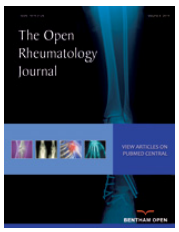

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Supplementary Material

First-in-human Study to Evaluate a Single Injection of KiOmedine®CM-Chitosan for Treating Symptomatic Knee Osteoarthritis

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Abstract:

Background:

Single-injection viscosupplementation is currently performed with cross-linked hyaluronan (*e.g.*, Durolane®) for treating symptomatic knee osteoarthritis.

Objective:

This first-in-human study evaluated the safety and performance of single-injection treatment with non-crosslinked KiOmedine®CM-Chitosan.

Methods:

Patients with painful knee osteoarthritis were randomly assigned to the KiOmedine®CM-Chitosan (n=63) or Durolane® (n=32) group. Patients were blinded to treatment and followed up for 26 weeks. Durolane® was used as scientific control to ensure the validity of the study and reliability of results. No direct comparison was performed between the two groups. The primary objective was defined as an intra-group effect size of 0.8 at 13 weeks post-injection compared to baseline on WOMAC-A (pain). Secondary outcomes included self-reported knee stiffness and knee function, responder rate, quality-of-life questionnaires, and safety.

Results:

The primary objective for both the KiOmedine®CM-Chitosan and the Durolane® groups was met: mean pain reduction of 62.5% (effect size 2.08) for the KiOmedine®CM-Chitosan group and 62.4% (effect size 2.28) for the Durolane® group. Secondary performance outcomes showed all clinically relevant treatment effects over 26 weeks for both groups ($p<0.05$). Treatment-related adverse events were more often reported in the KiOmedine®CM-Chitosan than Durolane® group and were limited to local reactions. No serious treatment-related adverse events were reported.

Conclusion:

A single intra-articular injection of non-crosslinked KiOmedine®CM-Chitosan is safe and effective for treating symptomatic knee osteoarthritis with a high responder rate. Pain reduction is maintained for 6 months with a high responder rate.

Keywords: Chitosan, Intra-articular injection, Single-injection, Knee, Osteoarthritis, Viscosupplementation.

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4.1. Demographics and Baseline Characteristics

There were no protocol deviations, thus all randomized patients were included in the safety cohort for analysis (available in the manuscript). Results from the per protocol cohort, constituting of all patients who adhered to the protocol and attended all visits up to 13 weeks post-injection, are provided in this document. The per protocol cohort includes 51 patients in the KiOmedine CM-Chitosan group and 28 patients in the Durolane group (Fig. **1**).

