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Osteoarthritis and Cartilage



A multicenter, randomized controlled trial comparing a single intra-articular injection of Gel-200, a new cross-linked formulation of hyaluronic acid, to phosphate buffered saline for treatment of osteoarthritis of the knee

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SUMMARY

Objective: To compare the safety and efficacy of a single intra-articular (IA) injection of a new cross-linked hyaluronic acid product, Gel-200, with phosphate buffered saline (PBS, control) in a multi-center randomized controlled trial in patients with symptomatic osteoarthritis (OA) of the knee.

Design: Patients were randomized 2:1 to receive a single injection of Gel-200 or PBS, after joint aspiration. The primary measure of effectiveness was Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscores by 100-mm Visual Analog Scale (VAS); secondary outcomes included: total WOMAC, physical function, and stiffness subscores; patient and physician global assessments of disease activity, Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International (OMERACT–OARSI) strict responders, as well as safety of Gel-200.

Results: Of 379 patients randomized, safety was evaluated in 377 and efficacy in 375 (98.9% randomized) in the intent-to-treat population. Effectiveness of Gel-200 by WOMAC pain subscores was statistically significant at week 13 ($P = 0.037$). Mean improvements from baseline in WOMAC pain subscores consistently favored Gel-200 at each visit. Effectiveness of Gel-200 treatment was statistically significant over weeks 3–13 by WOMAC total score, physical function, and physician global evaluations ($P < 0.05$). The number of “strict” OMERACT–OARSI responders was statistically significant from weeks 6 to 13 ($P = 0.022$). Adverse events were not significantly different between treatment groups, including serious adverse events considered related to study treatment.

Conclusions: This trial demonstrated that a single injection of Gel-200 was well tolerated and relieved pain associated with symptomatic OA of the knee over 13 weeks.

Trial registration number: ClinicalTrials.gov NTC 00449696.

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Introduction

Osteoarthritis (OA) is the most common arthritic condition and among the more frequent and symptomatic health problems for individuals ≥ 50 years of age¹. Symptomatic OA of the knee is a common presenting problem and its treatment can be frustrating for patients and physicians². Intra-articular hyaluronic acid (IA-HA) injections of the knee have been demonstrated to reduce pain in subjects with OA^{3,4}. Treatment guidelines for OA recommend IA-HA

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as useful therapeutic agents. However, a meta-analysis reported no evidence of improvement in function or clinically meaningful improvements in pain in placebo-controlled studies⁵. Five IA-HA products are currently available for use in the United States, requiring a series of 3–5 injections, as well as a recently approved larger volume single injection product^{6,7}. Newer cross-linked IA-HA formulations have been designed to offer longer term benefit following a single injection. Such a single injection product would be more convenient for patients and expected to be less invasive thus reducing the potential risk of joint infections or hypersensitivity reactions.

Gel-200 is a sterile, transparent, viscoelastic hydrogel composed of cross-linked hyaluronate⁸, a derivative of a highly purified

sodium hyaluronate product extracted from chicken combs. Non-cross-linked HA diffuses out of the synovial fluid rapidly after administration into the knee joint, while injected Gel-200 was found to persist in synovial fluid for up to 7 days and synovium for as long as 28 days in rabbits without IA inflammation⁹. The effects of a single injection of Gel-200 have been compared with phosphate buffered saline (PBS) in an established experimental animal model of OA: unilateral transection of the anterior cruciate ligament (ACL) in rabbits^{10–14}. In comparison with PBS, a single injection of Gel-200 significantly decreased articular cartilage degeneration at 9 weeks after ACL transection and was more effective than five injections of non-cross-linked HA in the rabbit model. In rats with arthritis pain induced by bradykinin and silver nitrate, pain scores with Gel-200 administration were lower than those administered PBS or non-cross-linked HA^{5,9,15}. Additionally, Gel-200 exhibited a longer analgesic effect compared with PBS in a monosodium urate induced joint inflammation model in dogs¹⁶. Based on these observations in pre-clinical animal studies, it was expected that a single injection of Gel-200 would provide more prolonged benefit than multiple injection IA-HA products. This report summarizes the results from a randomized controlled trial (RCT) comparing the safety and effectiveness of a single injection of Gel-200 vs PBS (control) in subjects with symptomatic OA of the knee over 13 weeks.

