

# Effect of a Single-Shot of a High-Density Viscoelastic Solution of Hyaluronic Acid in Patients with Symptomatic Primary Knee Osteoarthritis: The No-Dolor Study

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## Research Article

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# Abstract

## Background

Pronolis®HD mono 2.5% is a novel, one-shot, high-density sterile viscoelastic solution, recently available in Spain, which contains a high amount of intermediate molecular weight hyaluronic acid (HA), highly concentrated (120 mg in 4.8 mL solution: 2.5%). The objective of the study was to analyze the efficacy and safety of this treatment in symptomatic primary knee osteoarthritis (OA).

## Methods

This observational, prospective, multicenter, single-cohort study involved 166 patients with knee OA treated with a single-shot of Pronolis®HD mono 2.5% and followed up as many as 24 weeks.

## Results

Compared with baseline, the score of the Western Ontario and McMaster Universities Arthritis Osteoarthritis Index (WOMAC) pain subscale significantly reduced at the 12-week visit (primary endpoint, median: 9 interquartile range [IQR]: 7-11 versus median: 4; IQR: 2-6). The percentage of patients achieving >50% improvement in the pain subscale increased progressively from 37.9% (at 2 weeks) to 66.0% (at 24 weeks). Similarly, WOMAC scores for pain on movement, stiffness subscale, and functional capacity subscale showed significant reductions at the 12-week visit which were maintained up to the 24-week visit. The EuroQol visual analog scale score significantly increased after 12 weeks (median: 60 versus 70). The need for rescue medication (analgesics/nonsteroidal anti-inflammatory drugs) also significantly decreased in all post-injection visits. Three patients (1.6%) reported local adverse events (joint swelling) of mild intensity.

## Conclusions

In conclusion, a single intra-articular injection of the high-density viscoelastic gel of HA is effective and safe for the relief of symptoms in patients with knee OA.

## Trial registration:

ClinicalTrial# NCT04196764

## Background

Knee osteoarthritis (OA) is one of the most frequent causes of disability in elderly individuals [1]. The prevalence of symptomatic knee OA among men and women aged 60 or over is approximately 10% and 13%, respectively. However, the prevalence is increasing along with the raising of older and obese populations [2]. Knee OA is characterized by diverse pathophysiological changes, including decreased synovial fluid elastoviscosity and hyaluronan concentration [3]. The treatment of knee OA is only focused on the control of symptoms, especially pain [4]. Treatment guidelines recommend the use of nonoperative treatments before surgery [2]. The first approach for the relief of symptoms typically involves conservative therapies including exercise, physical therapy, and weight loss [2]. If it fails, analgesics (nonsteroidal anti-inflammatory drugs - NSAIDs -, or acetaminophen), symptomatic slow action drugs for osteoarthritis (SYSADOA; such as glucosamine, chondroitin), or intra-articular therapies (corticosteroids, hyaluronic acid HA-, platelet-rich plasma) are commonly prescribed [5]. If none of those treatments work, joint replacement would be the final solution. Unfortunately, to date, there are no approved disease-modifying drugs for OA [6]. Although effective for pain relief, analgesics and NSAIDs are accompanied by adverse effects (AEs) [7]. A summary of different treatments for knee osteoarthritis is provided in Fig. 1.

Regarding intra-articular injections with HA, they are getting attraction for the treatment of knee OA. Diverse randomized clinical trials have demonstrated the efficacy and safety of HA for the relief of symptoms in knee OA [8–10]. Bellamy et al., [8] in a Cochrane systematic review, evaluated the effects of diverse HA products for the treatment of knee OA in 76 randomized, controlled clinical trials. Pooled analyses versus placebo highlighted the efficacy of HA injections on pain, patient global assessment, and function after the injection, especially at the 5 to 13-week. Overall, the efficacy of HA injections was comparable with NSAIDs; however, the effect of HA injections was more durable than intra-articular corticosteroids. The HAs are frequently classified according to their molecular weight (MW): low (500–730 kDa), intermediate (800–2,000 kDa), or high (2,000–6,000 kDa) [11]. High-MWHAs have been associated with greater anti-inflammatory and proteoglycan synthesis effects, viscoelasticity maintenance, and joint lubrication. Comparative studies have revealed a greater improvement for pain relief with high-MWHAs than low-MWHAs and intra-articular placebo [12, 13]. In addition, high-MWHAs have been correlated to a higher percentage of AEs. Accordingly, injection site flare-ups with swelling, pain, and increased warmth [12, 14]. Overall, to minimize the risk of AEs, there is still a need for optimizing the HA treatment toward being single-shot and having a longer duration of action in the same time.

Pronolis®HD mono 2.5% (Procare Health, Spain) is a novel, one-shot, high-density sterile viscoelastic solution, recently marketed in Spain, which contains a high amount of intermediate-MWHA, highly concentrated (120 mg in 4.8 mL solution: 2.5%) [15–17].

The objective of the present study was to analyze the efficacy and safety of single-shot of this novel high-density viscoelastic gel of HA for the treatment of symptomatic primary knee OA.

