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Clinical Trial

Twelve-month efficacy of carboxymethyl-chitosan in refractory knee osteoarthritis: A randomized controlled trial (PIONEER)

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ABSTRACT

Objectives: The 12-month efficacy and safety of a novel bioresorbable fluid implant based on CM-chitosan for intra-articular injection was evaluated in knee osteoarthritis (OA) patients with predictive factors of failure to viscosupplementation.

Design: This pilot single-blind randomized controlled study was conducted in 104 patients with at least one of the following OA phenotypes: tricompartmental OA, patellofemoral involvement, K&L grade III or IV and/or body mass index >30 kg/m^2. Non-inferiority and superiority of CM-chitosan (KioMedine^{VS}one) in reducing pain were evaluated compared Hylan G-F 20 (Synvisc-One). Efficacy was evaluated using the WOMAC scores, OMERACT-OARSI responder rates, TKA eligibility and events, patient and physician satisfaction.

Results: At 6 months post-injection, mean WOMAC pain reduction vs. baseline was 69.4 ± 25.5 % for the CM-chitosan group and 66.3 ± 26.15 % for the Hylan G-F 20 group (non-inferiority p = 0.096; 95 % CI -16.94 %, 7.02 %). At 12 months, significant symptomatic improvement in both groups, with clinically important differences in WOMAC pain reduction in favor of CM-chitosan, were observed, including in the subgroups of patients with patellofemoral OA (Δ 11.5 %), obese patients (Δ 21.7 %) and patients eligible for TKA at baseline (Δ 13.5 %). CM-chitosan showed a high response rate (93.8 %), as well as high patient (93.8 %) and investigator (90.6 %) satisfaction. No new safety signals were identified.

Conclusions: In this difficult-to-treat population, CM-chitosan was non-inferior to Hylan G-F 20, but did show clinically important, though not statistically significant, differences in pain reduction at 12 months. CM-chitosan was effective in improving OA symptoms and physical function for 12 months.

1. Introduction

Knee OA is a common progressive multifactorial joint disease that is characterized by joint pain and dysfunction due to progressive articular cartilage loss, subchondral bone damage, inflammation/synovitis and osteophyte formation [1]. In 2020, 7.6 % of the global population was suffering from OA, with a projected increase of 74.9 % of knee OA by 2050 [2]. In people aged >40 years the global prevalence is even 22.9 % [3], which is a large burden, not only for the individual but also for the society due to socio-economic consequences [4]. The current treatment of OA consists of combined non-pharmacological educational approaches (e.g., lifestyle modification, diet, exercising), medical interventions (pain-relief drugs and devices), and intra-articular injections such as Hyaluronic Acid (HA) viscosupplementation [5,6]. However, the effect of viscosupplementation is often limited in patients with one of the following predictive factors of failure to HA, as identified by the EUROVISCO expert group [7]: isolated patellofemoral osteoarthritis, severe patellofemoral osteoarthritis, BMI ≥30 kg/m^2 and a radiographic Kellgren and Lawrence (KL) grade IV. These patients are likely to be non-responders to HA and may be classified as refractory.

KioMedine^{VS}one is a novel, single injection, bioresorbable fluid implant composed of 2.0 % (w/w) non-crosslinked chitosan derivatives of non-animal origin, obtained by proprietary chemistry after extraction from the edible white mushroom *Agaricus bisporus* [8]. Carboxymethyl-chitosan (CM-chitosan), the active component, works through two key mechanisms: lubrication and scavenging of free radicals. These properties potentially help interrupt the vicious cycle of OA, offering long-term relief from OA-related symptoms [9]. It was first

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proven to be a safe and effective option for the symptomatic treatment of knee OA in the pivotal, international multicenter APROOVE study [10]. The long-term efficacy was further confirmed to last for at least 9 months in a real-world setting [11]. Emans et al. described the efficacy of a single injection of CM-chitosan in refractory patients in a post hoc analysis of the APROOVE study, indicating that CM-chitosan could be an effective option in this difficult-to-treat population [12]. Moreover, post-market data on file collected in real-life suggest that CM-chitosan can have long-lasting effects in patients with predictive factors of viscosupplementation failure.

Therefore, to confirm these promising results, the current pilot trial (NCT05214807) investigated the safety and performance of an intra-articular injection of CM-chitosan over a 12-month follow-up period in patients with predictive factors of failure to HA and was intended to collect data that will guide future research.

2. Methods

2.1. Study design

This study was a pilot monocentric, comparative, single-blind (patient blinded), randomized, controlled trial with a 12-month follow-up period. According to best clinical practice, inclusion criteria required a single intra-articular corticosteroid (CS) injection in all subjects during the screening visit (V0), to resolve clinically apparent knee effusion and/or local signs of inflammation. After 10 days on average, the patients were checked again for eligibility and randomized in 1:1 ratio to receive a single injection of either CM-chitosan or Hylan G-F 20. The randomization sequence was completed by a statistician using permuted block design, with variable and random block sizes of 2 or 4. Follow-up visits were performed at 2 weeks, 3 months, 6 months, 9 months and 12 months.