Methods

Study design

This was a double-blind, multi-center RCT examining the safety and effectiveness of a single injection of Gel-200, a new cross-linked IA-HA product (Gel-One[®], Seikagaku Corporation, Tokyo,

Japan) vs PBS (control) for treatment of symptomatic OA of the knee. It was conducted from August 2006 to December 2007 (last patient visit) at 28 sites in the US in accordance with good clinical practices by International Conference on Harmonization guidelines and in conformity with the Declaration of Helsinki. A central Institutional Review Board (IRB) granted approval for the study and patients were provided a written informed consent form approved by the central IRB prior to enrollment. This study was registered with ClinicalTrials.gov (identification number: NCT 00449696).

A central randomization system was used to assign patients to receive an IA injection of either Gel-200 or PBS in a 2:1 ratio favoring Gel-200. An Interactive Voice Response System (IVRS) provided sequential treatment assignments. An unblinded “injecting physician” aspirated the knee if an effusion was present and then injected either treatment, packaged identically, taking appropriate measures to mask the treatment identity from the subject using a visual screening device. To maintain blinding of physician evaluations, a separate blinded “evaluating physician” performed all evaluations pre-injection and at all post-injection visits.

Treatment

Screening was performed 1–2 weeks prior to randomization. Following aspiration of synovial fluid if an effusion was present, patients received a single IA injection of Gel-200 (30 mg cross-linked HA in 3.0 mL) or PBS (3.0 mL) at week 0. Follow-up visits assessed safety and clinical benefit at weeks 1, 3, 6, 9 and 13 after injection. Acetaminophen up to 4,000 mg/day was provided as rescue medication except within 24 h of a treatment evaluation. Non-steroidal anti-inflammatory drugs (NSAIDs), nonprescription herbal therapies and chondroprotective agents (e.g., oral HA, glucosamine,

