

OSTENIL PLUS BOOK OF EVIDENCE

Published clinical data in osteoarthritis from 1995 to January 2023



Introduction

Osteoarthritis is the most common joint disease, especially in middle-aged and elderly people.¹ In patients suffering from this disease, the concentration and the quality of the synovial fluid is reduced.² Viscosupplementation with exogenous hyaluronic acid aims to improve the viscoelastic properties of the synovial fluid and restore the mechanical properties of the cartilage.³ Ostenil Plus has been developed to complement synovial joints in high quality hyaluronic acid and is currently approved to relieve pain and improve mobility in osteoarthritis of the knee joint and other big synovial joints.

This Book of Evidence has been prepared as a resource summarizing the publicly available data on the use of Ostenil Plus in osteoarthritis. Clinical trials publicly reported until January 2023 have been assessed, classified according to the clinical endpoints of the study, and summarized. It should be noted that all publicly available data have been gathered, including studies where the treatment scheme with Ostenil Plus does not respect the Instructions for Use (i.e. once per week). We hope it will help you to quickly find the scientific information that you need and support you to prepare your promotional material or answer medical enquiries. This Book of Evidence should not be seen as an exhaustive resource but more as an initial access to dedicated literature. We hope that this book will help you to quickly find the scientific information you might need and that it will support you in the preparation of your promotional material or of your answers to medical enquiries.

The material and literature detailed in this document are based on international guidelines and on the current European authorization of Ostenil Plus. Before using it locally, please ensure to adapt it according to your local authorizations and regulations. This Book of Evidence has been developed for information and training purposes only; do not share it with external stakeholders.

1. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis.* 2014;73(7):1323-30.
2. Tehranzadeh J, Booya F, Root J. Cartilage metabolism in osteoarthritis and the influence of viscosupplementation and steroid: a review. *Acta Radiol.* 2005;46(3):288-96.
3. Legré-Boyer V. Viscosupplementation: Techniques, indications, results. *Orthop Traumatol Surg Res.* 2015;101(1S):S101-S8.

Abbreviations

ACR	American College of Rheumatology
AE	Adverse event
CI	Confidence interval
ICRS	International Cartilage Repair Society
IKDC	International Knee Documentation Committee
ITT	Intention-to-treat
KOOS	Knee Injury and Osteoarthritis Outcome Score
KSS	Knee Society's Knee Scoring System
MRI	Magnetic resonance imaging
OMERACT-OARSI	Outcome Measures in Rheumatology Clinical Trials–Osteoarthritis Research Society International
OSS	Oxford Shoulder Score
PP	Per-protocol
PRP	Platelet-rich plasma
SD	Standard deviation
SF-36	36-Item Short Form Survey
VAS	Visual analogue scale
WOMAC	Western Ontario & McMaster Universities Osteoarthritis Index

Overview of studies

Study name	Date of publication	Comparator(s)	Pain score (VAS)	Joint-specific score (WOMAC, OSS)	Symptoms	Functional impairment	Rescue medication use	Patient's global assessment	Physician's global assessment	Quality of Life	Safety
Borras-Verdera et al.	2012	-	1	2				2	2		2
Shaik et al.	2015	Synvisc-One	1								
Dernek et al.	2016	Monovisc	1	2			2				
Dernek et al.	2017	Monovisc, Orthovisc	1	2							
Duymus et al.	2017	PRP, Ozone	1	2							
Barac et al.	2018	PRP	1	2		2				2	2
Astur et al.	2019	Physiotherapy	1			2					
Frobenius et al.	2009	-		1	2	2		2	2		2
Stoilov et al.	2011	Yaral forte Durolane		1		2		2			2
Maheu et al.	2019	Synvisc-One		1		2					2
Lertwanich et al.	2016	-		1			2				2
Oduoza et al.	2022	-	2	1		2					2
Guler et al.	2015	PRP	2			1					2
Pereira et al.	2019	Synolis VA, saline	2	2		1				2	2

*congress abstract only

1: primary endpoint

2: secondary endpoint

Bold: endpoint used for the classification. By clicking on the number, you will directly reach the corresponding page of the document.

