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ORIGINAL RESEARCH

Long-Term Efficacy Following Intra-articular Injection of Carboxymethyl-chitosan, a New Product Class for Knee Osteoarthritis: Results from an Observational Study in Germany

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ABSTRACT

Introduction: Evaluate the real-world efficacy of a single intra-articular injection of carboxymethyl-chitosan (CM-chitosan), a new product class for knee osteoarthritis (OA).
Methods: This post-marketing study included adult patients with knee OA, who received a single injection of 60 mg CM-chitosan (currently marketed as KioMedine^{vs}one) according to the instructions for use. Follow-up was performed at weeks 1, 12, 24, and 36. Efficacy was evaluated using a Visual Analog Scale (VAS) score for pain, the Knee injury and Osteoarthritis Outcome Score (KOOS), Patient's Global Assessment (PGA), and overall patient satisfaction.
Results: Forty-nine patients were included in the study. VAS pain score significantly decreased from a median of 49.0 mm at baseline to 24.0 mm at week 1 and to 18 mm at week 36. Pain improvement was stable since at week 36; 91.8% of patients confirmed pain reduction. All KOOS subscales (symptoms, pain, activities of daily living, sports and recreational activities, quality of life) improved significantly compared to baseline at all time points. KOOS pain improved progressively from a median of 58.3% at baseline (mean $56.2 \pm 18.8\%$) to 86.1% (mean $74.1 \pm 24\%$) at week 36 compared to baseline. Overall, more than 70% of patients reported a condition gain (PGA), matching well with the more than 75% of patients being satisfied with the treatment. At 6 months, 72.7% of the patients could be classified as responder according to the OMERACT-OARSI proposed set of responder criteria.
Conclusion: CM-chitosan showed a rapid onset of pain relief after 1 week and with a duration of 9 months. In a real-world setting, treatment with CM-chitosan would appear to be a potentially effective option to reduce pain and improve physical function and global condition in patients with knee OA, opening new perspectives in patients who are considered as refractory to current symptomatic therapies and where the unmet need is high.
Trial Registration Number: NCT04757051 (ClinicalTrials.gov).

Keywords: Osteoarthritis; CM-chitosan; Real-life setting; Knee; Joint; Real-world evidence

Prior Presentation: Interim 6-month results of this study were presented as a poster at WCO-IOF-ESCEO in March 24–26, 2022 (online congress) [19].

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Key Summary Points

Why carry out this study?

Carboxymethyl-chitosan is a new product class that has been proven to be a safe and effective option for the symptomatic treatment of knee osteoarthritis (OA) in the pivotal APROOVE clinical study showing significant reduction of all OA symptoms for at least 6 months.

This study was a prospective, observational, 36-week case cohort study to confirm the long-term effectiveness and safety of carboxymethyl-chitosan in a real-life clinical setting when used according to the instructions for use.

What was learned from the study?

In the real-world setting, a single intra-articular injection of carboxymethyl-chitosan showed pain relief after 1 week and for a duration of 9 months. It was effective at reducing pain and improving physical function and global condition in patients with knee OA, assessed using a visual analog scale and the Knee Injury and Osteoarthritis Outcome Score questionnaire at all time points. There were no new safety signals and the safety profile appears compatible with current Instructions For Use and existing safety data.

This observational study confirms that a single injection of a carboxymethyl-chitosan represents a safe and effective solution for knee osteoarthritis, showing a rapid onset of action with a duration sustained for 9 months, and opening new perspectives in patients who are considered as refractory to current symptomatic therapies and where the unmet need is high.

INTRODUCTION

Knee osteoarthritis (OA) is a common progressive multifactorial joint disease that is characterized by chronic pain and functional disability. In 2020, 7.6% of the global population was suffering from OA, with a projected increase of 74.9% of knee OA by 2050 [1]. OA is a complex, non-reversible condition with a major impact on patients' physical and psychological well-being and quality of life (QoL), not to mention socio-economic consequences. OA pathogenesis includes accelerated degradation and calcification of the cartilage, synovitis, and local and systemic immune system activation associated with an increase in the synthesis of pro-inflammatory cytokines, such as interleukin IL-6, IL-1, IL-8, tumor necrosis factor (TNF) alpha, IL-18, but a decrease in the regulatory cytokines, such as IL-10 [2, 3].

OA increases with obesity and age and the pooled global prevalence calculated from 88 studies was 22.9% (95% CI 19.8–26.1%) in individuals aged 40 and above [4]. Further risk factors are genetic predisposition, low bone density, trauma, and gender [5].