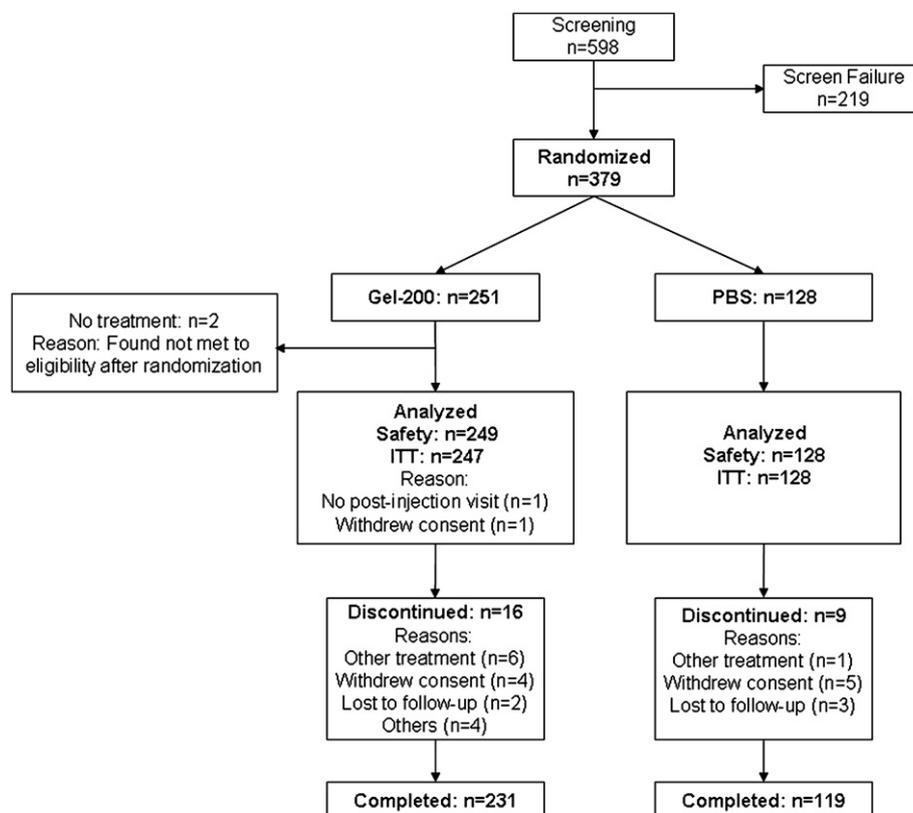


Fig. 1. Flow chart of patient disposition.

Table 1
Patient demographics and baseline disease characteristics

Parameter	Gel-200 (n = 247)	PBS (n = 128)
Gender		
Male	100 (40.5%)	51 (39.8%)
Female	147 (59.5%)	77 (60.2%)
Age, years (mean ± SD)	60.9 ± 10.24	60.3 ± 9.97
Body mass index, kg/m ² (mean ± SD)	28.3 ± 4.14	28.7 ± 3.83
Study knee		
Right	136 (55.1%)	62 (48.4%)
Left	111 (44.9%)	66 (51.6%)
K–L X-ray scores		
(Grade 1)	21 (8.5%)	18 (14.1%)
(Grade 2)	94 (38.1%)	47 (36.7%)
(Grade 3)	132 (53.4%)	63 (49.2%)
Duration of OA in study knee		
Months (mean ± SD)	42.0 ± 51.4	31.2 ± 41.2
WOMAC pain subscore	70.7 ± 14.42	68.0 ± 13.05
Total WOMAC score	69.5 ± 15.99	67.8 ± 14.68
WOMAC physical function subscore	68.9 ± 17.41	67.6 ± 15.80
WOMAC stiffness subscore	71.6 ± 17.48	69.3 ± 17.31

No statistically significant differences were identified between treatment groups.

chondroitin sulfate, minocycline) were allowed if patients did not change their treatment regimen and continued regular administration at stable doses from 4 weeks prior to randomization throughout protocol participation. Intermittent use of short-acting oral opiates was also allowed. Use of any medications for symptomatic pain relief was prohibited within 24 h prior to each visit evaluation. Physical therapy was prohibited throughout the study.

Protocol population

Patients were 40–80 years of age, with knee OA, and pain in the affected knee of ≥ 4 weeks in duration while standing or walking; Kellgren–Lawrence (K–L) grade 1–3 by X-ray; Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscores ≥ 40 mm in affected knee and ≤ 20 mm in contralateral knee by 100-mm Visual Analog Scale (VAS); and willing to discontinue current OA treatments other than allowed medications, stable for ≥ 4 weeks prior to entry. Patients were excluded from study participation for the following: K–L grade 4 of the treated knee, inflammatory diseases of the knee other than OA, severe knee joint effusion, severe malalignment of the knee, history of joint replacement of knee or hip within the previous 12 months,

arthroscopy of either knee within 3 months, IA injections with corticosteroids within the past 4 weeks, IA-HA injections within the past 6 months, and/or serious systemic diseases or infectious/inflammatory skin diseases in the area of the affected knee.