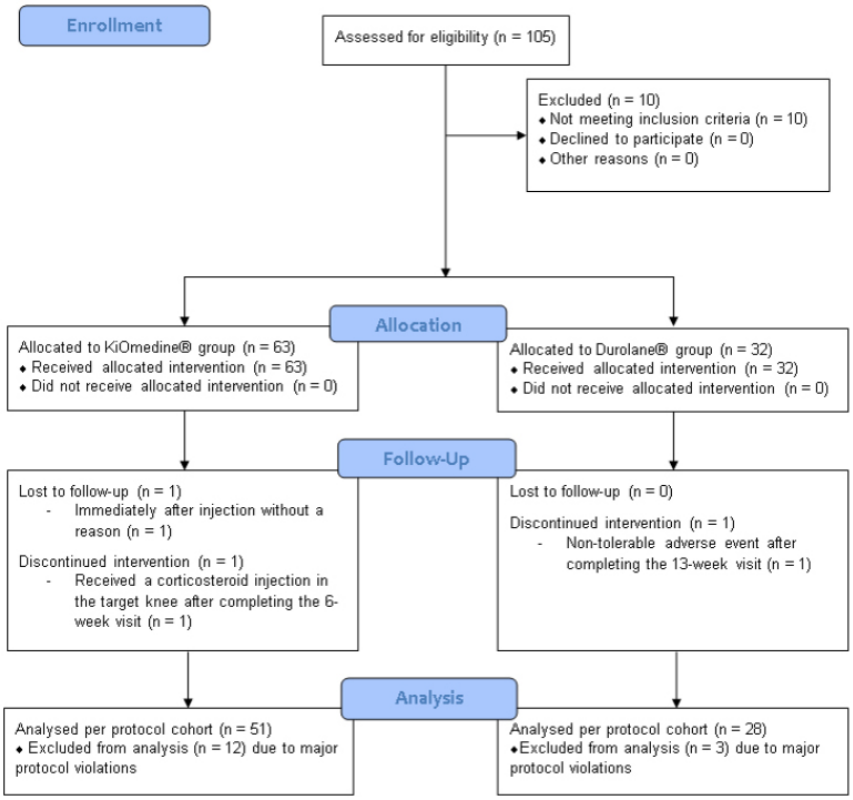

Fig. (1). CONSORT flow diagram of patients throughout the study.

The demographics and baseline characteristics of the per protocol (PP) cohort are shown in Table **1**. Patients were 60.9 ± 8.5 years-old on average (median = 60 years; min = 46 and max = 79 years). There were 26 males (32.9%) and 53 females (67.1%). All patients were White/Caucasians. The smoking status included never smoked in 61 patients (77.2%), current smoker in 6 patients (7.6%), and ex-smoker in 12 patients (15.2%).

Table 1. Demographics and baseline characteristics (PP cohort)

	N		Mean (SD)
	Valid	Missing	
Age	79	0	60.9 (8.5)
Height (cm)	79	0	169.6 (9.6)
Weight (kg)	79	0	82.6 (11.1)
BMI (kg/m^2)	79	0	28.7 (3.0)
HR (beat/min)	78	1	74 (8)
Systolic pressure (mmHg)	78	1	131 (15)
Diastolic pressure (mmHg)	78	1	82 (9)
Packyears	18	61	16.6 (11.0)
Years Ago Stopped Smoking	12	67	17.6 (12.8)
Alcohol consumption (unit/day)	27	52	0.5 (0.7)
Years ago stopped consuming alcohol	78	1	4.4 (4.9)
Disease duration (year)	79	0	60.9 (8.5)

The history of alcohol use included never consumed in 52 patients (65.8%) and current consumer in 27 patients (34.2%). Two women (2.5%) were using contraceptives.

The knee involved in the study was the left knee in 33 patients (41.8%) or the right knee in 46 patients (58.2%).

There were other osteoarthritis (OA) sites in 51 patients (64.6%). The other OA sites were the contralateral knee in 45 patients (57.0%; symptomatic in 5 patients [6.3%]), hip in 3 patients (3.8%; none of them symptomatic), hand in 4 patients (5.1%; bilateral and symptomatic in 2 patients [2.5%]), shoulder in 2 patients (2.5%; symptomatic in 1 patient [1.3%]) and other sites in 3 patients (3.8%; feet, lower back and right acromioclavicular joint; symptomatic in 1 patient [1.3%]).

The Kellgren-Lawrence classification is shown in Table **2**.

Table 2. Kellgren-Lawrence classification (PP cohort)

		Frequency	Percent	Cumulative Percent
Valid	Grade 2	50	63.3	63.3
	Grade 3	29	36.7	100.0
	Total	79	100.0	

The main following medical history was reported in 54 patients:

- Type II Diabetes in 8 patients (14.8%)
- Hypertension in 43 patients (79.6%)
- Hypercholesterolemia in 12 patients (22.2%)
- Hypothyroidism in 7 patients (13.0%)
- Allergy in 4 patients (7.4%)
- Other symptoms or diseases in 20 patients (37.0%)

The local skin was considered in good condition for all 79 patients (100.0%).

4.2. Primary Efficacy Outcome

In the KiOmedine CM-Chitosan group, WOMAC A (pain) score at 13 weeks post-injection decreased by 64.9% from baseline (11.1 ± 2.2 at baseline to 3.9 ± 4.1 at 13 weeks post-injection; paired Student's t test, $p < 0.001$). The effect size equaled 2.2.

In the Durolane group, there was a 65.2% reduction in WOMAC A (pain) score at 13 weeks post-injection compared to baseline (11.5 ± 2.4 at baseline to 4.0 ± 3.6 at 13 weeks post-injection; paired Student's t test, $p < 0.001$). The effects size equaled 2.5.