A SINGLE INJECTION OF OSTENIL PLUS DECREASES PAIN AND IMPROVES JOINT FUNCTION UP TO 6 MONTHS IN PATIENTS WITH KNEE OSTEOARTHRITIS

- Study design: multicentre, prospective, open-label, phase IV trial evaluating the efficacy of a single intra-articular injection of Ostenil Plus over 6 months.
- Study population: patients aged ≥ 40 years, suffering from knee osteoarthritis (American College of Rheumatology [ACR] criteria), Kellgren-Lawrence grade III, with pain in the affected knee for most of the days within the last 3 months. Exclusion criteria: other diseases that could interfere with the evaluation of osteoarthritis, intra-articular injections of corticosteroids or hyaluronic acid within the last 6 months, arthroscopic lavage within the last year, oral chondroprotectors (glucosamine, chondroitin, etc.) within the last 2 months. N = 80
- A statistically significant decrease of the VAS pain score was observed already after two weeks and was maintained until the end of the study, decreasing from 7.41 cm at baseline to 3.97 cm at Month 6 (Figure 1).
- The Western Ontario & McMaster Universities Osteoarthritis Index (WOMAC) total score was significantly improved at all timepoints and stayed significantly lower than baseline until Month 6 (- 47.5%). Similar results were obtained for the individual WOMAC pain, physical function and stiffness subscores.
- Treatment efficacy was rated as good or very good by patients and physicians throughout the study, with a statistically significant improvement of the rating between Week 2 and the following visits. Patient's assessment at Month 6 was however a bit lower, suggesting that some of the initial symptoms begin to reappear.
- The use of rescue medication decreased significantly after the injection: at baseline, 58.2% of patients were regularly using analgesics and/or anti-inflammatory drugs whereas this proportion decreased to 2.5% at Month 3 before increasing again to 17.7% at Month 6.
- Tolerance of the treatment was evaluated as excellent by patients and physicians throughout the entire study. No serious adverse event (AE) was reported during the study. Mild AEs (mild pain and inflammation at the injection site) were reported in 5.06% of patients at Week 2 and resolved in the subsequent visits.

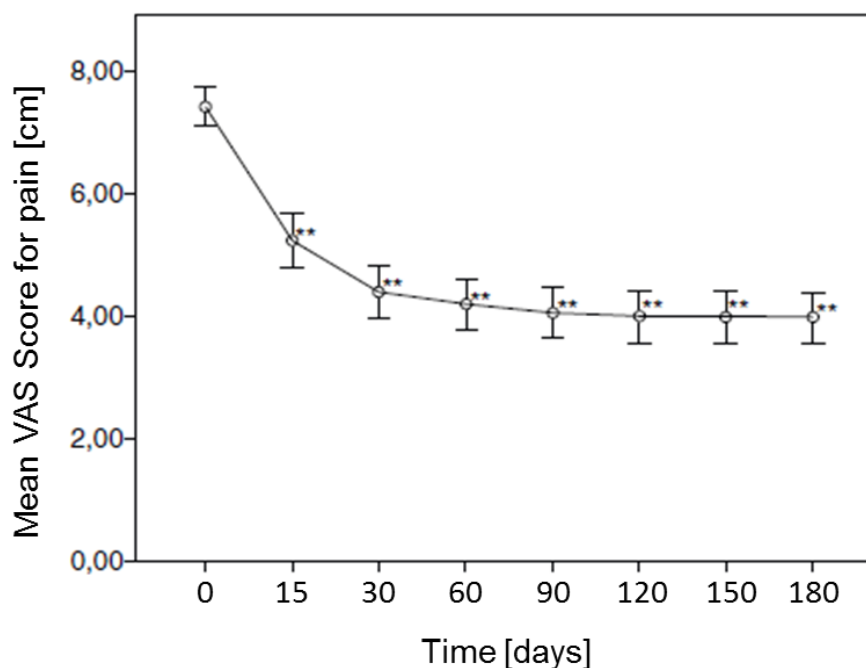


Figure 1: Evolution of joint pain measured on a VAS. Data are presented as mean \pm 95% CI. **, $p < 0.001$ versus baseline.

OSTENIL PLUS IS EQUIVALENT TO SYNVISC-ONE IN TERMS OF PAIN REDUCTION AFTER SIX MONTHS

- Study design: monocentric, prospective, open-labelled study comparing a single injection of Ostenil Plus or Synvisc-One over 6 months.
- Study population: patients suffering from knee osteoarthritis of the knee, Kellgren-Lawrence grade II-IV, unable to tolerate or not responding to oral NSAIDs and intra-articular corticosteroids, ineligible for knee replacement surgery. Exclusion criteria not mentioned. N = 33
- VAS score for pain decreased significantly versus baseline in both treatment groups at all time points. In the Ostenil Plus group, pain decreased from 7.78 at baseline to 4.95 at Month 6. In the Synvisc-One group, pain decreased from 6.8 at baseline to 3.86 after six months (Table 1).
- Despite a significantly higher VAS score at baseline in the Ostenil Plus group, there was no significant difference between the two groups in pain measured by the VAS score 1, 3, 4 and 6 months after the injection.
- The maximum improvement of pain was observed in both groups at Month 1 but the improvement was maintained up to 6 months post-injection with an average reduction in VAS pain of 36% for Ostenil Plus and 43% for Synvisc-One.