## Methods

## Study design

This observational, prospective, multicenter, single-cohort study involved patients with knee OA who initiated treatment with Pronolis<sup>®</sup>HD mono 2.5% following manufacturer instructions (No-dolor study; ClinicalTrial# NCT04196764). A total of 29 healthcare centers from Spain (including Services of Rheumatology, Traumatology, Sports Medicine, and Pain Medicine) participated in the study. Main inclusion criteria were: adult men and women (aged over 18); with the diagnosis of primary knee OA, according to American College of Rheumatology criteria [18]; having performed a radiographic assessment of knee OA within the previous 18 months to study inclusion; showing a visual analog scale (VAS) score for pain  $\geq 4$  (out of 10) at study inclusion; having started treatment with Pronolis<sup>®</sup> HD mono 2.5% (prescribed as part of routine clinical practice); and signing informed consent. Main exclusion criteria were: patients with intolerance to HA; hypersensitivity to intra-articular injections; infection in the knee joint; skin disorders or infections, either at the injection site or systemic; coagulation disorders that contraindicate the injection; prescription of intra-articular injections in both knees; diagnosis of autoimmune rheumatic diseases, connective tissue conditions, or microcrystalline disorders; and history of traumas in the knee joint; previous surgery in the knee joint. The complete list of inclusion and exclusion criteria is shown in Supplementary Table 1. The treatment consisted of a single-shot of Pronolis<sup>®</sup>HD mono 2.5% [14].

The study was approved by the Ethics Committee of the Hospital del Mar in Barcelona (CEIC-Parc de Salut Mar) and have been performed in accordance with the Declaration of Helsinki. Patients signed informed consent to participate in the study.

## Endpoints and variables

Patients were followed up for as many as 24 weeks. Visits were scheduled after 2, 4, 12, and 24 weeks of the injection. Visits were undergone in-person (face-to-face) at the hospital, except the 2-week visit that consisted of a phone call. The primary endpoint included the change of scores in the pain subscale from the Spanish version of the Western Ontario and McMaster Universities Arthritis Osteoarthritis Index (WOMAC) at the 12-week visit, compared with baseline. Secondary endpoints comprised the evaluation of pain (item evaluating pain on movement), joint stiffness, and functional capacity (by WOMAC subscales), the quality of life of patients, the need for rescue medication (analgesics/NSAIDs), the satisfaction with the treatment, and the development of AEs during the study period. The patient's quality of life was determined at the 12-week visit by using the EuroQoL-5D-5L (EQ-5D-5L) questionnaire [19]. The EQ-VAS is scored between 0 (the worst patient's self-rated health) and 100 (the best). Satisfaction with the treatment was analyzed at all post-injection visits with a 1-5 Likert scale, where 1 represented "very satisfied" and 5 indicated "very unsatisfied".

## Determination of the sample size

The primary objective included score changes in the WOMAC pain subscale, from baseline. Studies by Zhang et al. [20] and Pavelka et al. [21] assumed 20 mm and 21 mm as a standard deviation (SD) of

change, respectively, on a 100 mm VAS. Furthermore, Raynauld et al. [22] reported a mean change of -4.4 after 12 months of treatment, compared to baseline, using a Likert scale, and an SD of 3.9 (equivalent to 19.4 on a 100 mm VAS). Calculations estimated that a sample size of 270 patients could provide a precision of  $\pm 2.4$  mm for the change, with a 95% confidence interval (95%CI), and assuming an SD of 20 mm. Considering 10% of the loss to follow-up, the estimated number of patients to be recruited was 300. These estimations were carried out with PASS software (2011 version). Given the lack of available participants, the period of recruitment was extended from 8 (initially planned in the protocol) to 22 months.

## Statistical analysis

Categorical variables were expressed as absolute and relative frequencies; whereas continuous ones with the mean, SD, median, 95%CI, or interquartile range (IQR, i.e. percentile 25-75). Comparisons in variables between baseline and post-injection visits were performed using the paired-samples Student's t-test or Wilcoxon test, when appropriate. Statistical significance was established when  $p < 0.05$ . All statistical procedures were carried out with SAS 9.4 software.

## Results

### Patient Characteristics At Baseline

A total of 189 patients were initially recruited; however, 23 were not evaluable for the primary objective (Fig. 2). Patients were predominantly females (75.9% of total) and aged over 60 years (66.9%). Baseline sociodemographic and clinical characteristics of patients are shown in Table 1. Their mean age was 63.2 years (SD: 11.1). Considering the body mass index, 49.3% were overweight ( $25 < \text{kg/m}^2$ ), 34.5% were obese ( $\geq 30 \text{ kg/m}^2$ ), and 16.2% were normal weight ( $< 25 \text{ kg/m}^2$ ). The mean time from the diagnosis of knee OA to the current HA treatment was 7.2 years (SD: 7.5). Regarding pain, 12.0% of patients considered to control adequately the pain, whereas 79.5% indicated that the treatment, followed to that time (baseline), was not enough for controlling the pain and living a normal life.