According to the American College of Rheumatology (ACR) and the European League Against Rheumatic Diseases (EULAR) guidelines, the treatment of OA consists of combined non-pharmacological educational approaches (e.g., lifestyle modification, diet, exercising), therapeutic methods (pain-relief drugs and devices), and surgery [6, 7].

While many patients experience improvement in their symptoms with standard treatment, a substantive subset of patients is refractory to these therapies. Frequently used treatments such as hyaluronic acid (HA) injections, corticosteroids, and pain-relief medications, as well as more invasive approaches like surgery, are often not sufficiently effective. Thus, especially patients with refractory OA continue to suffer from discomfort and seek alternative solutions [8]. The EUROVISCO group of experts notably identified some patient phenotypes as potential predictors of HA viscosupplementation failure [9], highlighting an unmet need in OA.

One new treatment option is KioMedine^{vs}one® (KiOmed Pharma, Belgium), a liquid implant composed of carboxymethyl-chitosan (CM-chitosan). CM-chitosan, a new product class for knee OA, is a derivative of chitosan, a linear glucosamine polysaccharide. CM-chitosan is well suited for local OA treatment as it is biocompatible, biodegradable, and can mimic cartilage extracellular matrix. Compared to cross-linked hyaluronan, CM-chitosan has a higher lubrication capacity and a higher ability to fight against oxidative stress [10].

KioMedine^{vs}one is a CE certified class III medical device and contains 60 mg of highly purified linear (i.e., non-cross-linked) carboxymethyl derivative of non-animal chitosan. The 3-mL volume of KioMedine^{vs}one is optimal for knee intra-articular injection. It is a unique fluid implant that has been proven to be a safe and effective option for the symptomatic treatment of knee OA in the pivotal, international multicenter APROOVE study (NCT03679208). That study demonstrated a significant reduction of all OA symptoms for at least 6 months and a high responder rate of 76% [11]. The promising long-lasting results needed further confirmation in a real-life setting, investigating performance at 6 months and beyond. Therefore, the observational study described here aimed to confirm the short- and long-term efficacy after 1 week and up to 9 months after one injection of CM-chitosan for the symptomatic treatment of knee OA, exploring what the patients could expect in the longer term.

In the present study, a broad and relatively unselected patient population was treated and followed under routine conditions. Only patients who were foreseen to receive an injection of CM-chitosan for their knee OA prior to inclusion in the clinical observation were asked to participate.

METHODS

Study Design

This study was a post-market, prospective, observational, single-center, case cohort study. The objective of the study was to confirm the effectiveness and safety of CM-chitosan at short term (after 1 week) and for 9 months in the treatment of symptomatic knee OA in a real-life clinical setting when used according to the Instructions For Use (IFU). Follow-up visits were performed at weeks 1, 12, 24, and 36, representing one treatment day and a follow-up period of 9 months.

The study was conducted from March 11, 2021 to April 25, 2022.

Patients

Fifty patients with symptomatic knee OA of Kellgren–Lawrence grade II/III and $\geq$ 18 years for whom the use of CM-chitosan was recommended by their treating physician were enrolled into this study to receive a single intra-articular injection of 60 mg/3 mL of non-animal CM-chitosan (KioMedine^{vs}one) after signing informed consent. Patients were not included if any contraindication or precautionary condition listed in the IFU was present, e.g., infection, severe inflammation, lymphatic or venous stasis, or significant joint effusion.

Medical Device

The investigational medical device was KioMedine^{vs}one. This is non-animal CM-chitosan (60 mg/3 mL) for intra-articular injection. Each package unit contains one pre-filled syringe with 3 mL sterile contents. Each 1 mL contains 20 mg CM-chitosan, 35 mg sorbitol, and phosphate-buffered water for injection qs (pH 7.2 $\pm$ 0.2, 270–330 mOsmol/kg).

Objectives and Endpoints

Efficacy of the treatment was assessed using a Visual Analog Scale (VAS) to measure pain and the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire to assess five basic criteria of outcome. Furthermore, the satisfaction with the treatment was questioned using the Patient's Global Assessment scale (PGA), the subjects satisfaction scale (SS), and the satisfaction scale by the investigator.

The 100-mm VAS detects changes in pain with high sensitivity on a scale ranging from 0 mm "no pain" to 100 mm "worst pain".

The KOOS evaluates short-term and long-term symptoms and function in subjects with knee injury and OA and has five separately scored subscales: pain, other symptoms, activities of daily living, function in sport and recreation, and knee-related quality of life.