Outcome measures

The primary outcome measure of effectiveness was patient-reported WOMAC pain subscores by VAS in the affected knee at week 13. Secondary outcome measures included Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International (OMERACT–OARSI) “strict” responses^{17–19}; defined by improvements from baseline in WOMAC pain or physical function subscores $\geq 50\%$ with absolute changes ≥ 20 mm (termed “strict responders”) or $\geq 20\%$ with absolute changes ≥ 10 mm in two of three measures: WOMAC pain or physical function subscores; and/or patient global assessments of disease activity (termed “responders”). Mean changes from baseline in total WOMAC, physical function and stiffness subscores, patient and physician global assessments of disease activity by VAS, and acetaminophen consumption, were recorded at each visit. Medical Outcomes Survey Short-Form 36 (SF-36) for assessment of health related quality of life was collected at weeks 0 and 13. The percentage of patients reporting improvements meeting or exceeding minimum clinically important differences (MCID) e.g., ≥ 10 mm in WOMAC pain subscores, and/or “moderate” and “substantial” changes defined as $\geq 30\%$ and $\geq 50\%$, respectively, by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) working group were defined in an exploratory analysis^{20–23}. Times to response post injection (1–13 weeks) were also assessed. Safety evaluations included adverse events (AEs) coded by Medical Dictionary for Regulatory Activities (MedDRA Ver. 10.0) and examination of the affected knee for swelling, redness or effusion at each visit following injection. Hematology and serum chemistries were assessed at screening and week 13. Any adverse signs and symptoms or clinically significant laboratory abnormalities were collected as AEs during the study. Blinded investigators evaluated the severity of reported AEs and their potential relationship with treatment.

Statistical methods

Sample size calculations of 375 patients were determined based on the following assumptions: (1) two-sided *t*-test, (2) 90% power, (3) 5% significance level, (4) 2:1 randomization allocation in favor of Gel-200, (5) 10 mm detectable difference on a 100 mm VAS WOMAC pain subscore, (6) standard deviation (SD) of 25 mm for Gel-200 and 27 mm for PBS, and (7) an allowed 10% dropout rate per group.

Analyses of effectiveness were performed in the intent-to-treat (ITT) population, defined as all randomized patients

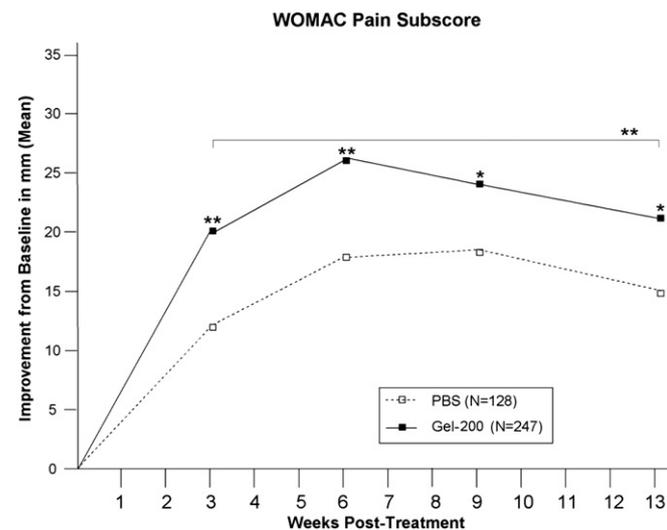


Fig. 2. Improvements from baseline in WOMAC pain subscores.

Table 1a
Mean improvements from baseline in WOMAC pain subscores; Gel-200 vs PBS

Week	Estimated difference [95% confidence interval (CI)]	P-value	Mean improvement from baseline
Week 3	8.12 (3.47, 12.78)	0.001	40.6%
Week 6	8.12 (2.73, 13.50)	0.003	44.1%
Week 9	5.77 (0.26, 11.29)	0.040	44.8%
Week 13	6.39 (0.37, 12.41)	0.037	39.3%
Weeks 3–13	7.10 (2.15, 12.05)	0.005	–

Analyses used the primary model and tested the model-estimated difference between two groups.