2.2. Patients

One hundred and four patients with symptomatic knee OA, in accordance with the clinical and radiological criteria set forth by the American College of Rheumatology, and with either severe patellofemoral involvement, isolated patellofemoral OA, tricompartmental OA, Kellgren & Lawrence grade III/IV, or obesity (BMI $\geq$30.0 kg/m^2), were enrolled into the study. Participants for the study were male or female individuals aged 40–85 years. Patellofemoral OA was diagnosed via both clinical and radiographic assessment, with symptoms (including pain) being principally of patellofemoral origin. Radiological grading was identified using a recent standing knee radiography. Participants were eligible to continue in the study only if they showed no clear signs of effusion or local inflammation before randomization. In addition, participants needed to report moderate to severe pain (with a score $\geq$12 on 5-point Likert WOMAC pain) in the treatment knee at the screening visit, despite first-line treatment with non-opioid analgesics and non-steroidal anti-inflammatory drugs. Participants were excluded if they met any contraindications specified in the instructions for use of CM-chitosan or Hylan G-F 20. These included known allergies or hypersensitivity to any components of the study products, presence of infections or skin disease at or near the injection site, severe inflammation, synovitis, or inflammatory arthritis of the knee joint. Additional exclusion criteria encompassed a history of autoimmune diseases, crystal-induced arthropathies, and evidence of lymphatic or venous stasis, or any serious blood disorders.

2.3. Medical device

The investigational medical device was KioMedine^{VS}one, composed of non-animal CM-chitosan (60 mg/3 mL) for knee intra-articular injection. Each package unit contains one pre-filled syringe with 3 mL sterile contents. As a comparator a single injection of Hylan G-F 20 (Synvisc-One) at a concentration of 8 mg/mL Hylan polymers (Hylan A + B) in a volume of 6 mL was used. The injection was performed using the lateral supra-patellar access route with the patient in supine position.

2.4. Objectives and endpoints

The primary performance endpoint was the percentage change from baseline in knee pain at 6 months post-injection measured by the 5-point Likert WOMAC pain scale. The secondary performance endpoints were to assess the effectiveness of CM-chitosan and the comparator device in alleviating knee osteoarthritis symptoms, as determined by the percentage change from baseline in the WOMAC subscales of pain, stiffness, physical function and WOMAC total score at the various timepoints over the 12-month follow-up period. Eligibility for Total Knee Arthroplasty (TKA) was assessed at baseline and then at the 6-, 9- and 12-months follow-up visits, determined following the three criteria of: (1) Functional disability, (2) clinical OA symptom manifestations and (3) shared decision with the patient. Subgroup analyses for the secondary performance endpoints were performed for the following phenotypes: tricompartmental osteoarthritis with patellofemoral involvement, BMI $\geq$30 kg/m^2 and patients who were eligible for TKA at baseline. Additionally, response to treatment was evaluated according to the OMERACT-OARSI responder criteria [13]. Exploratory endpoints encompassed the patient and physician satisfaction, evaluated using a self-administered 5-point Likert scale (i.e., very satisfied, satisfied, neutral, unsatisfied or very unsatisfied). Safety of both investigational medical devices was assessed immediately after injection and at all time points by documenting the incidence, severity, and causal relationship of Adverse Events (AE) and Adverse Device Effect (ADE) in accordance with ISO 14155:2020 definitions.

2.5. Statistics

A 3 % non-inferiority margin was set considering the hypothesis that the percentage mean reduction of pain from baseline at 6 months in the CM-chitosan group would be non-inferior to that of the Hylan G-F 20 group, with a 80 % power. Superiority testing was performed once the hypothesis of non-inferiority was met, with a superiority margin of 10 %, considered the Minimal Clinically Important Difference for pain reduction [14]. The non-inferiority and superiority one-sided, two-sample t-tests at significance level of 0.025 with a 3 % non-inferiority margin and a 10 % superiority margin, was also performed on the secondary endpoints. The full analysis set (FAS), which refers to all treated subject with an efficacy outcome, was the primary analysis set for the primary and secondary endpoints, using imputation methods for missing values. For subjects who withdrew prematurely due to TKA prior to completing the 6 months a last WOMAC questionnaire was collected just before study exit, when possible. Missing data were handled using monotone linear regression multiple imputation, with 50 datasets generated via a single Markov Chain Monte Carlo step. Imputation models included covariates such as demographics, BMI, treatment arm, and prior WOMAC scores. Data on the FAS without data imputation is hereby presented for the subgroup analyses. For exploratory purposes, student's T-test analysis was performed to compare the two cohorts in the identified subgroups. The safety analysis set, which included all treated subjects, was the primary analysis population for safety endpoints. For the statistical programming and analysis, the software SAS 9.4 was used.

2.6. Regulatory requirements

This study was carried out in accordance with ethical principles of the Declaration of Helsinki and the principles of good clinical practice outlined in ISO 14155:2020. The study started following a positive advisory opinion of the responsible Ethics Committee (University Hospital of Antwerpen, Belgium, reference 2021-1734). No patient was included before signing the informed consent form.

3. Results

3.1. Patient demographics

3.1.1. Population

A total of 130 patients were assessed for eligibility and 104 patients who met the eligibility criteria were randomized at 1:1 ratio and enrolled at a single site in Belgium, meaning that 52 patients received CM-chitosan and 52 patients received Hylan G-F 20. The recruitment period extended from January 2022 through January 2023, with the last patient follow-up in January 2024. The per protocol population included 88 patients, 44 in each group. There was a higher-than-expected drop-out rate with 26 % and 41 % of subjects dropping out at 6 months and 12 months post-injection, respectively. The drop-out of subjects throughout the duration of the study was similar in the CM-chitosan group (n = 21) and Hylan G-F 20 group (n = 24). The patient flow is referred to the CONSORT diagram (Fig. 1).

Baseline patient's demographics were well balanced and are summarized in Table 1.

Overall, the study comprised more females than males and with a mean age of 61.9 ± 9.9 years in the CM-chitosan group and 61.7 ± 9.5 years in the Hylan G-F 20. Mean BMI of the whole population was 28 kg/m^2. Demographics were comparable in both groups and most patients were cumulating multiple phenotypes. Patellofemoral involvement was observed in 100 % of the patients and more than 75 % of the patients were considered as eligible for TKA in each group at baseline.