4.4. Secondary Efficacy Outcome

4.4.1. Self-administered WOMAC Questionnaire for Pain, Stiffness, and Function

The repeated measures analysis of variance for WOMAC pain (Fig. **2A**), WOMAC stiffness (Fig. **2B**), and WOMAC function (Fig. **2C**) revealed a statistically significant effect of time for the KiOmedine CM-Chitosan and Durolane groups ($p < 0.001$ for all comparisons, Table **4**). Post-hoc Bonferroni's tests revealed a statistically significant reduction in WOMAC pain and WOMAC function scores between baseline and all further time points (all $p < 0.001$) and between week 2 and all further time points (all $p < 0.05$). Moreover, WOMAC stiffness score significantly decreased from baseline to all further time points (Post-hoc Bonferroni's tests, all $p < 0.001$).

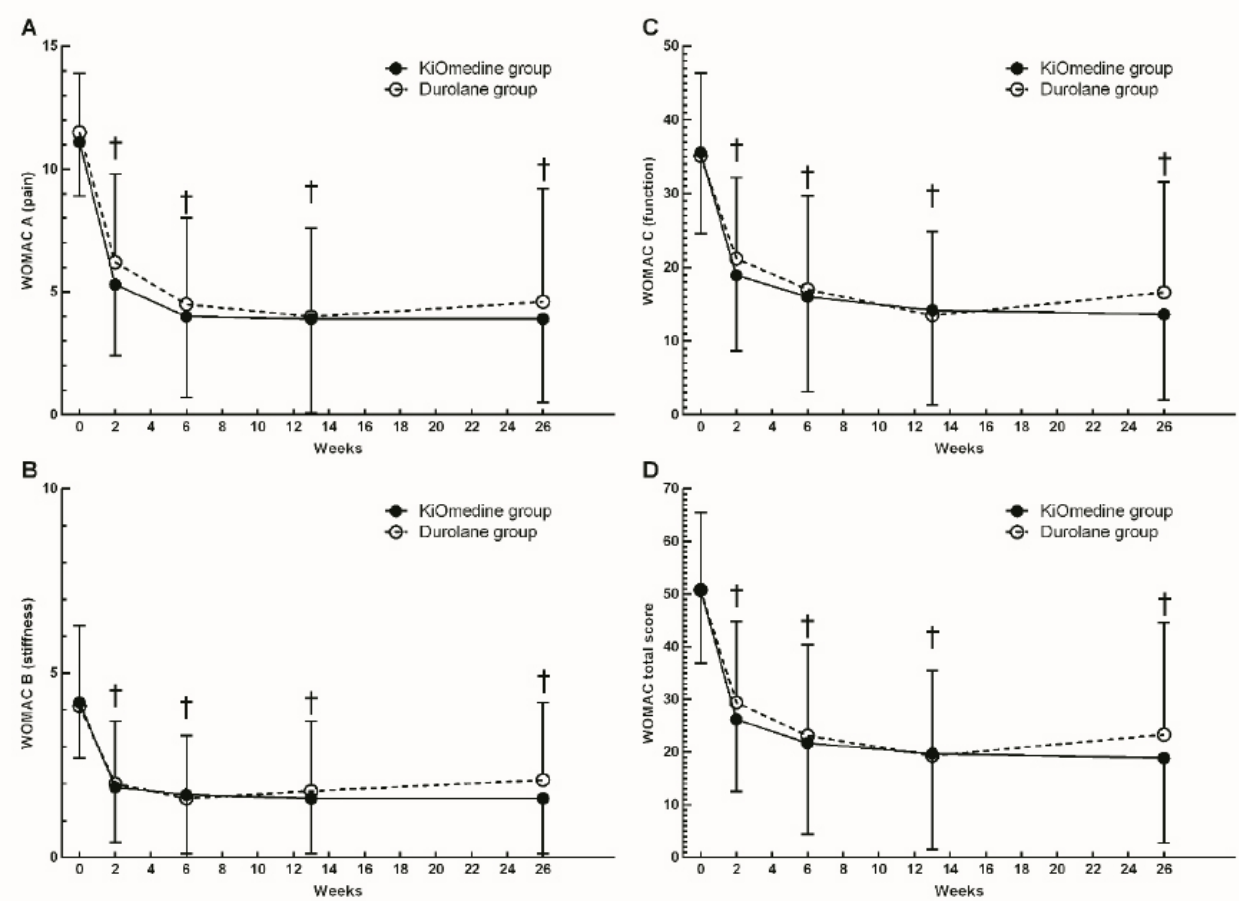

Fig. (2). WOMAC scores for each visit over 26 weeks after blinded single intra-articular injection of KiOmedine CM-Chitosan or Durolane among the safety population. (**A**) WOMAC pain scores. (**B**) WOMAC stiffness scores. (**C**) WOMAC function scores. (**D**) WOMAC total scores. Data are presented as means ±SD. †, $p < 0.001$ versus baseline (ANOVA for repeated measures).