Table IIb

Effectiveness results at week 13 and over weeks 3–13

Measurements	At week 13*		Over weeks 3–13†	
	Estimated difference (95% CI)	P-value	Estimated difference (95% CI)	P-value
WOMAC pain subscores	6.39 (0.37, 12.41)	0.037	6.31 (1.11, 11.51)	0.018
Total WOMAC score	5.64 (−0.20, 11.47)	0.058	5.59 (0.41, 10.78)	0.035
WOMAC physical function subscores	5.42 (−0.47, 11.31)	0.071	5.29 (0.02, 10.55)	0.049
WOMAC stiffness subscores	4.91 (−1.31, 11.14)	0.122	5.27 (−0.14, 10.69)	0.056
Physician global assessment	3.56 (−1.48, 8.60)	0.166	5.97 (1.34, 10.59)	0.012
Patient global assessment	0.92 (−4.63, 6.47)	0.746	3.82 (−1.44, 9.09)	0.154

* Analyses used the primary model and tested the model-estimated difference between two groups.

† Additional exploratory longitudinal models assessed mean differences over weeks 3–13.

who received treatment with at least one post-injection visit. Improvement from baseline in WOMAC pain subscores was used in the primary model, which tested the superiority of Gel-200 treatment using all available data through week 13, accommodating a change in slope of VAS pain response at week 6. The difference between the two groups in model-estimated improvement from baseline at week 13 was the prospectively defined primary endpoint which tested the superiority of the treatment using two-sided 95% lower bounds exceeding 0 mm for Gel-200 – PBS. Secondary outcome measures supporting the effectiveness of Gel-200 utilized the same models. The actual and model-estimated differences between the two groups in changes from baseline at weeks 3, 6, 9 and over weeks 3 through 13 were calculated as well. Additional exploratory longitudinal models assessed the superiority of Gel-200 for continuous endpoints using least squares mean differences between groups in mean changes from baseline between weeks 3 and 13 in all major outcome measures. OMERACT–OARSI responders/strict responders were similarly compared between treatment groups across weeks 6 and 13 using a generalized estimating equation (GEE) regression model.

Safety analyses included all patients who received treatment. All *P*-values were based on two-sided tests to compare Gel-200 with PBS treatment with *P*=0.05 used as a threshold for statistical significance.

Results

Patient population

A total of 598 patients were screened; 379 patients met eligibility criteria and were randomized to treatment; 377 patients were analyzed for safety; 375 patients comprised the pre-defined ITT population, having received IA injection of study drug, with one post baseline assessment. Of 375 patients in the ITT population, 247 received Gel-200 and 128, PBS; 350 patients (92.3%) completed the study (Fig. 1). Patient demographics and baseline disease characteristics were comparable between treatment groups (Table I).

Effectiveness measures

Mean changes from baseline in WOMAC pain subscores demonstrated a statistically significant advantage of 6.39 mm for Gel-200 treatment over PBS at week 13 (*P*=0.037; Fig. 2 and Table IIa). Treatment differences at weeks 3 and 6 exceeded 8 mm (*P*=0.001 and *P*=0.003, respectively), and the overall difference over weeks 3 through 13 was 7.10 mm (*P*=0.005). Mean improvements from baseline in WOMAC pain subscores consistently favored Gel-200 at each visit, with improvements of 40.6% at week 3 and 44.1% at week 6. Effectiveness in the Gel-200 treated

group was sustained over weeks 3–13 by WOMAC total score, physical function, and physician global evaluations with statistical significance (*P*<0.05, Table IIb) in addition to WOMAC pain. In the ITT population, the odds ratio (OR) for “strict” OMERACT–OARSI responders was statistically significant for Gel-200 vs PBS from weeks 6 to 13 [OR = 1.59; *P*=0.022; Table III and Fig. 3(a)]. There were no statistically significant differences in SF-36 between weeks 0 and 13, although benefit was demonstrated in both treatment groups.

In terms of clinically meaningful responses over weeks 3–13, 64.5–72.8% of patients reported improvements ≥MCID in Gel-200; compared with 57.1–69.5% in PBS, moderate improvements ≥30% in a maximum of 62.1% vs 54.0% at week 6 and substantial improvements ≥50% in a maximum of 49.4% vs 37.9% at week 6 (Fig. 3).