Table 1  
Baseline sociodemographic and clinical characteristics of patients

	<b>Total patients (N=166)</b>
Age, mean years (SD)	63.2 (11.1)
Gender, n (%)	
Male	40 (24.1)
Female	126 (75.9)
Body mass index, mean Kg/m <sup>2</sup> (SD)	28.6 (4.3)
Time from OA diagnosis to treatment, mean years (SD)	7.2 (7.5)
Type of primary knee OA, n (%) *	
Patellofemoral	70 (42.4)
Femorotibial	95 (57.6)
Radiological grading (Kellgren-Lawrence classification), n (%)	
Grade 2 (Mild)	39 (23.5)
Grade 3 (Moderate)	113 (68.1)
Grade 4 (Severe)	14 (8.4)
Previous intra-articular injections for knee OA, n (%)	
No	103 (62.0)
Yes	63 (38.0)
Type of injection, n (%)	
Corticosteroids	50 (79.4)
HA	23 (36.5)
Time since last corticosteroid injection, mean months (SD)	38.8 (48.1)
Time since last HA injection, mean months (SD)	26.4 (23.4)
SD, standard deviation; OA, osteoarthritis; HA, hyaluronic acid	
* Information from one patient was missing	

## Efficacy Of The Ha Injection: Womac Results

Compared with baseline, the score of the WOMAC pain subscale significantly reduced at the 12-week visit (primary endpoint, median: 9; IQR: 7-11 versus median: 4; IQR: 2-6;  $p < 0.001$ ; Table 2 and Fig. 3). The mean relative reduction was 48.2% (95%CI: 41.4-55.0). The percentage of patients achieving >50% improvement in the pain subscale (with respect to baseline) increased from the 2-week (37.9%) to the 4-week (52.4%), 12-week (61.4%), and 24-week visits (66.0%; Supplementary Fig. 1). Similarly, scores for pain on movement item (median: 2; IQR: 1-2 versus median: 1; IQR: 0-1), stiffness subscale (median: 4; IQR: 3-5 versus median: 2; IQR: 1-3), and functional capacity subscale (median: 31; IQR: 24-37 versus median: 15; IQR: 7-22) showed significant reductions at the 12-week visit ( $p < 0.001$  in all; Fig. 3). Mean relative reductions were 47.1% (95%CI: 38.9-55.4), 45.9% (95%CI: 39.0-52.9), and 42.4% (95%CI: 36.0-48.9), respectively. A total of 61.5% of patients (for pain on movement item), 74.7% (for joint stiffness subscale), and 84.8% (for functional capacity subscale) achieved an improvement in WOMAC scores at the 12-week visit, compared with baseline. Furthermore, the clinical benefit in WOMAC pain, stiffness, and functional capacity subscales, and pain on movement item was maintained up to the 24-week visit (Table 2). The complete information about efficacy outcomes, relative reductions, and change in WOMAC results at all post-injection visits compared with baseline are shown in Supplementary Tables 2-4.

Table 2  
Efficacy of the treatment at the 12-and 24-week visits

	Baseline	12-week visit	p *	24-week visit	p *
N	166	166		150	
WOMAC questionnaire					
Pain subscale					
Median score (IQR)	9 (7-11)	4 (2-6)	<0.001	3 (1-5)	<0.001
Mean (SD)	9.0 (3.5)	4.3 (3.4)		4.0 (3.8)	
Pain on movement					
Median score (IQR)	2 (1-2)	1 (0-1)	<0.001	1 (0-1)	<0.001
Mean (SD)	1.7 (1.0)	0.8 (0.8)		0.8 (0.9)	
Stiffness subscale					
Median score (IQR)	4 (3-5)	2 (1-3)	<0.001	1 (0-2)	<0.001
Mean (SD)	3.7 (1.7)	1.9 (1.4)		1.7 (1.7)	
Functional capacity subscale					
Median score (IQR)	31 (24-37)	15 (7-22)	<0.001	13 (5-23)	<0.001
Mean (SD)	31.0 (12.7)	16.3 (11.8)		15.1 (12.5)	
EQ-5D-5L					
Mobility					
Median score (IQR)	3 (2-3)	2 (1-3)	<0.001	NA	NA
Mean (SD)	2.8 (0.9)	2.1 (0.8)		NA	

WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; IQR, interquartile range (percentile 25-75); SD, standard deviation; VAS, visual analogue scale; NSAIDs, nonsteroidal anti-inflammatory drugs

\* If not indicated otherwise, the statistical analysis was Wilcoxon test, \*\* McNemar test



	Baseline	12-week visit	p *	24-week visit	p *
Self-care					
Median score (IQR)	2 (1-3)	1 (1-2)	<0.001	NA	NA
Mean (SD)	2.2 (1.1)	1.6 (0.8)		NA	
Usual activities					
Median score (IQR)	3 (2-3)	2 (1-2)	<0.001	NA	NA
Mean (SD)	2.7 (0.9)	2.0 (0.9)		NA	
Pain/discomfort					
Median score (IQR)	3 (3-4)	2 (2-3)	<0.001	NA	NA
Mean (SD)	3.0 (0.8)	2.2 (0.8)		NA	
Anxiety/depression					
Median score (IQR)	2 (1-3)	1 (1-2)	<0.001	NA	NA
Mean (SD)	2.1 (1.1)	1.5 (0.8)		NA	
EQ VAS					
Median score (IQR)	60 (40-75)	70 (60-85)	<0.001	NA	NA
Mean (SD)	55.4 (22.4)	69.2 (19.7)		NA	
Consumption of analgesics/NSAIDs as rescue medication, n (%) patients	120 (72.3)	63 (38.0)	<0.001**	58 (38.7)	<0.001**
WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; IQR, interquartile range (percentile 25-75); SD, standard deviation; VAS, visual analogue scale; NSAIDs, nonsteroidal anti-inflammatory drugs					
* If not indicated otherwise, the statistical analysis was Wilcoxon test, ** McNemar test					