The repeated measures analysis of variance for WOMAC total revealed a statistically significant effect of time for the KiOmedine CM-Chitosan and Durolane groups (both $p < 0.001$, Table **3**, (Fig. **2D**). Post-hoc Bonferroni's tests revealed a statistically significant reduction in WOMAC total score between baseline and all further time points (all $p < 0.001$), between week 2 and all further time points (all $p < 0.01$), and between weeks 6 and 13 ($p = 0.025$).

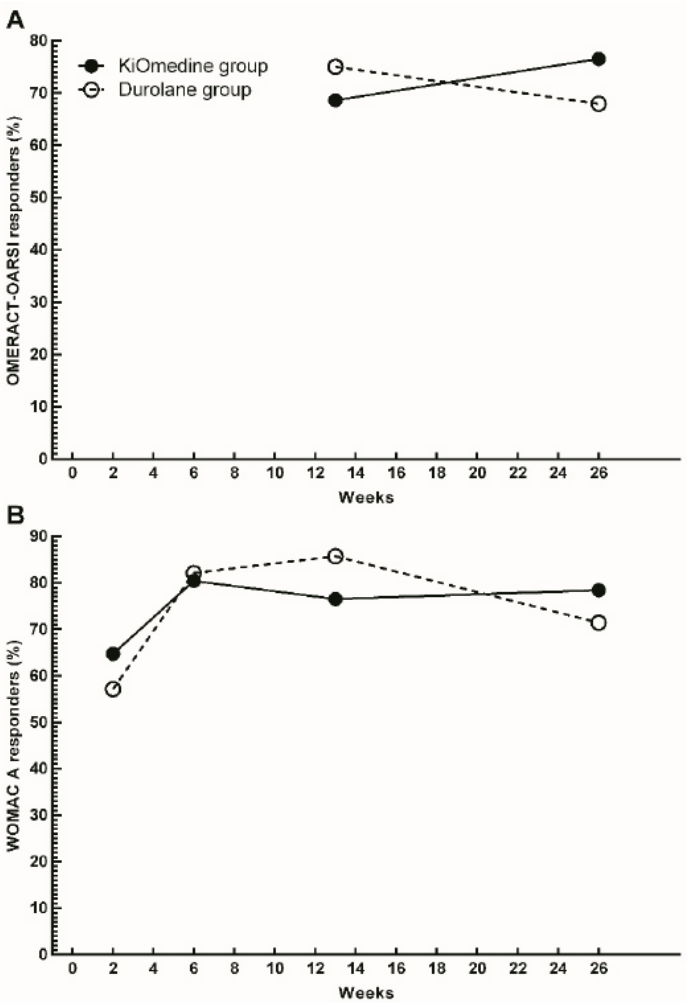

Fig. (3). OMERACT-OARSI responder rates and WOMAC A following blinded single intra-articular injection of KiOmedine CM-Chitosan or Durolane among the safety population. (A) OMERACT-OARSI responder rate at 13- and 26-weeks post-injection. (B) WOMAC A (pain) responder rate at all timepoints post-injection.

Table 3. Efficacy analysis over 26 weeks for the KiOmedine CM-Chitosan and Durolane groups (mean (SD).