Safety measures

The safety profile following a single Gel-200 injection was comparable to PBS over 13 weeks; reported AEs are shown in Table IVa. The incidence of AEs was similar in both treatment groups; 182 treatment-related AEs were reported in 100 patients: 67 (26.9%) in Gel-200 and 33 patients (25.8%) in PBS groups, respectively. Most common treatment-related AEs included joint swelling, effusions and arthralgia, without significant differences between treatment groups. Serious adverse events (SAEs) were reported in eight patients, including five cases of cancer (Table IVb). None were judged by investigators to be related to study treatment, although all SAEs occurred in the Gel-200 group, including one death. No clinically notable changes in laboratory results were identified.

Discussion

This RCT compared treatment with a single IA injection of Gel-200 with PBS over 13 weeks in patients with symptomatic OA of the knee. Onset of effectiveness of Gel-200 was evident by week 3

Table III
Summary of OMERACT–OARSI responders

	Responder [n (%)]		OR* in weeks 6 through 13 (Gel-200 – PBS)	
	Gel-200 (n = 247)	PBS (n = 128)	Estimate (95% CI)	P-value
Strict OMERACT–OARSI responders				
Week 6	120 (51.1%)	49 (39.5%)	1.59 (1.07, 2.37)	0.022
Week 9	125 (54.1%)	55 (46.6%)		
Week 13	106 (45.9%)	46 (38.7%)		
OMERACT–OARSI responders				
Week 6	155 (66.0%)	76 (61.3%)	1.27 (0.85, 1.90)	0.242
Week 9	151 (65.4%)	74 (62.7%)		
Week 13	141 (61.0%)	65 (54.6%)		

* When odds ratio >1, then in favor of Gel-200.

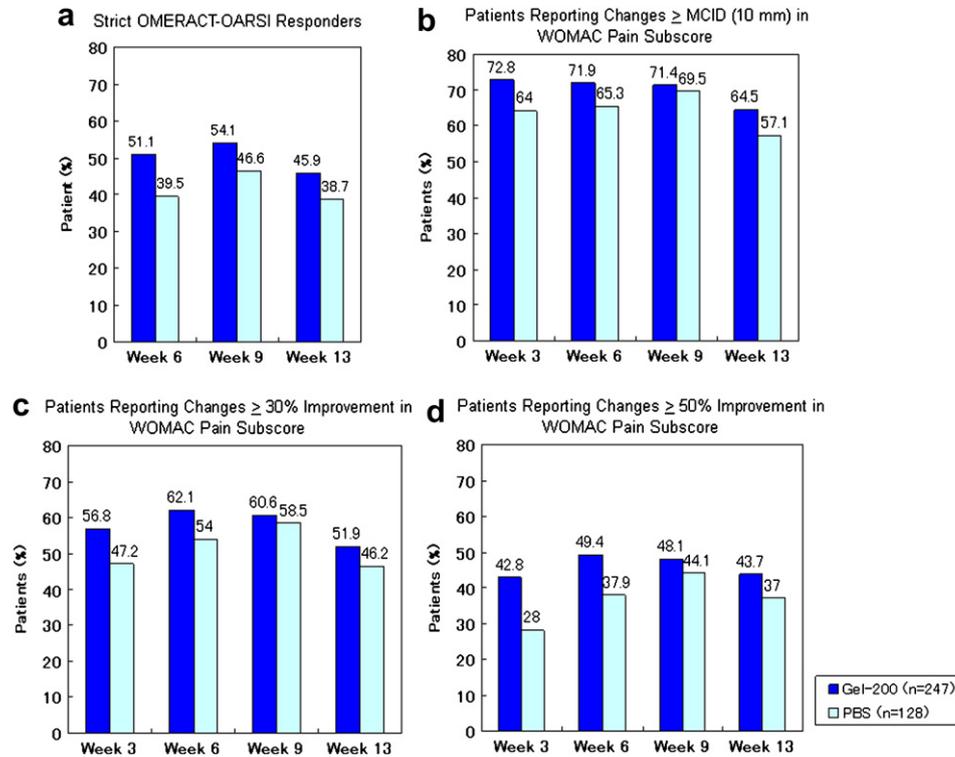


Fig. 3. OMERACT–OARSI strict responders and patients reporting improvements ≥ 10 mm (MCID), $\geq 30\%$, $\geq 50\%$ in WOMAC pain subscores.