## Quality Of Life, Rescue Medication And Patient Satisfaction Results

Scores from all dimensions in EQ-5D-5L significantly reduced from baseline to the 12-week visit: mobility (median: 3, IQR: 2-3 at baseline versus median: 2, IQR: 1-3 at the 12-week visit;  $p < 0.001$ ), self-care (median: 2, IQR: 1-3 versus median: 1, IQR: 1-2;  $p < 0.001$ ), usual activities (median: 3, IQR: 2-3 versus median: 2, IQR: 1-2;  $p < 0.001$ ), pain/discomfort (median: 3, IQR: 3-4 versus median: 2, IQR: 2-3;  $p < 0.001$ ), and anxiety/depression (median: 2, IQR: 1-3 versus median: 1, IQR: 1-2;  $p < 0.001$ ). Similarly, the EQ-VAS score significantly increased after 12 weeks (median: 60, IQR: 40-75 versus median: 70, IQR: 60-85;  $p < 0.001$ ). The need for rescue medication (analgesics/NSAIDs) also significantly decreased in all post-injection visits ( $p = 0.007$  at the 2-week and  $p < 0.001$  at the remaining visits), compared with baseline (Fig. 4). Of patients, 56.6% were very satisfied or satisfied with the treatment at the 2-week visit. This percentage increased to 64.5%, 79.5%, and 82.7% at the 4-, 12-, and 24-week visits, respectively. Median scores for satisfaction were 2 (IQR: 2-3) in all post-injection visits.

## The safety profile of the treatment

Three patients (1.6%) reported 4 local AEs (joint swelling,  $n = 3$ ; and ligament sprain,  $n = 1$ ). None of the AEs was serious, and all of them were mild in severity. A total of 150 patients (90.4%) completed the study; however, 16 did not so. Loss to follow-up was the reason for early withdrawal in 6 out of 7 patients with available information (85.7%).

## Discussion

Our study, involving a novel high-density viscoelastic gel of HA, has demonstrated its efficacy in terms of pain relief for patients with symptomatic knee OA. This significant clinical benefit was indeed achieved early (2 weeks after the injection) and maintained for, at least, 24 weeks. In general, clinical improvement has been established with a minimum difference of 20% in efficacy outcomes [23], like scores in the WOMAC questionnaire. Our results are in agreement with the literature implicating diverse HA products [8–10, 12, 24, 25]. For instance, Berenbaum et al., [24] in a randomized, double-blind, controlled trial compared the efficacy of 3-weekly injections between an intermediate- versus a low-MWHA in 426 patients with symptomatic knee OA. The decrease in WOMAC pain score at the 24-week (after the end of treatment) was significantly greater with the intermediate-MWHA preparation (mean: 22.9 mm, SD: 1.4) than the low one (mean: 18.4, SD: 1.5 mm). Moreover, the proportion of responders (OMERACT-OARSI criteria) with the intermediate-MWHA was also significantly higher (73% versus 58%). The percentage of patients reporting AEs was similar in both groups (35.2% versus 33.2%). Raman et al., [25] in a prospective, randomized, clinical trial compared the effectiveness of a high- versus low-MWHA in 392 patients with knee OA. Compared with baseline, scores in the WOMAC pain subscale at the 24-week post-injection visit were significantly lower with the high-MWHA (mean: 9.2 versus 5.1) than with the low one (mean: 8.8 versus 8.3). Nevertheless, the number of patients suffering from treatment-related AEs was higher with the high-MWHA ( $n = 39$ ) than the low one ( $n = 30$ ). In fact, one patient receiving the high-MWHA experienced a serious AE (pseudo-sepsis in the knee) and required hospitalization [25]. Our study also revealed the efficacy of the high-density viscoelastic gel of HA regarding pain on movement, joint

stiffness, functional capacity, and quality of life, in agreement with previous studies [8–10, 12, 22]. Raynauld et al. [22], in a prospective, randomized, multicenter study compared the effectiveness of a high-MWHA product versus conventional care in 255 patients with knee OA. Changes at 12-month post-injections were significantly greater for the high-MWHA in WOMAC pain score (-38.4% versus -13.3% with conventional care), stiffness (-34.7% versus -10.4%), and physical function (-31.4% versus -14.5%). Nonetheless, the percentage of patients experiencing AEs was numerically greater with high-MWHA (96%) than conventional care (90%).