The patient's as well as the physician's perception of the clinical severity of the knee OA was assessed on a 0–10 numerical rating scale (0 = very good; 10 = very poor) and the satisfaction with the treatment in general was evaluated on a 5-point Likert scale.

Furthermore, the responder rate was determined on the basis of the criteria of the OMERACT-Osteoarthritis Research Society International (OARSI).

As part of this post-marketing study, safety was monitored, and the focus was primarily on identifying unexpected events or adverse reactions that were not previously documented in pre-market trials or outlined in the IFU. This vigilant approach aimed to detect and analyze any unforeseen occurrences, such as new side effects or interactions, to ensure continuous documentation of safety profile of the CM-chitosan.

Statistics

Quantitative values were described as mean value and standard deviation (SD), minimum and maximum, as well as the quartiles including the median. These variables were checked for normal distribution using the Kolmogorov–Smirnov test.

Depending on the distribution, statistical comparisons with the baseline measurement were performed using the paired samples *t* test (parametric) or the Wilcoxon matched pairs test (non-parametric), when the comparison was made between one time point post-injection and baseline.

Qualitative variables were described as absolute and percentage frequencies; comparative analysis between time points (especially to baseline) was performed with contingency tables and as needed using McNemar's or Bowker's symmetry test; and 95% confidence intervals (CIs) were given to estimated rates, especially for the occurrence of adverse events (AEs).

The statistical analysis was essentially a purely descriptive analysis. Missing values were not replaced. No correction for multiple testing was performed, and the results were of a purely exploratory and descriptive nature. Tests were performed two-sided with a significance level of 5%. A descriptive safety interim analysis was performed at 1 week post-injection to ensure the safe continuation of the study.

Regulatory Requirements

This study was carried out in accordance with ethical principles that have their origin in the Declaration of Helsinki adopted by the 18th World Medical Assembly in Helsinki (Finland) since 1964, as last amended by the World Medical Assembly. Furthermore, the study was carried out in accordance with the principles of good clinical practice (GCP) outlined in ISO 14155:2020 "Clinical investigation of medical devices for human subjects—Good Clinical Practice". The study started following a positive advisory opinion of the responsible ethics committee (reference number "2020402", Ethikkommission der Ärztekammer Nordrhein).

RESULTS

Patient Demographics

Population

A total of 50 patients were assessed for eligibility and included in this post-marketing clinical follow-up (PMCF) study. One patient had to be excluded from the analysis after meeting an exclusion criterion following inclusion. Therefore 49 patients comprised the full analysis set. A total of 44 patients completed the study according to protocol and 5 patients terminated the study prematurely. For patient flow, refer to the CONSORT diagram (Fig. 1).

CM-chitosan was used to treat 35 women (71.4%) and 14 men (28.6%) with a mean age of 65.6 years and a body mass index (BMI) of 30.1 kg/m^2. The Kellgren–Lawrence grade was II in 23 patients (46.9%) and III in 26 patients (53.1%). All subjects underwent extended clinical examination, prior to any injection, to exclude potential contraindications. All subjects received injections under ultrasound guidance.

Patients' baseline demographics are summarized in Table 1.

Efficacy Results

VAS Pain Score

There was a rapid onset of effect and pain decreased significantly ($p \leq 0.001$) from a median value of 49.0 mm at baseline ($n = 49$) to 24 mm at week 1 ($n = 49$) and to 18 mm at week 12 ($n = 48$). VAS pain score decreased further to a median value of 11.0 mm at week 24 ($n = 44$), and it was 18 mm at week 36 ($n = 45$). Corresponding mean values were 47.3 ± 26.1 mm at baseline, 29.1 ± 26.0 mm at week 1, 29.8 ± 28.1 mm at week 12, 21.6 ± 23.0 mm at week 24, and 25.4 ± 23.9 mm at week 36. Mean results are presented in Fig. 2.

Hence, at all time points VAS scores were significantly lower compared to baseline (Wilcoxon matched pairs test, $p < 0.001$ at week 1, $p = 0.001$ at week 12, $p < 0.001$ at week 24, and $p < 0{,}001$ at week 36). From week 1 until week 36, at least 70% of patients showed an improvement in pain, indicating a long-lasting effect.