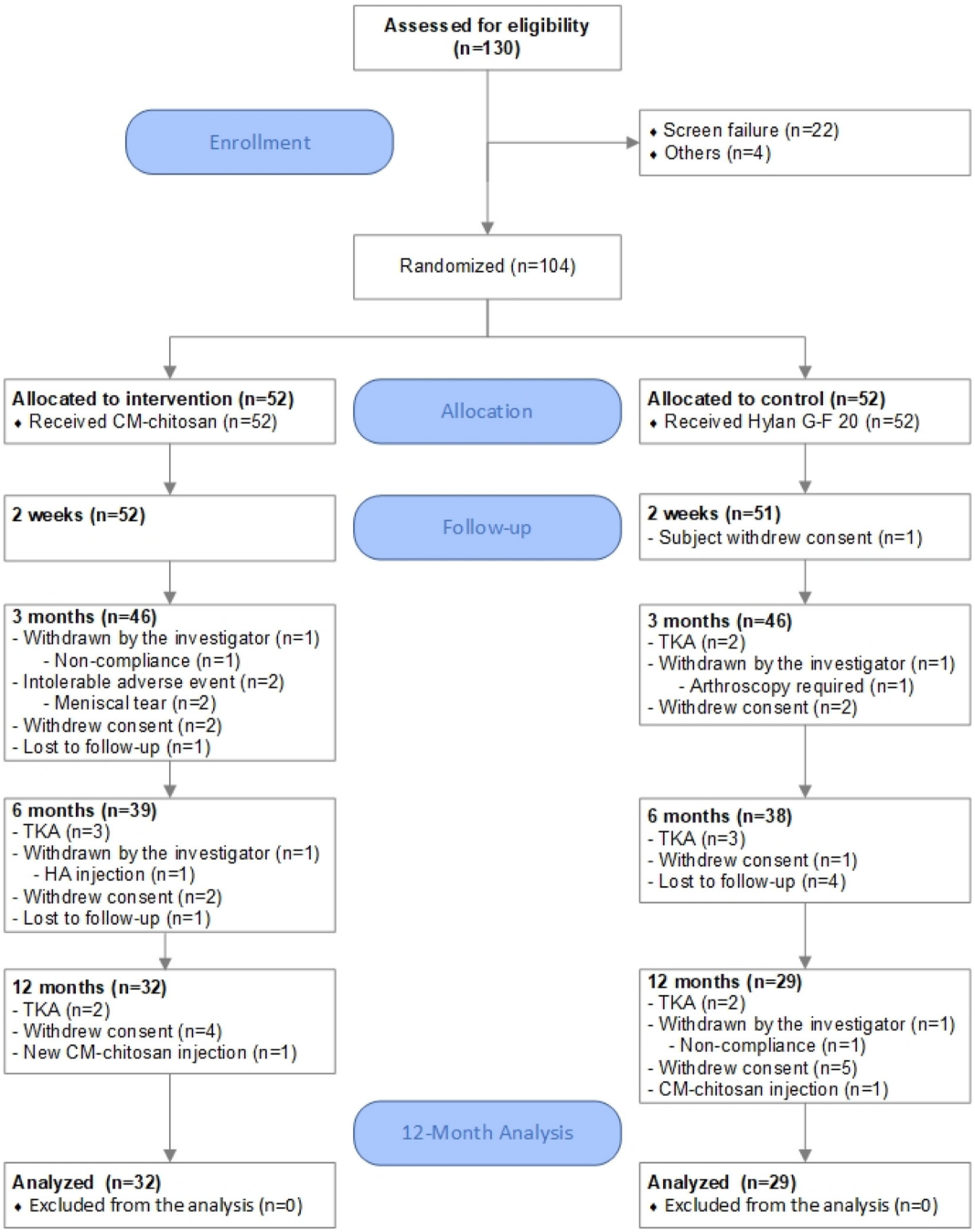

Fig. 1. CONSORT diagram.

Table 1
Baseline patient's demographics according to treatment.

	CM-chitosan	Hylan G-F 20
Females, mean ± SD (N)	69.2 % (36/52)	73.1 % (38/52)
Age [years], mean ± SD (N)	61.9 ± 9.9 (52)	61.7 ± 9.5 (52)
Body Mass index [kg/m^2],		
Mean ± SD (N)	28.8 ± 4.38 (52)	28.3 ± 4.73 (51)
Median (Q1, Q3)	28.2 (26.1, 31.3)	27.5 (24.9, 30.7)
(Min, Max)	(20.0, 39.6)	(20.7, 42.4)
Eligible for Total Knee Arthroplasty		
Yes	76.5 % (39/51)	78.8 % (41/52)
No	23.5 % (12/51)	21.2 % (11/52)
Knee osteoarthritis phenotype		
Patellofemoral involvement	100 % (52/52)	100 % (52/52)
Tricompartmental OA	80.8 % (42/52)	73.1 % (38/52)
Isolated patellofemoral OA	9.6 % (5/52)	5.8 % (3/52)
Severe patellofemoral OA	42.3 % (22/52)	57.7 % (30/52)
BMI ≥30 kg/m^2	34.6 % (18/52)	26.9 % (14/52)

BMI = body mass index; N = number of patients; OA = osteoarthritis; Q = Quartile; SD = standard deviation.