Overall, the efficacy of high-MWHA has been demonstrated to be superior to intermediate- and low-MWHA. Altman et al., [12] in a meta-analysis determined the efficacy of HA products according to their MW in 11 randomized clinical trials and 2,094 patients. Pooled efficacy results revealed a greater pain relief for high-MWHA (effect size: -0.52, 95%CI: -0.56 to -0.48) than intermediate- (effect size: -0.31, 95%CI: -0.42 to -0.20) and low-MWHA (effect size: -0.18, 95%CI: -0.19 to -0.17). By contrast, the percentage of AEs is also higher in products with high-MWHA [24, 25]. Reichenbach et al., [26] in a systematic review and meta-analysis, revealed a double risk for local AEs and post-injection flares with high-MW, cross-linked HA formulations than with intermediate- or low-MWHA preparations. In addition, pseudosceptic reactions (granulomatous inflammation of the synovium) have been reported in few cases, especially with cross-linked formulations of the highest-MWHA [9, 27]. In our study, only mild AEs were reported and were predominantly resolved within few days.

On the other hand, most HA preparations implicate between 3 and 5 injections, nevertheless, there are cross-linked formulations that require a single-shot, delivering the same HA dose as multi-injection preparations. Petterson et al., [28] in a multicenter, double-blind, randomized, placebo-controlled trial demonstrated the superior success rate ( $\geq 50\%$  improvement and  $\geq 20$  mm absolute improvement, concerning baseline, in WOMAC pain subscale at the 26-week) with a 4-mL single HA injection than with saline. The clinically meaningful reduction of pain was evidenced within the 2-week post-injection. Although studies specifically designed are required, single-shots formulations of HA may also contribute to minimizing the risk for the development of AEs.

In our opinion, the notable results obtained in our study, especially the 48% reduction in WOMAC pain subscale, 66.0% of patients achieving more than 50% improvement in pain subscale, the early initiation of the clinical benefit (within 2 weeks), and its maintenance for a long-term period of time (24 weeks, at least), are greater than expected by an intermediate-MWHA preparation. These superior effects might be associated with the high concentration and amount of HA, and thus to the high-density of the viscoelastic gel. In HA-based aqueous solutions, higher concentrations of HA are correlated (linear relationship) with higher densities of the viscoelastic solution [29, 30]. Therefore, it could be hypothesized that high-density viscoelastic gels of HA provide higher efficacy (similar to high-MWHA) while avoiding the higher incidence of AEs. To our knowledge, to date, none of the studies have specifically evaluated the efficacy of HA products considering the density of the viscoelastic gel.

The main limitation of our study was the absence of a control or comparator group. Although the treatment of OA has an important placebo effect [31], and acknowledging that a control group would have strengthened the conclusions, results are in concordance with controlled studies, revealing a superior effect of HA injections. Another limitation was related to the limited sample size of the study (n=166), not fulfilling the estimated one in the protocol (n=300). Despite extending considerably the recruitment period, the availability of patients was insufficient. Yet, results found in our study are in concordance with other HA products [8–10, 12, 24, 25].

## Conclusions

In conclusion, a single intra-articular injection of the high-density viscoelastic gel of HA is effective and safe for the relief of symptoms in patients with knee OA. Further long-term studies, with a larger cohort of patients, and head-to-head non-inferiority analyses are required to corroborate the present results.

## Abbreviations

Hyaluronic acid (HA), Interquartile Range (IQR), Molecular weight (MW), Nonsteroidal anti-inflammatory drugs (NSAIDs), Osteoarthritis (OA), The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

## Declarations

**Ethics approval and consent to participate:** The study was approved by the Ethics Committee of the Hospital del Mar in Barcelona (CEIC-Parc de Salut Mar) and have been performed in accordance with the Declaration of Helsinki. Patients signed informed consent to participate in the study.

**Consent for publication:** Patients gave their consent for publication of the data included in the present study.

**Availability of data and materials:** The dataset(s) supporting the conclusions of this article is(are) included within the article (and its additional file(s)).

**Competing interests:** Authors declare: JC has received financial support from Procure Health for training sessions. DK has received research grants from Procure Health. LT declares no conflict of interest. JM has received financial support from Procure Health for scientific lectures and attending to medical congresses.

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**Authors' contributions:** All authors contributed to the study conception and design, material preparation, data collection and analysis. All authors commented on previous versions of the manuscript and read and approved the final manuscript.