KOOS Questionnaire

This analysis was performed according to current KOOS scoring instructions. All subscales of the KOOS (pain, symptoms, activities of daily living, sport and recreation, and quality of life) were calculated independently and were converted into a scale from 0% to 100% where 0%

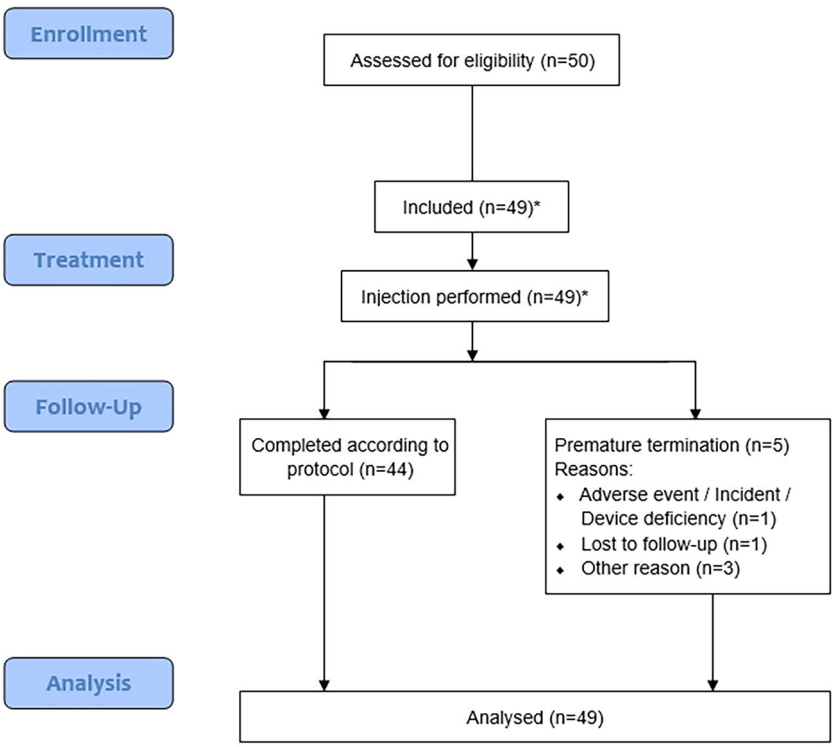

Fig. 1 CONSORT diagram. *One patient excluded from analysis after meeting an exclusion criterion following inclusion. *n* number of patients

Table 1 Patients' baseline demographics

Parameter	Population
Age [years], mean ± SD	65.6 ± 11.0
Body mass index [kg/m^2], mean ± SD	30.1 ± 7.0
Gender, *n* [%]	
Female	35 (71.4)
Male	14 (28.6)
Kellgren–Lawrence grade, *n* [%]	
II	23 (46.9)
III	26 (53.1)

SD standard deviation, *n* number of patients

represents "the most severe symptoms" and 100% means "no symptoms".

In all KOOS subscales patients showed a statistically significant improvement as presented in the following tables and figures, with a summary in Fig. 3.

KOOS Pain

KOOS pain improved progressively from a median of 58.3% at baseline (mean 56.2% ± 18.8%) to 86.1% (mean 74.1% ± 24%) at week 36 compared to baseline. Median scores were 66.7%, 79.2%, and 82.3% (mean = 67.4%, 73.5%, and 76.4%) at week 1, 12, and 24, respectively (Table 2 and Fig. 4).

Improvement of KOOS pain was statistically significant at all time points (Wilcoxon matched pairs test, $p < 0.001$ each).

KOOS ADL

KOOS ADL (activities of daily living) increased markedly from a median of 54.4% (mean 57.4% ± 20.6%) at baseline to 82.35% (mean 77.6% ± 20.8%) at week 36. Starting with week 1 all percentages related to activities were increased to greater than 73.5% (Table 3 and Fig. 5).

Improvement of KOOS ADL was statistically significant at all time points (Wilcoxon matched pairs test, $p < 0.001$ each).

KOOS Symptoms

KOOS symptoms improved from a median of 64.3% (mean 64% ± 19.5%) at baseline to 89.3% (mean 77.4% ± 21.1%) at week 24. Thereafter, there was a small decrease to 82.1% (mean 74% ± 23.1%) at week 36 (Table 4).

Improvement of KOOS symptoms was statistically significant at all time points (Wilcoxon matched pairs test, $p = 0.004$ at week 1, $p = 0.003$ at week 12, $p < 0.001$ at week 24, and $p = 0.003$ at week 36).