3.2. Efficacy results

3.2.1. WOMAC pain score

3.2.1.1. Overall population. At 6 months post-injection (primary endpoint), mean WOMAC pain reduction was 69.4 ± 25.5 % for the CM-chitosan group and 66.3 ± 26.15 % for the Hylan G-F 20 group, representing an absolute difference in percentage change of −5.0 % in favor of the CM-chitosan group (non-inferiority p-value = 0.096; 95 % CI -16.94 %, 7.02 %). Overall, knee pain was significantly reduced for all follow-up timepoints (2 weeks–12 months) compared to baseline (all $p < 0.001$) in both groups. After 12 months, mean pain reduction was −73.5 ± 24.06 % (n = 32) for the CM-chitosan group and was 62.0 ± 30.75 % (n = 29) for the Hylan G-F 20 group (Fig. 2). This represents a difference of −11.8 % in favor of CM-chitosan (non-inferiority p-value = 0.024; 95 % CI -26.45 %, 2.92 %). While the difference was clinically important, statistically significant superiority at 12 months post-injection was not demonstrated (p = 0.407). Similar results were observed in the per protocol population with a −13.6 % difference (95 % CI -28.19 %, 0.95 %) in favor of the CM-chitosan group (non inferiority p-value: 0.013).

3.2.1.2. Subgroup analysis of studied phenotypes. In patients with tricompartmental OA, the percentage reduction from baseline for the CM-chitosan group was −71.4 ± 26.24 % (N = 25, $p < 0.001$) at 12 months post-injection whereas for the Hylan G-F 20 group, it was −58.8 ± 30.41 % (N = 29, $p < 0.001$). In obese patients, the CM-chitosan group showed a −80.1 ± 13.06 % (N = 7, $p < 0.001$) decrease and the Hylan G-F 20 group showed a decrease of −58.4 ± 33.76 % (N = 10, $p < 0.001$). Finally, for patients who were eligible for surgery at baseline, a percentage reduction of −75.9 ± 23.0 % (N = 24, $p < 0.001$) and −62.4 ± 32.4 % (N = 21, $p < 0.001$) was observed for the CM-chitosan and Hylan G-F 20 groups respectively (Table 2).

A direct comparison over time between the subgroups is shown in Fig. 3. After 12 months, clinically important differences in favor of CM-chitosan were identified: −11.5 % (95% CI [−25.8, 2.8], p = 0.113) in the overall population with patellofemoral involvement, −12.6 % (95 % CI [−29.1, 3.9], p = 0.131) in the patients with tricompartmental OA, −21.7 % (95%CI [−47.3, 3.8], p = 0.089) for the obese patients, and −13.5 % (95%CI [−30.8, 3.7] p = 0.120) for the patients eligible for TKA (Fig. 4).

3.2.1.3. Effect of corticosteroid injection. All subjects received a single intra-articular CS injection during the screening visit and three different options were used in the trial: Depo-Medrol® 40 mg (n = 55), Depo-Medrol 80 mg (n = 38) and Diprophos® (n = 11). Overall, an initial decrease of −32.8 ± 26.4 % in the WOMAC Pain was shown at randomization, due to the CS alone.

3.2.2. WOMAC stiffness, physical function and total score

Changes in the WOMAC subscores (Stiffness, Physical Function, Total Score) over 12 months were investigated (Table 3). Knee stiffness was significantly reduced for all follow-up timepoints compared to V0 (all $p < 0.001$). For the CM-chitosan group, the percentage reduction from baseline was −53.1 ± 33.2 % at 12 months post-injection whereas for the Hylan G-F 20 group, it was −54.4 ± 33.1 % at 12 months post-injection. Physical functioning was significantly improved for all follow-up timepoints compared to baseline (p-values ranging from <0.001 to 0.003). For the CM-chitosan group, the percentage improvement from V0 was −63.8 ± 29.9 % at 12 months post-injection and it was −52.4 ± 58.2 % for the Hylan G-F 20 group. Looking at changes in the total WOMAC score over 12 months, the total WOMAC score was significantly reduced for all follow-

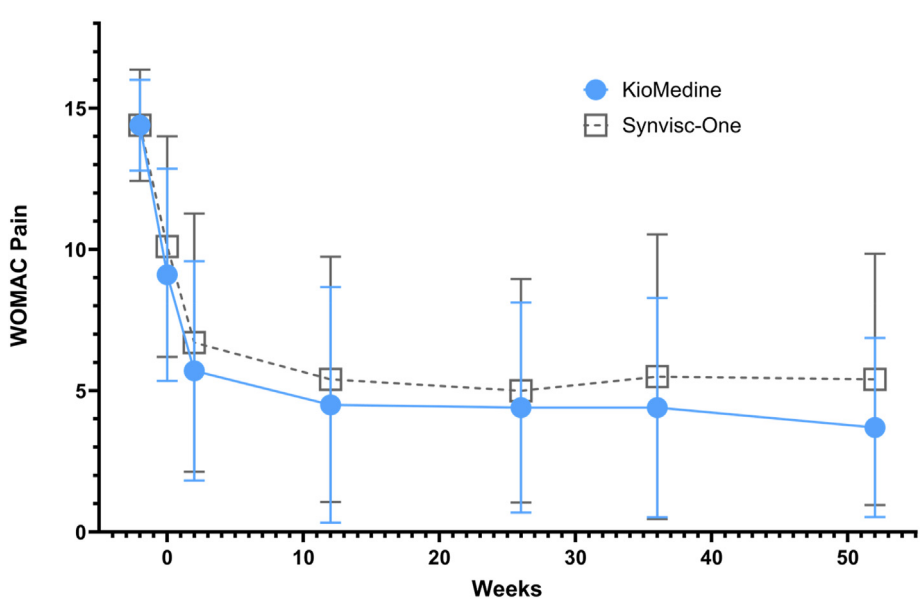

Fig. 2. WOMAC pain over time: comparison of CM-chitosan vs Hylan G-F 20. Data are presented as means ± SD.