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## Figures

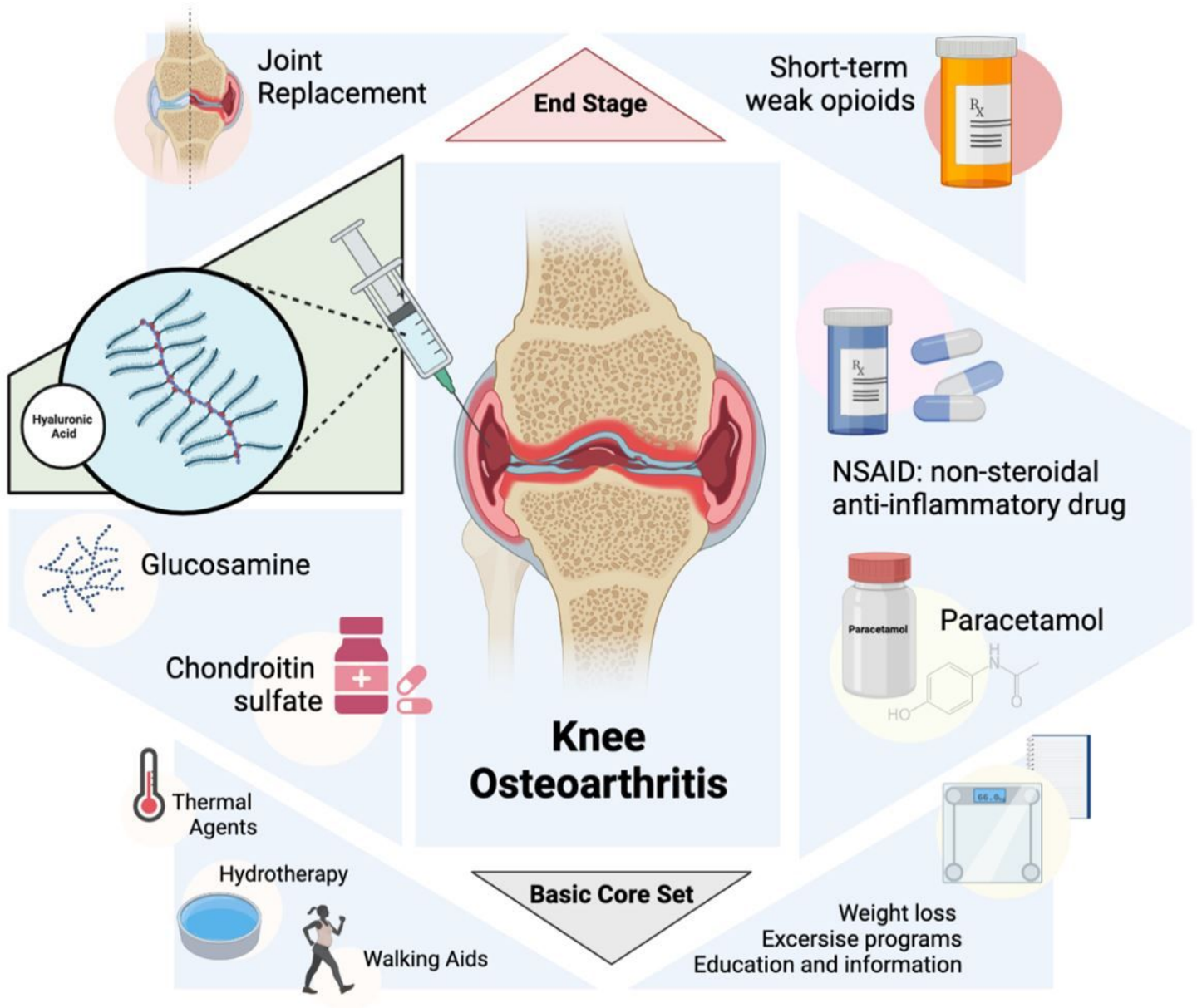
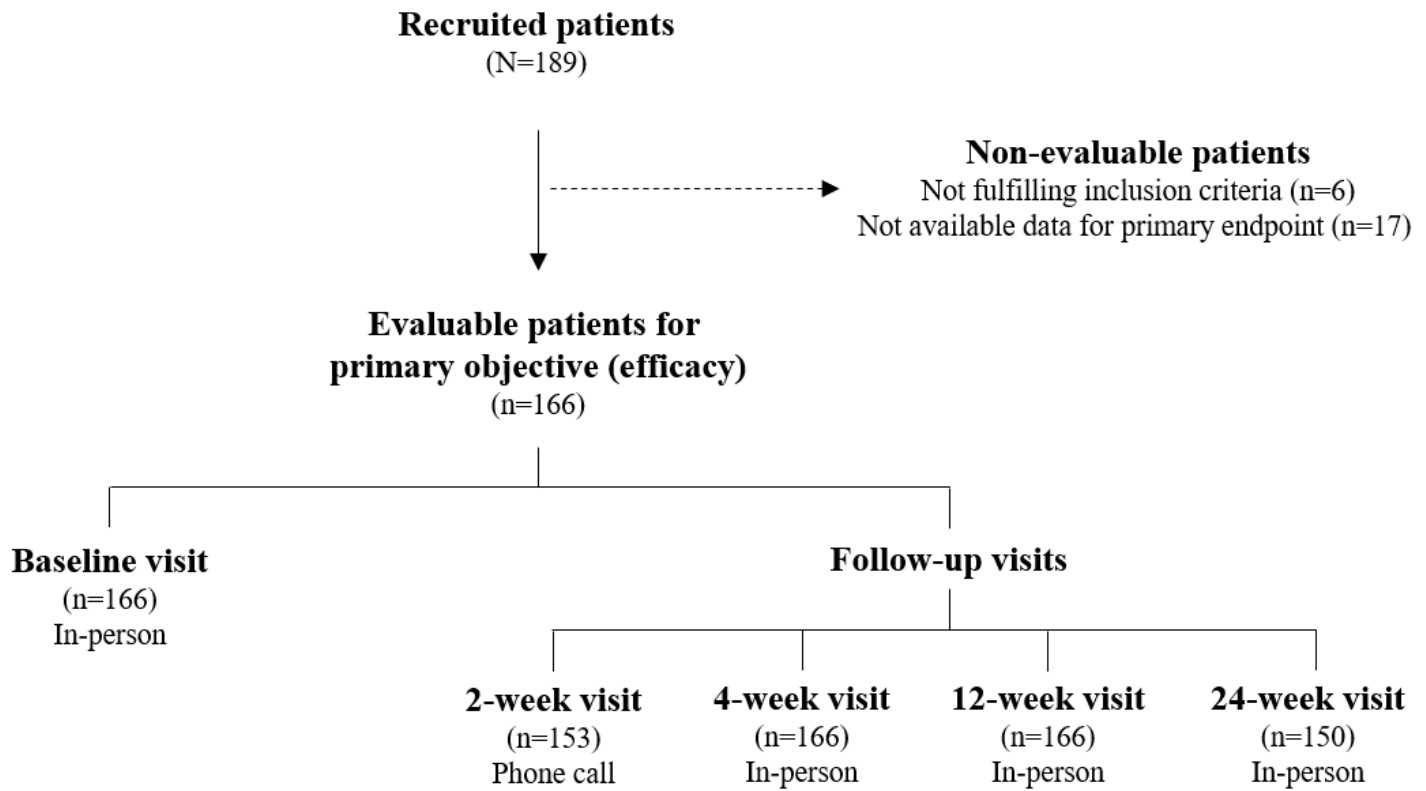