and the effect lasted through end of study week 13, based on significant improvements in WOMAC pain subscores at study endpoint, week 13, the primary outcome measure, and over weeks 3–13. These advantages were further demonstrated by strict OMERACT–OARSI responders, including subjects reporting “moderate” e.g., $\geq 30\%$ and “substantial” e.g., $\geq 50\%$ changes from baseline in WOMAC pain subscores also exceeding MCID. Improvements in total WOMAC scores, WOMAC physical function and physician global assessments of disease activity over weeks 3–13 further support the efficacy of Gel-200 treatment; a lesser degree of improvement was observed for patient global assessment of disease activity. Mean improvements in WOMAC pain subscores with Gel-200 exceeded 20 mm and were consistently better than PBS treatment throughout end of study week 13 reaching a maximum of 31.7 mm. Subjects in the Gel-200 treatment group reported at least 40% mean improvement from baseline in WOMAC pain subscores at each post-injection visit.

This study prospectively enrolled patients with K–L grade 1–3 to be consistent with several other pivotal studies for this indication. Our inclusion criteria further required both knee pain for at least 4 weeks and radiographic evidence of tibio-femoral osteophytes, osteosclerosis of the femoral or tibial endplates, or joint space narrowing. Patients also were required to have ≥ 40 mm in WOMAC pain subscore at the screening visit. Hart and Spector reported that K–L grade 1 patients benefitted from early intervention²⁴. This PBS-controlled randomized study established Gel-200 effectiveness in OA patients meeting these prospective criteria.

When comparing differences in mean changes from baseline in WOMAC pain subscores between Gel-200 treatment and PBS, a statistically significant advantage of 8.12 mm was evident by week 3 and sustained through end of study week 13 at 6.39 mm. In contrast to other IA-HA injections^{25,26}, Gel-200 demonstrated earlier onset of benefit. Despite meta-analysis reporting large placebo effects in studies examining treatment with IA-HA

injections in OA of the knee^{27,28}, a single injection of Gel-200 demonstrated treatment advantages over control (PBS) comparable to other OA therapies, including oral NSAIDs²⁹.

Although few trials of IA-HA products have reported a statistically significant effect on physical function^{30,31}, Gel-200 treatment resulted in absolute mean changes exceeding 20 mm in WOMAC physical function subscores over weeks 3–13, reflecting $\geq 30\%$ improvements at each post-injection visit. Strict OMERACT–OARSI responses requiring $\geq 50\%$ improvements in this trial were evident as soon as 6 weeks following injection as were clinically meaningful changes from baseline in both WOMAC pain and physical function subscores over weeks 3 through 13; 62% of patients reported $\geq 30\%$ pain relief, and approximately 50% of patients reported $\geq 50\%$ pain relief. On the other hand, there was no statistically significant difference between Gel-200 and PBS groups in patient global assessment of disease activity. However, the

Table IVa
AEs overview

	Gel-200 (n = 249)		PBS (n = 128)	
	Patients [n (%)]	Events (n)	Patients [n (%)]	Events (n)
Total AEs	172 (69.1%)	483	81 (63.3%)	216
SAEs	8 (3.2%)	19	0	0
Unanticipated related adverse events	0	0	0	0
Total related AEs	67 (26.9%)	124	33 (25.8%)	58
Related AEs occurring within 24 h of IA injection	35 (14.1%)	43	14 (10.9%)	19
Related AEs occurring in $\geq 5\%$				
Joint swelling	35 (14.1%)	43	15 (11.7%)	18
Joint effusion	28 (11.2%)	31	13 (10.2%)	13
Arthralgia	19 (7.6%)	24	12 (9.4%)	14

No statistically significant difference was identified between treatment groups.