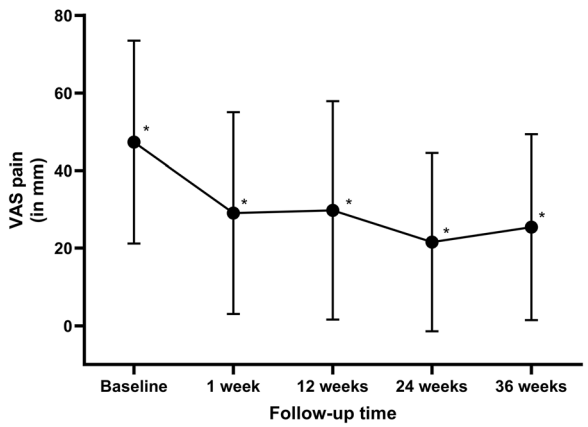

Fig. 2 Evolution of VAS pain score [mm]. Data are presented as mean value, and standard deviation (error bars), *$p < 0.001$ versus baseline. *VAS* Visual Analog Scale

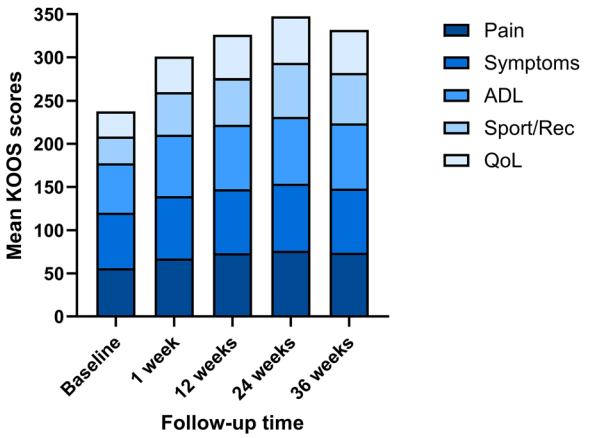

Fig. 3 Summary of mean KOOS scores at the different time points. *ADL* activities of daily living, *QoL* quality of life, *Sport/Rec* sports and recreational activities

Table 2 Subscale KOOS pain from baseline to week 36

KOOS pain [%]	*N*	Mean	SD	Min	Max	Percentiles		
						25th	50th (median)	75th
Baseline	49	56.17	18.83	25.00	97.22	40.28	58.33	72.22
Week 1	49	67.44	17.91	16.67	97.22	55.56	66.67	80.56
Week 12	48	73.50	20.19	27.78	100.00	55.56	79.17	91.67
Week 24	44	76.38	18.32	36.11	100.00	59.03	82.29	90.97
Week 36	45	74.08	23.98	0.00	100.00	54.17	86.11	94.10

Max maximum, *min* minimum, *N* number of patients, *SD* standard deviation

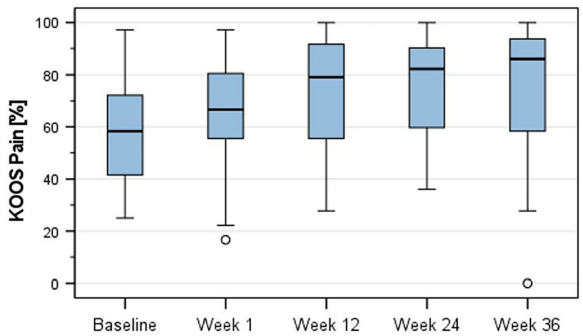

Fig. 4 Subscale KOOS pain from baseline to week 36. Data are presented as median value, and 25th and 75th percentiles, minimum and maximum (error bars), $p < 0.001$ versus baseline

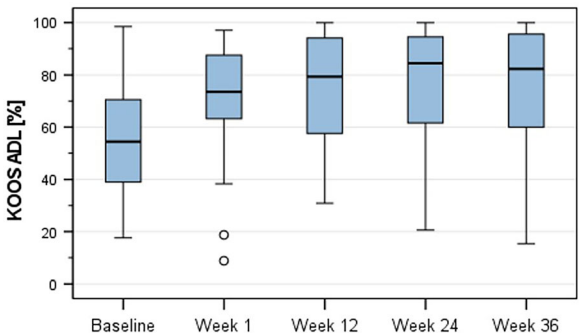

Fig. 5 Subscale KOOS ADL from baseline to week 36. Data are presented as median value, and 25th and 75th percentiles, minimum and maximum (error bars), $p < 0.001$ versus baseline

KOOS Sport and Recreation

The KOOS Sport/Rec increased markedly from a median of 25.0% (mean 30.9% ± 26.7%) at baseline to 72.5% (mean 62.4% ± 29%) at week 24. It remained high with 65.0% (mean 58.1% ± 32%) at week 36 (Table 5).

