	M1 PP*N* = 164%, CI	M1 ITT *N* = 181%, CI	O3A1 *N* = 90%, CI	O3 *N* = 83%, CI	O3A1/O3 *N* = 17%, CI	O4 *N* = 104%, CI	A4 *N* = 100%, CI	Saline *N* = 81%, CI
20% Improvement in WOMAC	74.2 (67.7, 80.7)	72.4 (65.8,79.1)	63.0[a] (52.8, 73.2)	70.8 (60.8, 80.8)	67.0[a] (52.8, 81.3)	73.1 (64.4, 81.8)	62.9[b] (53.7, 72.2)	60.2[b] (49.3, 71.1)
40% Improvement in WOMAC	61.8 (54.5, 69.0)	58.9 (51.6, 66.2)	50.2[a] (39.6, 60.7)	54.5 (43.5, 65.4)	52.5[a] (37.3, 67.7)	63.4 (54.0, 72.9)	48.0[a] (38.4, 57.6)	41.0[b] (30.1, 52.0)
50% Improvement in WOMAC	53.6 (46.2, 61.0)	51.2 (43.8, 58.6)	43.3[a] (32.9, 53.8)	46.3 (35.4, 57.3)	45.0[a] (29.9, 60.1)	55.6 (45.9, 65.4)	42.6[b] (33.2, 52.1)	34.4[b] (23.8, 44.9)
Change WOMAC Pain Score from Baseline to Week 7/8	− 26.9 (24.3)	− 25.8 (24.6)	− 22.3[a] (21.9)	− 22.9[a] (22.8)	− 22.6[a] (23.0)	− 30.7 (22.0)	− 23.8[a] (23.9)	− 18.2[b] (20.7)
Change WOMAC Pain Score from Baseline to Week 11/12	− 27.2 (25.0)	− 26.5 (25.1)	− 23.4[a] (20.8)	− 23.2[a] (23.0)	− 23.3[a] (22.7)	− 30.3 (23.7)	− 24.3[a] (23.7)	− 17.7[b] (19.9)
Change WOMAC Pain Score from Baseline to Week 20–22	− 27.5 (24.8)	− 26.9 (24.9)	− 21.0 (22.3)	− 21.2[a] (23.8)	− 21.1[a] (23.6)	− 25.8 (24.6)	− 21.4[a] (22.8)	− 17.8[b] (19.2)
Change Pain on Standing from Baseline to Week 7/8	− 27.0 (28.3)	− 26.2 (27.9)	− 19.6(29.5)	− 28.7[a] (28.8)	− 26.0[a] (29.2)	− 34.6 (28.2)	− 27.8[a] (29.7)	− 14.8[b] (26.2)
Change Pain on Standing from Baseline to Week 11/12	− 28.3 (28.4)	− 27.8 (27.9)	− 22.3 (30.2)	− 25.0[a] (29.1)	− 24.8[a] (29.2)	− 34.9 (30.0)	− 26.2[a] (27.9)	− 12.3[b] (29.1)
Change Pain on Standing from Baseline to Week 20–22	− 28.7 (27.7)	− 28.1 (27.2)	− 21.4 (30.5)	− 25.5[a] (30.2)	− 24.5[a] (30.2)	− 29.5 (31.4)	− 24.6[a] (27.9)	− 13.3[b] (27.1)
Change Investigator Global Score from Baseline to Week 7/8	− 29.1 (25.4)	− 28.4 (24.9)	− 17.2[b] (21.4)	− 24.1[b] (24.5)	− 21.2[b] (24.1)	− 28.3[a] (22.5)	− 20.6[b] (20.7)	− 12.7[b] (23.1)
Change Investigator Global Score from Baseline to Week 11/12	− 28.3 (27.4)	− 27.4 (27.1)	− 21.1[b] (27.2)	− 22.7[b] (24.6)	− 22.2[b] (25.1)	− 29.3[a] (23.9)	− 19.2[b] (20.4)	− 11.7[b] (26.5)

Table 6 (continued)

Variable	M1 PP*N* = 164%, CI	M1 ITT *N* = 181%, CI	O3A1 *N* = 90%, CI	O3 *N* = 83%, CI	O3A1/O3 *N* = 17%, CI	O4 *N* = 104%, CI	A4 *N* = 100%, CI	Saline *N* = 81%, CI
Change Investigator Global Score from Baseline to Week 20–22	− 29.7 (26.0)	− 28.8 (26.0)	− 16.3[b] (26.9)	− 19.7[b] (27.2)	− 18.1[b] (26.7)	− 22.0[a] (24.7)	− 15.4[b] (21.7)	− 9.6[b] (22.9)
Change Patient Global Score from Baseline to Week 7/8	− 30.7 (28.4)	− 29.5 (27.8)	− 18.7[a] (24.0)	− 29.6[b] (30.9)	− 26.2[b] (29.3)	− 38.4 (27.6)	− 27.2[a] (25.8)	− 13.3[b] (25.9)
Change Patient Global Score from Baseline to Week 11/12	− 29.0 (31.2)	− 28.1 (30.7)	− 22.6[a] (27.5)	− 26.5[b] (30.9)	− 26.0[b] (29.7)	− 38.8 (28.4)	− 26.3[a] (26.1)	− 11.7[b] (28.8)
Change Patient Global Score from Baseline to Week 20–22	− 30.6 (29.0)	− 29.5 (28.8)	− 17.8[a] (28.6)	− 25.5[b] (30.8)	− 23.4[b] (30.2)	− 33.3 (28.6)	− 25.4[a] (27.3)	− 9.9[b] (24.6)