Variables	Randomization	Day 0	Week 2	Week 6	Week 13	Week 26
Sample size, n	KiOmedine CM-Chitosan	51	51	51	51	51
	Durolane	28	28	28	28	28
WOMAC A (pain)	KiOmedine CM-Chitosan	11.1 (2.2)	5.3 (2.9)†	4.0 (3.3)†	3.9 (4.1)†	3.8 (3.4)†
	Durolane	11.5 (2.4)	6.2 (3.6)†	4.5 (3.5)†	4.0 (3.6)†	4.6 (4.6)†
WOMAC B (stiffness)	KiOmedine CM-Chitosan	4.2 (1.5)	1.9 (1.5)†	1.7 (1.9)†	1.6 (1.7)†	1.6 (1.7)†
	Durolane	4.1 (2.2)	2.0 (1.7)†	1.6 (1.7)†	1.8 (1.9)†	2.1 (2.1)†
WOMAC C (function)	KiOmedine CM-Chitosan	35.6 (11.0)	18.9 (10.2)†	16.0 (12.9)†	14.2 (12.9)†	13.6 (11.6)†
	Durolane	35.1 (11.3)	21.2 (11.0)†	17.0 (12.7)†	13.5 (11.4)†	16.6 (15.0)†
WOMAC (total)	KiOmedine CM-Chitosan	50.9 (14.0)	26.2 (13.7)†	21.7 (17.3)†	19.7 (18.2)†	18.9 (16.2)†
	Durolane	50.8 (14.7)	29.4 (15.4)†	23.1 (17.4)†	19.3 (16.2)†	23.3 (21.3)†
Pain at rest	KiOmedine CM-Chitosan	6.3 (1.5)	2.8 (1.9)†	1.8 (2.1)†	1.6 (2.1)†	1.5 (1.6)†

(Table 3) contd.....

Variables	Randomization	Day 0	Week 2	Week 6	Week 13	Week 26
	Durolane	6.1 (1.6)	3.3 (2.1)†	1.9 (2.0)†	1.6 (1.8)†	1.6 (2.3)†
Patients' global assessment	KiOmedine CM-Chitosan	6.9 (7.0)	3.1 (3.0)†	2.3 (2.0)†	2.0 (2.0)†	2.0 (2.0)†
	Durolane	6.6 (7.0)	3.7 (3.5)†	2.5 (2.0)†	2.4 (2.5)†	2.2 (0.5)†
OMERACT-OARSI responders	KiOmedine CM-Chitosan	N/A	N/A	N/A	68.6%	76.5%
	Durolane	N/A	N/A	N/A	75.0%	67.9%
WOMAC A (pain) responders	KiOmedine CM-Chitosan	N/A	64.7%	80.4%	76.5%	78.4%
	Durolane	N/A	57.1%	82.1%	85.7%	71.4%
SF-12 physical component	KiOmedine CM-Chitosan	32.1 (6.2)†	42.7 (7.0)†	44.5 (8.3)†	46.0 (9.2)†	46.5 (7.6)†
	Durolane	34.7 (5.2)†	40.4 (6.5)†	43.9 (7.6)†	46.2 (8.9)†	45.6 (10.4)†
SF-12 mental component	KiOmedine CM-Chitosan	47.3 (10.7)	50.4 (8.6)†	55.4 (8.2)†	55.3 (7.3)†	53.3 (7.7)†
	Durolane	48.4 (8.0)	51.9 (8.5)†	55.1 (7.2)†	52.1 (10.6)†	53.5 (9.2)†

†, $p < 0.05$ versus baseline (ANOVA for repeated measures).

4.4.2. Self-administered Questionnaire for Pain and Global Assessment

The repeated measures analysis of variance for both pain and the global assessment score showed a statistically significant effect of time for the KiOmedine CM-Chitosan and Durolane groups (both $p < 0.001$, Table **4**). Post-hoc Bonferroni's tests revealed a statistically significant reduction in both pain and the global assessment score between baseline and all further time points (all $p < 0.001$) and between week 2 and all further time points (all $p < 0.001$).