Table 2
WOMAC Pain evolution at 12-month follow-up.

Subgroup (Phenotype)	Parameter	CM-chitosan % Change vs Baseline	Hylan G-F 20 % Change vs Baseline	Treatment-Control % difference [a]
Overall population	Mean ± SD (N)	−73.5 ± 24.06 (32)	−62.0 ± 30.75 (29)	−11.5 %
	Median (Q1, Q3)	−81.7 (−87.9, −65.5)	−58.3 (−93.8, −37.5)	−23.4 %
	P-value	<0.001	<0.001	
Tricompart mental OA patients	Mean ± SD (N)	−71.4 ± 26.24 (25)	−58.8 ± 30.41 (23)	−12.6 %
	Median (Q1, Q3)	−85.7 (−87.5, −53.8)	−53.8 (−86.7, −33.3)	−31.9 %
	P-value	<0.001	<0.001	
Obese patients	Mean ± SD (N)	−80.1 ± 13.06 (7)	−58.4 ± 33.76 (10)	−21.7 %
	Median (Q1, Q3)	−80.0 (−92.9, −68.8)	−58.3 (−93.8, −27.8)	−26.2 %
	P-value	<0.001	<0.001	
Eligible for TKA at baseline	Mean ± SD (N)	−75.9 ± 23.01 (24)	−62.4 ± 32.43 (21)	−13.5 %
	Median (Q1, Q3)	−82.9 (−90.0, −69.0)	−53.8 (−100.0, −33.3)	−29.1 %
	P-value	<0.001	<0.001	

% = percentage; N = number of patients; Q = quartile; TKA = total knee arthroplasty; SD = standard deviation.
[a] On available data, without imputation for missing data.

up timepoints compared to baseline (all $p < 0.001$). For the CM-chitosan group, the percentage reduction from baseline was −66.0 ± 27.1 % at 12 months post-injection. For the Hylan G-F 20 group, the percentage reduction from baseline was −58.9 ± 33.4 % at 12 months post-injection. The results observed in the FAS population for the WOMAC scores were similar and further confirmed in the per protocol cohort.

3.2.3. *OMERACT-OARSI responder rate*

The CM-chitosan responder rates were 86.8 % (33/38), 87.9 % (29/33) and 93.8 % (30/32), respectively after 6, 9 and 12 months after treatment. In the Hylan G-F 20 group, responder rates were 86.1 % (31/36), 72.4 % (21/29) and 82.8 % (24/29), respectively after 6, 9 and 12 months after treatment.