Table 3 Subscale KOOS ADL from baseline to week 36

KOOS ADL [%]	*N*	Mean	SD	Min	Max	Percentiles		
						25th	50th (median)	75th
Baseline	49	57.40	20.63	17.65	98.53	38.65	54.41	72.06
Week 1	49	71.35	19.88	8.82	97.06	60.37	73.53	87.87
Week 12	48	74.81	20.09	30.88	100.00	57.47	79.41	94.12
Week 24	44	77.61	20.76	20.59	100.00	60.81	84.56	94.78
Week 36	45	75.71	22.40	15.38	100.00	58.91	82.35	95.59

ADL activities of daily living, *Max* maximum, *Min* minimum, *N* number of patients, *SD* standard deviation

Improvement of KOOS Sport/Rec was statistically significant (Wilcoxon matched pairs test, $p = 0.001$ at week 1 and $p < 0.001$ at weeks 12, 24, and 36).

KOOS Quality of Life

KOOS QoL improved clearly from a median score of 25.0% (mean 29.2% ± 18.3%) at baseline to a median score of 43.8% (mean > 50%) at weeks 12, 24, and 36 (Table 6).

Improvement of KOOS QoL was statistically significant (Wilcoxon matched pairs test, $p < 0.001$ each).

KOOS Improvement/Worsening

An increase in score values compared to baseline, regardless of the extent, was interpreted as improvement of the KOOS subscales. A summary of the values of the five subcategories, pain, symptoms, ADL, Sport/Rec, and QoL is provided in Table 7.

An improvement in all KOOS subscales was noted in more than 70% of patients at 6 months, specifically 75.0%, 70.5%, 84.1%, 88.2%, and 84.1% in KOOS pain, symptoms, ADL, Sport/Rec, and QoL, respectively. Improvement in KOOS pain continued to 9 months with 80.0% of patients improved compared to baseline.

Responder Analysis

The responder rate was calculated at week 24 follow-up visit according to the OMERACT-OARSI proposed set of responder criteria [12]. The therapy response was calculated for each patient and for each performance criterion. Six months after treatment, 32 patients (72.7%) could be classified as responder and 12 patients (27.3%) as non-responder. As a result of missing data, no response status could be calculated for five patients.

Patient's Global Assessment and Patient's and Investigator's Satisfaction Scales

The PGA was based on a question asked by the physician on how the patient was affected by their knee OA and how the patient would rate their condition on the day of the visit. The answer was scored on a scale of 0 to 10, where 0 is "very good condition" and 10 is "very poor condition".

Overall, the patients' condition had significantly improved. An improvement was noted in at least 70% of patients at all time points compared to baseline. At week 1 follow-up, 69.4% of subjects reported subjective improvement; at week 24, the proportion had risen to 84.1%. PGA scores at each follow-up time point were statistically significant compared to baseline (Wilcoxon's matched pairs test, $p < 0.001$).

There was a good match with patient's satisfaction, since more than 75% of patients stated they were either "satisfied" or "very satisfied" with the treatment.

Satisfaction with the treatment was expressed by the investigator for at least 65% of patients and the condition of most patients had improved according to the investigator.

Table 4 Subscale KOOS symptoms from baseline to week 36

KOOS Symptoms [%]	*N*	Mean	SD	Min	Max	Percentiles		
						25th	50th (median)	75th
Baseline	49	63.99	19.46	21.43	100.00	50.00	64.29	78.57
Week 1	49	71.87	19.71	25.00	100.00	55.36	78.57	89.29
Week 12	48	73.88	20.04	21.43	100.00	57.14	76.79	92.86
Week 24	44	77.35	21.09	25.00	100.00	60.71	89.29	92.86
Week 36	45	73.97	23.10	10.71	100.00	57.14	82.14	92.86

Max maximum, *Min* minimum, *N* number of patients, *SD* standard deviation

Table 5 Subscale KOOS Sport/Rec from baseline to week 36

KOOS Sport/Rec [%]	*N*	Mean	SD	Min	Max	Percentiles		
						25th	50th (median)	75th
Baseline	44	30.91	26.74	0.00	90.00	6.25	25.00	48.75
Week 1	41	49.34	27.34	0.00	100.00	25.00	50.00	70.00
Week 12	40	53.91	29.53	0.00	100.00	30.00	55.00	75.00
Week 24	34	62.39	29.02	0.00	100.00	43.75	72.50	85.63
Week 36	38	58.07	31.96	0.00	100.00	28.75	65.00	85.00

Max maximum, *Min* minimum, *N* number of patients, *SD* standard deviation, *Sport/Rec* sport and recreation