M1 PP—Patients receiving 1 injection of Monovisc in the present study from the Per Protcol (PP) arm, M1 ITT—Patients receiving 1 injection of Monovisc in the present study from the Intention to Treat (ITT) arm, O3A1—Patients receiving 3 injections of Monovisc™ followed by 1 arthrocentesis in the study by Neustadt et al., O3—Patients receiving 3 injections of Orthovisc™ in the study by Brandt et al., O3A1/O3—Combination of patients receiving 3 injections of Monovisc™ followed by 1 arthrocentesis (Neustadt et al.) and patients receiving 3 injections of Orthovisc™ (Brandt et al.), O4—Patients receiving 4 injections of Orthovisc™ in the study by Neustadt et al., A4—Patients undergoing 4 arthrocenteses in the study by Neustadt et al., Saline (9501)—Patients receiving 3 injections of Saline in the study by Brandt et al.

[a]Denotes Monovisc is Non-inferior

[b]Denotes Monovisc is Non-inferior and Superior

Additionally, results of the present study are comparable to two other studies of different single-injection HA viscosupplementation products. In our study ITT population, greater than 63% of all Monovisc™ patients were OMERACT-OARSI responders at each time point (63.0–71.8%). Strand et al reported results of Gel-One®, a cross-linked HA derived from rooster combs (Siekagaku Corporation, Tokyo, Japan), and found that 61.0% of their cohort were responders at a 13-week follow-up [37]. Nearly 10% more of our Monovisc™ cohort were responders at 12 weeks, suggesting a stronger treatment response for Monovisc™ compared to Gel-One®. Similarly, Monovisc™ (68.5%) had a higher percentage of OMERACT-OARSI responders compared to Synvisc-One® (58.9%), a cross-linked HA derived from rooster combs (Genzyme Corporation, Ridgefield, NJ, USA), at 26 weeks [12]. Moreover, the magnitude of reduction in pain scores from baseline was greatest in patients receiving Monovisc™ (36%) compared to the other single-injection HA products including Gel-One® and Synvisc-One® [12, 37]. This reduction in pain was maintained for at least 26 weeks in patients receiving Monovisc™.

The strong clinical and symptomatic improvement of the saline control group is not novel. Saline injections can alter the intra-articular environment and reduce joint pain by providing joint lavage and cleaning joint debris, which may explain the large placebo response by our control group [15, 34]. Others have also postulated the mechanism of action to be through a dilution of local inflammatory mediators yielding symptomatic improvement [36]. The strong response of the saline group is similar to other published viscosupplementation studies for knee OA [42], with OMERACT-OARSI responder rates for saline controls exceeding 50% [12, 37]. Zhang et al (2008) investigated the clinical effects of placebo in OA and concluded that placebo is effective in the treatment of OA particularly for pain, stiffness, and self-reported function [42]. The strength of the placebo effect was influenced by the strength of the active treatment, symptom severity, route of

delivery, and sample size and was the strongest for subjective outcome measures. Additionally, placebo had effect sizes > 0.51 in other intra-articular hyaluronan studies.

The management of knee OA should be a multi-faceted approach. Previous research has demonstrated the positive benefit of weight loss, exercise, and physical therapy on strength, ROM, and function in this population [13]. Pain may preclude participation or decrease the effectiveness of these adjunct therapeutic interventions. Patients in the present study demonstrated substantial improvement in the initial 2–4 weeks after the injection that persisted throughout the remainder of the 26-week study. It is important to take advantage of the resultant decrease in pain from intra-articular HA injections to decrease or reverse impairments in strength and function, to enhance quality of life [30].

The safety of Monovisc™ was equivalent to that of the Saline control. The most common device- or treatment-related adverse events were arthralgia and joint swelling. There were no incidences of pseudosepsis, an adverse event associated with another chemically-modified cross-linked HA viscosupplement, Hylan G-F20 [16, 32, 33].

Conclusions

Monovisc™ is a safe and effective treatment for reducing knee pain in patients with moderate idiopathic knee OA. Significant improvements in knee pain can be expected within 2 weeks of the injection, with effects lasting for at least 6 months. Monovisc™ offers the advantage of treatment with a single injection, which can improve patient compliance and offers convenience to both patients and physicians, and provides patients with a minimally invasive alternative to treat the symptoms of knee OA.

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Compliance with ethical standards

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