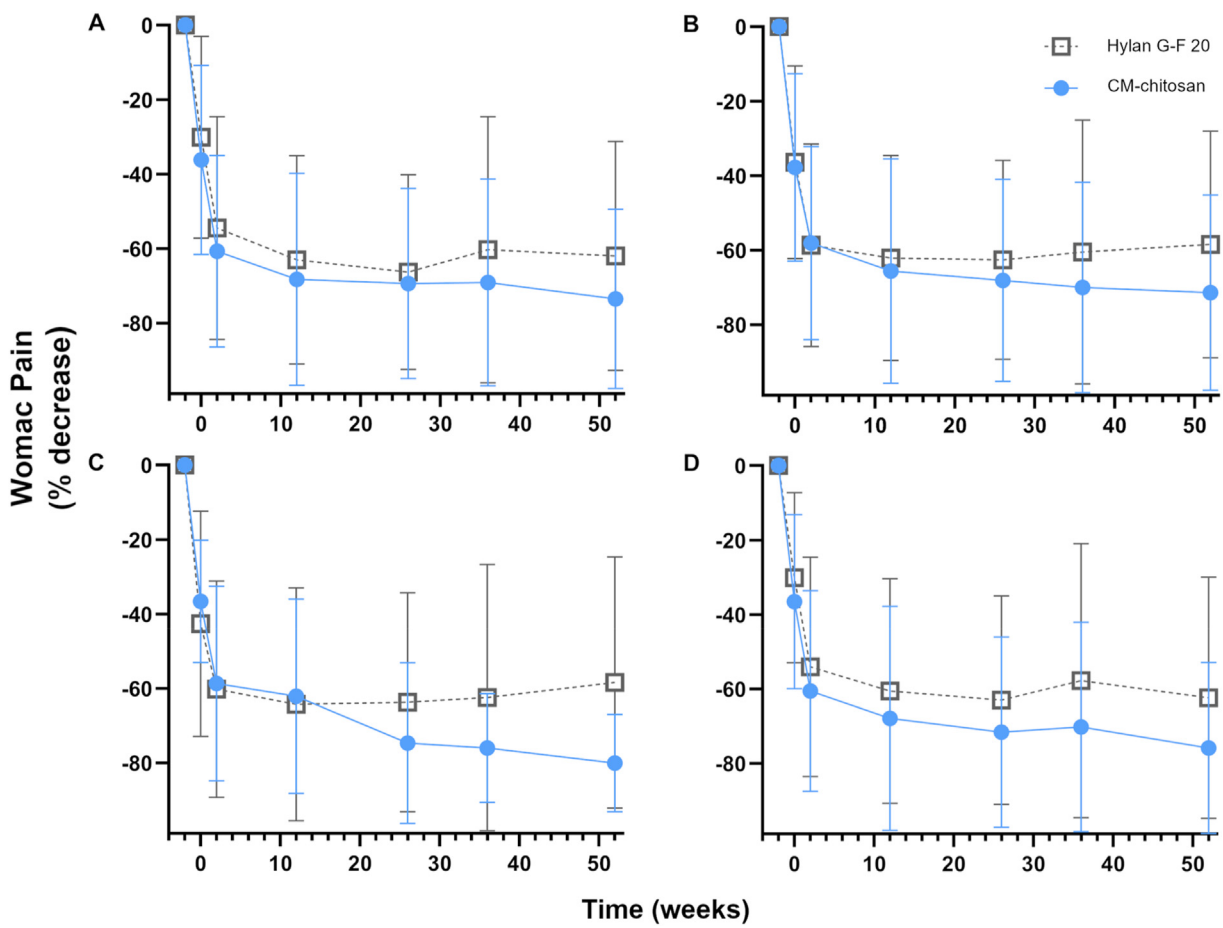

Fig. 3. Percentage decrease of WOMAC pain score over time: comparison of CM-chitosan vs Hylan G-F 20 in the subgroups of phenotypes. A: Overall population (patellofemoral OA) [N = 32 CM-chitosan, N = 29 Hylan G-F 20 at 12 months]; B: Tricompartmental OA patients [N = 25 CM-chitosan, N = 23 Hylan G-F 20 at 12 months]; C: Obese patients [N = 7 CM-chitosan, N = 10 Hylan G-F 20 at 12 months]; D: Patients eligible for TKA at baseline [N = 24 CM-chitosan, N = 21 Hylan G-F 20 at 12 months]. Data are presented as means ± SD.

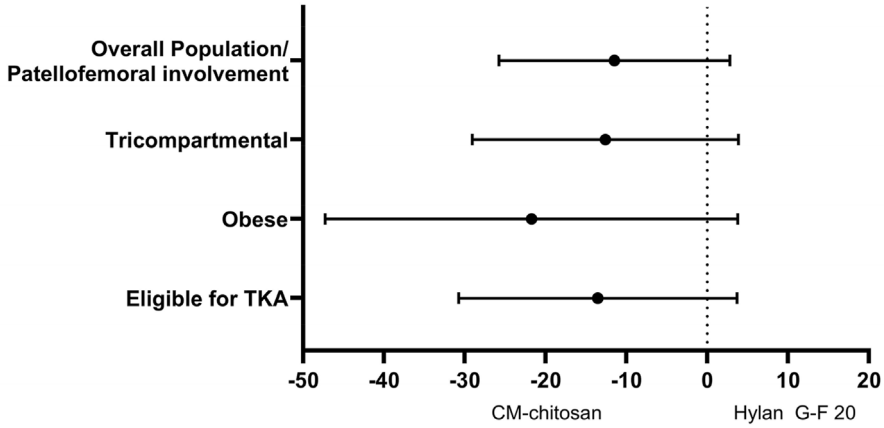

Fig. 4. Comparison between groups for the subgroups of phenotypes at 12 months Data are presented as means and 95 % CI. Negative difference: favoring CM-chitosan, Positive difference: favoring Hylan G-F 20).

3.2.4. Satisfaction after 1 year of follow-up: Patient's and Investigator's satisfaction scales

3.2.4.1. Patient's satisfaction. At 12 months post-procedure, the mean score for the CM-chitosan group was 4.5 ± 0.62 (N = 32), 95 % CI [4.24–4.69], with a satisfaction rate of 93.8 % (30/32). For the Hylan G-F 20 group, the mean score was 4.1 ± 1.03 (N = 29), 95 % CI [3.75–4.53], with a satisfaction rate of 79.3 % (23/29).

3.2.4.2. Physician's satisfaction. Clinical evolution of knee pain score for the CM-chitosan group was 4.3 ± 0.64 (N = 32), with a satisfaction rate of 90.6 % (29/32) versus a mean score of 3.6 ± 0.75 (N = 27), 95 % CI [3.3–3.9], with a satisfaction rate of 66.7 % (18/27) for Hylan G-F 20. Clinical Evolution of knee function for the CM-chitosan group was 4.3 ± 0.63 (N = 32), 95 % CI [4.1, 4.5], with a satisfaction rate of 90.6 % (29/32). For the Hylan G-F 20 group, the mean score was 3.6 ± 0.75 (N = 27), 95 % CI [3.3–3.9], with a satisfaction rate of 66.7 % (18/27). Clinical evolution of patient health for the CM-chitosan group was 4.2 ± 0.61 (N = 32), 95 % CI [4.0–4.4], with a satisfaction rate of 90.6 % (29/32). For the Hylan G-F 20 group, the mean score was 3.6 ± 0.69 (N = 27), 95 % CI [3.3–3.9], with a satisfaction rate of 63.0 % (17/27).

3.2.5. Total Knee Arthroplasty analysis

Table 4 shows the eligibility for TKA in the treatment knee due to the severity of OA across different timepoints and TKA surgical interventions occurring during the study in each group. Most subjects were eligible for TKA prior to treatment with CM-chitosan (n = 39, 76.5 %) or Hylan G-F 20 (n = 41, 78.8 %). Eligibility for TKA decreased considerably post-injection and remained low to reach 8.3 % in the case of the CM-chitosan patients and 20.0 % in the case of the Hylan G-F 20 patients after 12 months. The decrease of eligibility was higher at all timepoints for the patients who received CM-chitosan, especially at 9 months (p = 0.049). TKA analysis revealed that surgeries happened earlier and more often for the Hylan G-F 20 group. All these patients suffered from tri-compartmental OA.