Table 6 Subscale KOOS QoL from baseline to week 36

KOOS QoL [%]	*N*	Mean	SD	Min	Max	Percentiles		
						25th	50th (median)	75th
Baseline	49	29.21	18.33	0.00	75.00	18.75	25.00	43.75
Week 1	49	40.94	20.61	0.00	87.50	25.00	37.50	56.25
Week 12	48	50.13	22.68	6.25	100.00	31.25	43.75	68.75
Week 24	44	53.84	25.94	18.75	100.00	31.25	43.75	81.25
Week 36	45	50.00	25.70	0.00	100.00	31.25	43.75	71.88

Max maximum, *Min* minimum, *N* number of patients, *QoL* quality of life, *SD* standard deviation

DISCUSSION

The present study was a prospective, observational, single-center, case cohort PMCF study in a real-life setting to confirm the efficacy and safety of a single injection of the CM-chitosan fluid implant, KioMedine^{vs}one, for treating symptomatic knee OA. Therefore, treatment as well as all evaluation measurements corresponded to routine procedure and the medical standard and CM-chitosan was used in accordance with the terms of the marketing approval and the IFU.

CM-chitosan differs from HA and natural chitosan. CM-chitosan is unique and derived from chitosan, the natural polysaccharide, and optimized with potent intrinsic capabilities such as lubrication, free radical scavenging, and hydration. It is biodegradable, non-toxic, and chemically modifiable. These properties of the CM-chitosan derivative present in CM-chitosan have been demonstrated in several in vitro and ex vivo models; preclinical results revealed higher coefficient of friction reduction, a significantly better recovery of joint motion, and a significantly higher free radical scavenging capacity than single-injection, cross-linked HA formulations [10].

The effectiveness of CM-chitosan was confirmed using subjective and objective variables for evaluation by the treating physicians as well as by the treated patients. The included subjects represent the target population very well in terms of age, BMI, and concomitant diseases. A major objective of this evaluation—reduction in pain—is considered especially clinically important since pain affects the QoL of patients with OA to a high degree and long-term treatment of pain is often associated with adverse effects [13]. This study demonstrated that a single intra-

Table 7 Assessment overview on improvement, worsening, and no change over time of all five subscales, given as absolute (*N*) and percentage (%) frequency distribution

	Week 1		Week 12		Week 24		Week 36	
	N	%	*N*	%	*N*	%	*N*	%
Pain								
Improvement	35	71.4	35	72.9	33	75.0	36	80.0
Worsening	12	24.5	10	20.8	7	15.9	9	20.0
No change	2	4.1	3	6.3	4	9.1	0	0.0
Sum	49		48		44		45	
Symptoms								
Improvement	29	59.2	28	58.3	31	70.5	30	66.7
Worsening	15	30.6	14	29.2	11	25.0	11	24.4
No change	5	10.2	6	12.5	2	4.5	4	8.9
Sum	49		48		44		45	
ADL								
Improvement	36	73.5	36	75.0	37	84.1	35	77.8
Worsening	13	26.5	11	22.9	7	15.9	9	20.0
No change	0	0.0	1	2.1	0	0.0	1	2.2
Sum	49		48		44		45	
Sport/Rec								
Improvement	26	63.4	27	71.1	30	88.2	26	70.3
Worsening	8	19.5	8	21.1	4	11.8	9	24.3
No change	7	17.1	3	7.9	0	0.0	2	5.4
Sum	41		38		34		37	
QoL								
Improvement	30	61.2	35	72.9	37	84.1	35	77.8
Worsening	10	20.4	6	12.5	4	9.1	8	17.8
No change	9	18.4	7	14.6	3	6.8	2	4.4
Sum	49		48		44		45	

ADL activities of daily living, *QoL* quality of life, *Sport/Rec* sports and recreational activities

articular injection of CM-chitosan results in a statistically significant and clinically relevant reduction of knee pain in the long term. Pain, measured on a VAS scale, decreased significantly ($p \leq 0.001$) from a median value of 49.0 mm at baseline to a median value of 11.0 mm at week 24 and 18.0 mm after 9 months, showing a 77.6% and 63.3% reduction of pain at 6 and 9 months, respectively.

This relative change in baseline pain of more than 50% is considered a substantial clinically important difference according to the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) working group [14, 15].