Table IVb
List of SAEs

No.	Gender	Age	Treatment	SAE	Days post injection	Device related	Anticipated
1	Female	65	Gel-200	Ductal carcinoma (Right breast)	16	No	No
2	Female	67	Gel-200	Cardiac arrest	76	No	No
				Respiratory arrest	76	No	No
				Cryptogenic cirrhosis	76	No	No
				Acute bilateral pulmonary edema	77	No	No
				Respiratory failure	85	No	No
				Acute renal failure	87	No	No
				Hypokalemia	87	No	No
3	Female	49	Gel-200	Transient ischemic attack	78	No	No
4	Female	75	Gel-200	Exertional dyspnea	41	No	No
				Transient blurry vision	41	No	No
				Dizziness	41	No	No
5	Female	43	Gel-200	Incarcerated right femoral hernia	33	No	No
				Abdominal pain left side	39	No	No
				Abdominal pain	51	No	No
6	Male	76	Gel-200	Basal cell carcinoma of the face (left eyelid and cheek)	45	No	No
				Malignant melanoma	45	No	No
7	Male	80	Gel-200	Prostate cancer	56	No	No
8	Male	78	Gel-200	Squamous cell carcinoma	74	No	No

advantage of Gel-200 administration was evident by clinically meaningful improvements in WOMAC pain and physical function scores, and in statistically significantly more strict OMERACT/OARSI responders.

Eight cases of SAEs were reported in the Gel-200 group; all judged unrelated to study treatment, including five cancers diagnosed soon after treatment administration. These are consistent with the age of the study population and neither their timing of occurrence nor pre-clinical data would suggest a plausible relationship to administration of Gel-200^{32,33}. In pre-clinical studies, Gel-200 was not shown to be associated with carcinogenicity. AE rates were generally comparable between treatments. No unanticipated treatment-related AEs were reported. As might be expected, the most common treatment-related AEs were joint swelling, joint effusion and arthralgia, frequently reported in other IA-HA studies²⁹. Importantly, pseudosepsis, an AE associated with another cross-linked IA-HA product, hylan G-F 20^{34–36}, and allergic reactions were not reported in the 249 patients receiving Gel-200 in this trial. Results are subject to further studies which would enlarge the patient population receiving Gel-200.

Together these results indicate that treatment with Gel-200 offers statistically significant and clinically meaningful improvements both in pain and physical function, of early onset, in patients with knee OA, thereby demonstrating the multi-dimensional effectiveness of this therapy. The absence of allergic reactions or 'pseudosepsis' and the low incidence of treatment associated AEs support a favorable safety profile for this cross-linked IA-HA product for treatment of symptomatic OA of the knee.

Contributions

V. Strand: study conception and design, data analysis and interpretation, drafting and revising the article, final approval of the article to be published, presentation of data to investigators, posters at OARSI.

H. S. B. Baraf: drafting and revising the article, final approval of the article to be published, presentation of data to investigators, posters at OARSI.

P. T. Lavin: study conception and design, data collection, data analysis and interpretation, drafting and revising the article, final approval of the article to be published.

H. Hosokawa and S. Lim: analysis and interpretation of data, drafting and revising the article, final approval of the article to be published, presentation of data to investigators, posters at OARSI.

Conflict of interest

V. Strand has served as a consultant to Seikagaku Corporation as well as Cypress, Logical Therapeutics, Nicox and Pfizer. H. S. B. Baraf was an investigator in this study and served as a consultant to Seikagaku Corporation after the study was completed. P. T. Lavin was the statistical consultant to Seikagaku Corporation. H. Hosokawa and S. Lim are employees of Seikagaku Corporation working in Research & Development Division.

Role of the funding source

This study was conducted by Seikagaku Corporation.

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