3.3. Safety: Analysis of Adverse events

The results of the AE analysis found that the absolute number of AE was 69 for the CM-chitosan group and 66 events for the Hylan G-F 20 group. No serious adverse event was related to the study procedures. A minority of the AE were device-related (n = 24) and Hylan G-F 20 group (n = 7). Table 5 shows all AEs that were assessed as being related to the investigational device (Adverse Device Effect). In the CM-chitosan group, the majority of ADE was related to musculoskeletal and connective tissue disorders (n = 23) with arthralgia being the most often reported (n = 20). Arthralgia was mild to moderate in severity and with a median duration of 3.0 days (IQR [2.0, 4.0]), as well as easily manageable with paracetamol and non-steroidal anti-inflammatory drugs when needed, as authorized per protocol. This arthralgia is a manifestation of a normal inflammatory reaction following the injection of CM-chitosan and should not be linked to a hypersensitivity reaction, that is sometimes observed in repeated doses of HA. All TRAEs in the Hylan G-F 20 group, except one, were also related to arthralgia (n = 6).

4. Discussion

This pilot clinical investigation aimed to assess the safety and performance of CM-chitosan over a 12-month period following a single intra-articular injection in knee OA subjects with predictive factors of failure to

Table 3
WOMAC scores results at 12-month follow-up.

Endpoint	Parameter	CM-chitosan % Change vs Baseline	Hylan G-F 20 % Change vs Baseline	Treatment-Control % difference [95 % CI]
WOMAC-A pain	Mean ± SD (N)	−73.5 ± 24.06 (32)	−62.0 ± 30.75 (29)	−11.8 [-26.45, 2.92]
	Median (Q1, Q3)	−81.7 (−87.9, −65.5)	−58.3 (−93.8, −37.5)	
	P-value	<0.001	<0.001	0.024
WOMAC-Bstiffness	Mean ± SD (N)	−53.1 ± 33.16 (31)	−54.4 ± 33.09 (28)	5.0 [-11.63, 21.62]
	Median (Q1, Q3)	−60.0 (−75.0, −33.3)	−50.0 (−75.0, −33.3)	
	P-value	<0.001	<0.001	0.594
WOMAC-C physical Function	Mean ± SD (N)	−63.8 ± 29.92 (31)	−52.4 ± 58.23 (29)	−4.8 [-23.27, 13.75]
	Median (Q1, Q3)	−69.0 (−86.8, −52.8)	−63.3 (−94.6, −34.7)	
	P-value	<0.001	<0.001	0.204
WOMAC total score	Mean ± SD (N)	−66.0 ± 27.06 (31)	−58.9 ± 33.40 (29)	−4.0 [-18.56, 10.62]
	Median (Q1, Q3)	−70.6 (−87.3, −55.1)	−60.8 (−90.5, −38.9)	
	P-value	<0.001	<0.001	0.174

% = percentage; N = number of patients; Q = quartile; SD = standard deviation.

Table 4
Eligibility for TKA over time and TKA surgery events occurring during the study period.

	CM-chitosan [% (n/N)]	Hylan G-F 20 [% (n/N)]
Eligible for TKA at timepoint [a]		
Pre-treatment	76.5 % (39/51)	78.8 % (41/52)
Follow-up 6 Months	10.0 % (3/30)	35.7 % (10/28)
Follow-up 9 Months	4.2 % (1/24)	27.3 % (6/22)
Follow-up 1 Year	8.3 % (2/24)	20.0 % (4/20)
TKA surgery events		
Overall	9.6 % (5/52)	13.5 % (7/52)
Time to TKA	232.4 ± 88.64 (5)	160.1 ± 104.74 (7)

% = percentage; n = number of cases; N = total number of patients.
[a] The denominator (N) is inclusive only of those subjects for whom a response was provided at the stated timepoint.

HA. A single injection of crosslinked HA (Hylan G-F 20) was used as control. At study enrollment, more than 75 % of the patients were classified as being eligible for TKA and most subjects had more than one of the identified knee OA phenotypes. All subjects were shown to have OA with patellofemoral involvement. Subjects with these phenotypes have been identified as being at risk of viscosupplementation failure and are therefore considered a difficult-to-treat population [7] and may be considered as refractory. The included subjects represent the targeted population very well in terms of age, body mass index and eligibility for TKA and the demographic characteristics were well balanced between both treatment groups. The FAS was the primary analysis set for this investigation but results were further confirmed in the per protocol population.

In the study, treatment with a single injection of CM-chitosan reduced pain by −73.5 ± 24.06 % ($p < 0.001$) at 12 months post-injection, matching well with the high satisfaction scores from treated patients and treating physicians. These data support the satisfaction data from the previous studies on CM-chitosan [9,10] and can be considered as a substantial improvement according to the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) working group [12]. Therefore, these results can be considered especially clinically important since pain affects the QoL of patients with an OA at a high degree and long-term treatment of pain is often associated with adverse effects [15].

Both treatments were shown to reduce knee pain, stiffness, and improve physical functioning. The comparison between the two treatment groups showed that, while not statistically significant due to the explorative nature of this study, a clinically important difference of 11.8 % was observed between the two treatment groups for WOMAC pain reduction at 12 months in favor of CM-chitosan. This relative change in pain of more than 10 % is considered a clinically important difference in OA [16,17]. The responder rate was observed to be higher in patients treated with CM-chitosan. Benefits of treatment of CM-chitosan and Hylan G-F 20 were confirmed in the different subgroups of the studied phenotypes. While not statistically significant due to small subgroup sizes, differences in favor of CM-chitosan were observed, with clinically important differences for the reduction in WOMAC pain at 12 months that were observed for the following phenotypes: tricompartmental osteoarthritis (mean difference = −12.6 %), obese (mean difference = −21.7 %) and patients eligible for TKA at baseline (mean difference = −13.5 %). According to Eymard et al., especially obese patients with a BMI >30 are patients that are known to be significantly associated with viscosupplementation failure [18]. Results of this subgroup analysis were also supported by Lynen et al. who evaluated the real-world efficacy in subjects with a mean BMI of 30.1 ± 7.0 and KL grade II or III [11]. Of importance to note is that results of the subgroup analyses should be interpreted with the fact that all of these subgroups are underrepresented within the literature, due to the natural course of this condition.