This treatment also provided a statistically significant improvement in all KOOS subscales (pain, ADL, symptoms, Sport/Rec, and QoL), also showing efficacy for 9 months. The KOOS pain median score kept increasing steadily over time to attain a value of 86.11, indicating that pain relief could be maintained in the very long term. The 75th percentile also indicates that 25% of the patients had a high KOOS pain score of at least 94.10 at 9 months. Similar results were observed for the other KOOS scales such as KOOS ADL, with a median of 82.35 and a 75th percentile value of 95.59. At the 9-month follow-up in this study, the relative change of 27.78, 27.94, and 18.75 in median scores of KOOS pain, ADL, and QoL, respectively, were above the highest values of what could be tentatively considered as the minimal clinically important changes in the literature for non-operative treatments [16, 17]. The treatment responder rate was calculated at the month 6 follow-up visit according to the OMERACT-OARSI proposed set of responder criteria and was 72.7%.

Overall, there was a good match between patient satisfaction and improvement in patient condition, since more than 75% of patients stated they were "satisfied" or "very satisfied" with the treatment and a statistically significant improvement was noted in at least 70% of patients at all time points compared to baseline.

It should also be noted that the median BMI of the patients included was 30.2 kg/m^2, meaning that more than half of them were obese, a population of patients known to be significantly associated with traditional visco-supplementation failure [18]. A post hoc analysis involving this particular refractory OA subgroup is therefore of interest, exploring efficacy of CM-chitosan in this challenging-to-treat population, as also described by the EUROVISCO group [9].

These results confirm those from the first-in-human study (APROOVE) that showed a significant, clinically relevant, and sustained reduction in pain over the observation period of 24 weeks. Furthermore, in APROOVE, more than 80% of patients were satisfied with the treatment at 13 weeks and 24 weeks [11]. A reduction in pain combined with reduced joint stiffness and improved daily activities are critical to improve the rehabilitation process in patients for which CM-chitosan seemed to work effectively.

There was no new signal related to the safety of the injection as compared to the APROOVE study [11], which described treatment-related events of arthralgia, effusion, swelling, and cases of synovitis. All adverse events were transient, post-injection, self-limited local effects. The affected patients responded very well to cooling, rest, analgesics, or non-steroidal anti-inflammatory drugs (NSAIDs).

The aim of the study was to confirm the efficacy of CM-chitosan under routine conditions, i.e., patient selection was only slightly restricted primarily to comply with the IFU and there was no constraint in concomitant medication or therapies. Since there was no restriction in the concomitant treatments, positive overlapping treatment effects cannot be completely excluded, and the results have to be ranked accordingly.

As this study included only patients for whom their physician recommended treatment with CM-chitosan, there was no control group and therefore no direct comparison of treatment with CM-chitosan versus hyaluronic acid or other alternatives was done and no thorough analysis can be performed at this stage for both the patient-reported outcome and the physician assessments.

Data collected in this study are generalizable since significant attention and efforts were made to ensure that data quality was high. The recorded parameters were valid, reliable, and robust and the assessments performed, in addition to the duration of the study phase, were considered appropriate to meet the objectives of this evaluation.

A randomized controlled trial is currently being conducted to investigate whether CM-chitosan remains effective up to 12 months post-injection.

CONCLUSION

The goal of this study was to collect data reflecting the impact of treatment with CM-chitosan on patients' symptomatology, satisfaction with treatment, and QoL in routine clinical practice. KioMedine^{vs}one, a new product class for knee OA based on CM-chitosan, showed a rapid onset of pain relief after 1 week and it was also confirmed to last for a at least 9 months. Finally, there was no finding in this study that points to a new safety signal and the safety profile appears compatible with current IFU and existing safety data. In the real-world setting, treatment with CM-chitosan, with its unique protection as well as lubrication and hydration capacities, was effective to reduce pain and improve physical function and global condition in patients with knee OA, measured and evaluated via patient-reported outcome questionnaires such as VAS and KOOS score.

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Data Availability. The datasets generated or analyzed during the current study are available upon reasonable request in writing to the corresponding author.

Declarations

Conflict of Interest. Nicolas Portelange, Mickael Chausson and Wim Weyenberg are employees for KiOmed Pharma, Herstal, Belgium. Nils Lynen and Christoph Eichhorn have nothing to disclose.

Ethical Approval. This study was carried out in accordance with ethical principles that have their origin in the Declaration of Helsinki adopted by the 18th World Medical Assembly in Helsinki (Finland) since 1964, as last amended by the World Medical Assembly. Furthermore, the study was carried out in accordance with the principles of good clinical practice (GCP) outlined in ISO 14155:2020 "Clinical investigation of medical devices for human subjects—Good Clinical Practice". The study started following a positive advisory opinion of the responsible ethics committee (reference "2020402", Ethikkommission der Äerztekammer.

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