4.4.3. Responders to Treatment

OMERACT-OARSI responders

The number and percentage of patients that responded to the treatment have been determined at 13 and 26 weeks post-injection in line with the OMERACT-OARSI [25]. For the KiOmedine CM-Chitosan group, the percentage of responders was 68.6% (n = 35) at 13 weeks post-injection and 76.5% (n = 39) at 26 weeks post-injection. For the Durolane group, the percentage of responders was 75.0% (n = 21) at 13 weeks post-injection and 67.9% (n = 19) at 26 weeks post-injection (Table **4**; Fig. **3A**).

Responders in terms of WOMAC A (pain) change

For the KiOmedine CM-Chitosan group, the percentage of responders was 76.5% (n = 39) at 13 weeks post-injection, and 78.4% (n = 40) at 26 weeks post-injection. For the Durolane group, the percentage of responders was 85.7% (n = 24) at 13 weeks post-injection, and 71.4% (n = 20) at 26 weeks post-injection (Table **4**; (Fig. **3B**)).

4.4.4. Self-administered SF-12 Health Survey of Functional Health and Well-being

The repeated measures analysis of variance for both functional health and well-being showed a statistically significant effect of time for the KiOmedine CM-Chitosan and Durolane groups (both $p < 0.001$, Table **4**). Improvements in functional health between baseline and all further time points were significant (Post-hoc Bonferroni's tests, $p < 0.001$ for all comparisons) and between week 2 and all further time points ($p < 0.05$ for all comparisons). Improvement in well-being between baseline and all further time points (Bonferroni's tests, $p < 0.05$ for all comparisons) and between weeks 2 and 6 were significant (Bonferroni's tests, both $p < 0.001$).

4.4.5. Patient and Physician Satisfaction

Patient Satisfaction

The repeated measures analysis of variance for patient satisfaction showed a statistically significant effect of time for the KiOmedine CM-Chitosan and Durolane groups (both $p = 0.008$). Post-hoc Bonferroni's tests showed a statistically significant increase in patient satisfaction between week 2 and week 13 post-injection (both $p = 0.019$) and between week 2 and week 26 post-injection (both $p = 0.038$). Overall, most patients in both groups reported to be satisfied or very satisfied post-injection (86.3% in the KiOmedine CM-Chitosan group and 71.4% in the Durolane group at week 26).

The repeated measures analysis of variance for patient's health revealed a statistically significant effect of time for the KiOmedine CM-Chitosan and Durolane groups (both $p < 0.001$). Post-hoc Bonferroni's tests showed a statistically significant improvement in patient's health between week 2 and all further time points ($p < 0.01$ for all comparisons). Overall, most patients in both groups reported that their health was improved or very much improved post-injection (78.4% in the KiOmedine CM-Chitosan group and 67.9% in the Durolane group at week 26).

Physician Satisfaction

The repeated measures analysis of variance for the clinical evaluation of knee pain did not show a statistically significant effect of time for the KiOmedine CM-Chitosan and Durolane groups (both $p = 0.11$).

The repeated measures analysis of variance for the clinical evaluation of knee function showed a statistically significant effect of time for the KiOmedine CM-Chitosan and Durolane groups (both $p = 0.02$). The clinical evaluation of knee function showed a significant improvement from week 2 to week 6 post-injection (Post-hoc Bonferroni's tests; both $p = 0.02$).

The repeated measures analysis of variance for the clinical evaluation of patient's health showed a statistically significant effect of time for the KiOmedine CM-Chitosan and Durolane groups (both $p < 0.001$). Patient's health significantly improved from week 2 to week 6 (Post-hoc Bonferroni's test, both $p = 0.001$) and from week 2 to week 13 post-injection (Post-hoc Bonferroni's test, both $p = 0.002$).

Overall, the physicians were satisfied to very satisfied with

the improvement in health (78.4% for KiOmedine CM-Chitosan and 71.4% for Durolane), knee function (86.3% for KiOmedine CM-Chitosan and 78.6% for Durolane group), and reduction in knee pain (90.2% for KiOmedine CM-Chitosan and 71.4% for Durolane) for patients of both treatment methods at week 26.