Eligibility for TKA and events of TKA were also described, and while most subjects were eligible for TKA prior to treatment (>75 % in both groups) it was shown that the need for TKA decreased considerably post-injection and remained low with 8.3 % (n = 2/24) in the case of the CM-chitosan patients and 20.0 % (4/20) in the case of the Hylan G-F 20 patients after 12 months. Analysis for TKA revealed that surgeries tended to happen earlier and more often for the Hylan G-F 20. These results showed encouraging results in the possibility to postpone TKA after CM-chitosan treatment and they warrant further investigation.

Regarding safety, a minority of the AEs were classified as (possibly) related to the device for the CM-chitosan group (n = 24) and Hylan G-F 20 group (n = 7). The good tolerability of CM-chitosan that had been shown already in the APROOVE study was confirmed, with no new safety signal identified [10]. Arthralgia was the main observed AE, reported as mild to moderate in severity, with a median duration of 3.0 days (IQR [2.0, 4.0]). While short-term reactions are expected and manageable, the long-term safety profile of CM-chitosan remained favorable.

Finally, the study design also comprised a single intra-articular CS injection during the screening visit, according to standard clinical practice and being among the most frequently injected substances to resolve local signs of inflammation [19]. However, there is evidence that it should only be considered for short-term relief in knee OA [20]. Studies show that although CS appears to be more beneficial in pain reduction and function improvement than control interventions, this difference was gradually lost after up to 13 weeks of follow-up [21]. According to the multidisciplinary Brazilian consensus group, CS injection leads to an improvement in pain and function for 2–4 weeks only [22]. The early effect of CS is also confirmed in this study, with an initial decrease of pain observed between the screening visit and the randomization (Fig. 2). Further research is needed to better understand the impact and the potential synergistic effect of the CS injection on short- and long-term results.

There are limitations to this pilot clinical investigation. There is currently lack of available and published data on the studied OA phenotypes, making it difficult to estimate the required sample size to reach sufficient power or to make comparisons with existing data. The study was single blind which can lead to potential bias from the investigators. However, most of the measured endpoints (WOMAC, patient satisfaction) were collected directly from the patient, who was blinded to the received treatment. Furthermore, a high drop-out rate was observed with 26 % and 41 % of subjects dropping out at 6 months and 12 months post-injection, respectively, thus resulting in an attrition bias, contributing to a small sample size and a lack of statistical power for some of the analyses in this

Table 5
Adverse device effects - safety population.

Related AEs (ADE)	CM-chitosan		Hylan G-F 20	
	Number of Events	% Subjects with Event (% (n/N))	Number of Events	% Subjects with Event (% (n/N))
All categories	24	45.3 % (24/53)	7	13.7 % (7/51)
Arthralgia	20	37.7 % (20/53)	6	11.8 % (6/51)
Injection site Warmth	1	1.9 % (1/53)	0	0.0 % (0/51)
Joint Swelling	1	1.9 % (1/53)	0	0.0 % (0/51)
Muscle Spasms	1	1.9 % (1/53)	0	0.0 % (0/51)
Pain In Extremity	1	1.9 % (1/53)	0	0.0 % (0/51)
Herpes Zoster	0	0.0 % (053)	1	2.0 % (1/51)

ADE = adverse device effect; AE = adverse events; n = number of cases; N = total number of patients.

investigation. The drop-out of subjects throughout the duration of the study was similar in the CM-chitosan group (n = 21) and Hylan G-F 20 group (n = 24) and did not seem to be related to the treatment allocation.

5. Conclusion

In this difficult-to-treat population, CM-chitosan was non-inferior to Hylan G-F 20, but did show clinically important, though not statistically significant, differences versus the HA group in pain reduction at 12 months. These clinically important differences in favor of CM-chitosan were observed in subgroups including subjects with patellofemoral OA, obese patients, tricompartmental OA and patients eligible for TKA at baseline. A larger-scale study is needed to confirm the comparative results. This pilot study showed that a single injection of CM-chitosan was safe and effective in an OA population with predictive factors of failure to HA. Both treatments showed long-lasting effects for 12 months, with a statistically significant and clinically important reduction of 73.5 % and 62.0 % on WOMAC pain for CM-chitosan and Hylan G-F 20, respectively. This study demonstrated that CM-chitosan was effective in improving OA symptoms and physical function in refractory OA patients for 12 months.

Patients

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Authorship

All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this article, taking responsibility for the accuracy and integrity of the work, and have given their approval for this version to be published.

Authors Contributions

Study Investigators: Dr Van Overschelde (PVO) (principal investigator) and Dr Vansintjan (PV) (Hip and Knee Unit in AZ Maria Middelares, Gent).

Conception and design: PVO,PV, NP; Analysis and interpretation of the data: PVO,PV, NP, WW; Drafting of the article: Sigrun Niemitz (independent medical writer); Critical revision of the article for important intellectual content: NP, MC, WW, PVO, PV; Final approval of the article: NP,MC, WW, PVO, PV; Provision of study materials or patients: PVO, PV; Statistical expertise Razieh Taghavi (independent biostatistician, AVANIA CRO); Visualization: NP; Collection and assembly of data: Sigrun Niemitz (independent medical writer), NP.

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Declaration of Generative AI and AI-assisted technologies in the writing process

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Declaration of competing interest

NP and MC are employees for KiOmed Pharma, Herstal, Belgium. WW is an external consultant for KiOmed Pharma, Herstal, Belgium.

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