Figure 1

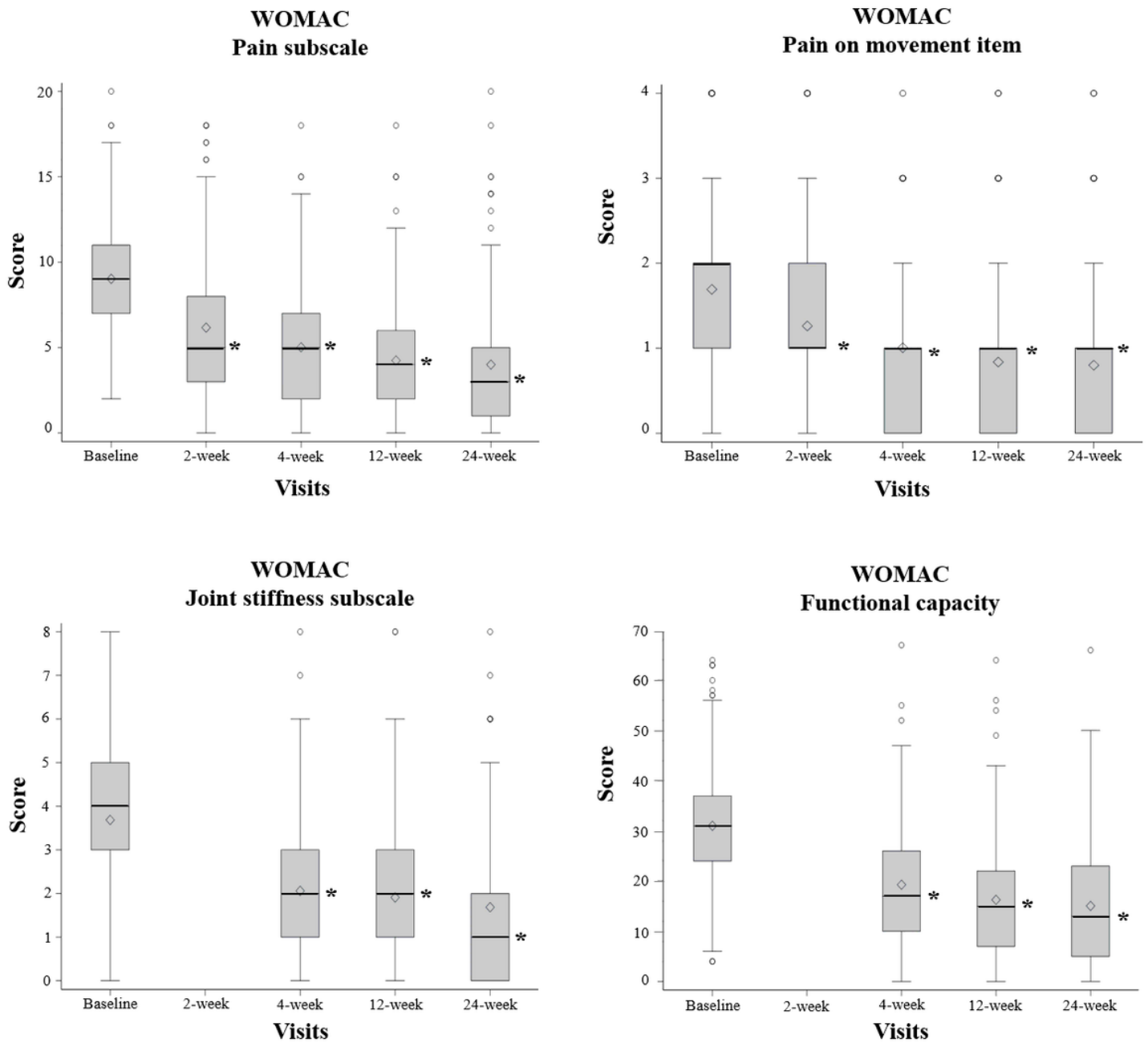
Different available treatments for knee osteoarthritis





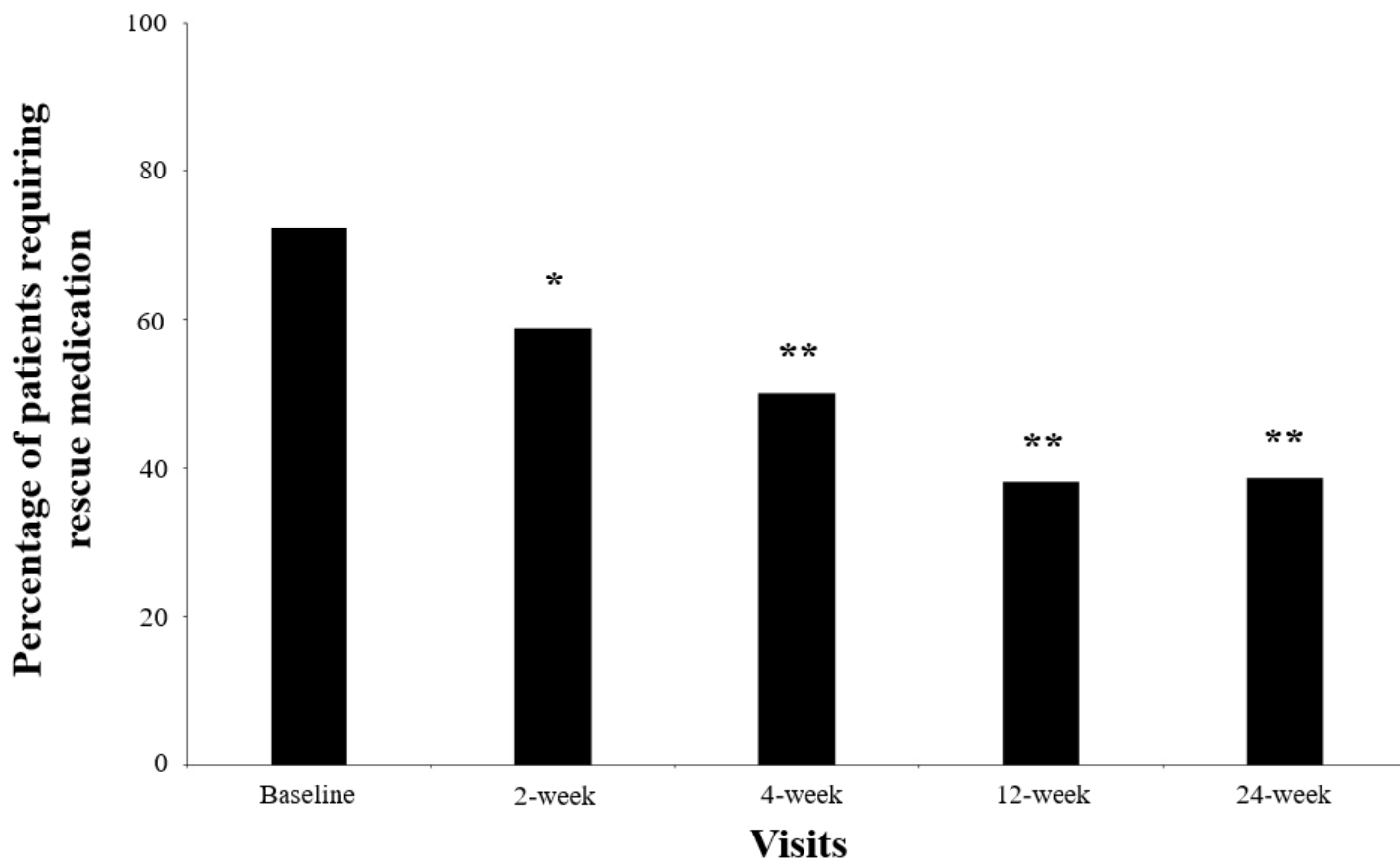
**Figure 2**

Flowchart of patients and design of the study



**Figure 3**

Boxplots showing the evolution of WOMAC scores WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index The rhombus shows the mean value of the respective subscale/item. Asterisks represent statistical differences (Wilcoxon test) found with respect to baseline ( $p < 0.001$ ). Data for WOMAC joint stiffness and functional capacity subscales at the 2-week visit were no collected.



**Figure 4**

Evolution of need for rescue medication during the post-injection visits Statistical significance (McNemar test): \*  $p=0.007$ , \*\*  $p<0.001$

## Supplementary Files

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- [Supplementarymaterial060921.docx](#)