	Baseline	Month 1	Month 3	Month 4	Month 6
Ostenil Plus					
Mean (SD)	7.78 (1.96)	4.22 (3.28)	4.84 (3.09)	4.97 (3.05)	4.95 (2.91)
Median	8	4	4	4	5.5
p value	-	<0.0001	<0.0001	<0.0001	<0.005
Synvisc-One					
Mean (SD)	6.8 (0.89)	4.57 (2.65)	4.14 (2.07)	4.14 (2.79)	3.86 (2.97)
Median	7	6	4	3	3
p value	-	<0.005	<0.0001	<0.05	<0.05

Table 1: VAS scores for pain over the follow-up period. SD, standard deviation.

OSTENIL PLUS IS EFFECTIVE TO TREAT KNEE OSTEOARTHRITIS AND IS EQUIVALENT TO MONOVISC

- Study design: monocentric, retrospective study comparing Monovisc (single injection) and Ostenil Plus (single injection).
- Study population: patients suffering from symptomatic early knee osteoarthritis, with stable knees without malalignment, treated with Ostenil Plus or Monovisc. Exclusion criteria: inflammatory joint disease, previous intra-articular fracture of the knee, renal impairment, allergy to the study medication, metastatic tumours. N = 74
- Patients were Kellgren-Lawrence grade II or III and patients were a bit more severe in the Ostenil Plus group.
- Visual-analogue scale (VAS) score for pain was improved significantly versus baseline at Month 1, 3 and 6 in both groups. There was no statistically significant difference between the two groups at any of the time points (Table 2).
- Similar results were obtained for the WOMAC total score as well as for the WOMAC pain, stiffness, and physical function subscores. The only difference observed was related to the WOMAC stiffness score: the improvement of the stiffness score appears to persist longer with Ostenil Plus than with Monovisc.
- Two patients in the Monovisc group versus none in the Ostenil Plus group reported an adverse event (swelling and redness of the joint).

	Ostenil Plus	Monovisc
VAS		
Baseline	8.3 ± 0.5	8.1 ± 0.3
Month 1	3.2 ± 2.3*	3.6 ± 2.5*
Month 3	3.2 ± 2.3*	3.6 ± 2.4*
Month 6	4.0 ± 1.8*	4.5 ± 2.1*
WOMAC pain		
Baseline	20.0 ± 0.0	20.0 ± 0.0
Month 1	11.5 ± 4.4*	12.0 ± 4.2*
Month 3	11.6 ± 4.1*	12.1 ± 4.1*
Month 6	13.2 ± 4.6*	13.0 ± 4.4*
WOMAC stiffness		
Baseline	8.0 ± 0.0	8.0 ± 0.0
Month 1	4.4 ± 1.9*	4.2 ± 2.2*
Month 3	4.6 ± 1.7*	4.8 ± 1.7*
Month 6	5.1 ± 1.8*	5.3 ± 1.8*
WOMAC physical function		
Baseline	68.0 ± 0.0	66.3 ± 3.7
Month 1	40.0 ± 13.9*	38.6 ± 15.6*
Month 3	38.5 ± 14.3*	40.8 ± 14.0*
Month 6	45.1 ± 15.4*	45.3 ± 14.4*
WOMAC total		
Baseline	96.0 ± 0.0	94.3 ± 3.7
Month 1	55.9 ± 19.9*	54.8 ± 21.8*
Month 3	54.8 ± 20.0*	57.7 ± 19.8*
Month 6	63.8 ± 21.7*	63.5 ± 20.5*

Table 2: Comparison of pre- and post-injection VAS and WOMAC scores of the groups. Data are presented as mean ± SD. *, p<0.05 for intragroup change versus baseline

OSTENIL PLUS DRAMATICALLY REDUCES PAIN DUE TO EARLY-STAGE MENISCUS LESIONS UP TO 6 MONTHS

- Study design: monocentric, retrospective study comparing Monovisc (single dose), Ostenil Plus (single dose) and Orthovisc (three injections at one-week intervals).
- Study population: patients with early-stage meniscus lesions (Kellgren-Lawrence grade I or II) of the knee in the tibiofemoral compartment and who received hyaluronic acid, with 6-month data available and with magnetic resonance imaging (MRI) data. Exclusion criteria: late-stage meniscus damage, contraindication for intra-articular injections, inflammatory joint disease, previous fracture of the knee, allergy to the study medication, metastatic tumours. N = 55
- The VAS pain score decreased significantly in the three groups at Month 1, 3 and 6 but no statistical difference between the groups was identified (Figure 2). In terms of absolute change compared to baseline, the highest numerical change was observed with Ostenil Plus; however, this change was not significantly higher than in the other groups ($p>0.05$).
- Similar results were obtained with the WOMAC score. A numerically but not significantly higher absolute change in WOMAC score compared to the baseline was detected with Monovisc during the sixth month visit (69.8 points). Similar absolute change was observed with Ostenil Plus with a 69.4 point reduction at Month 6.

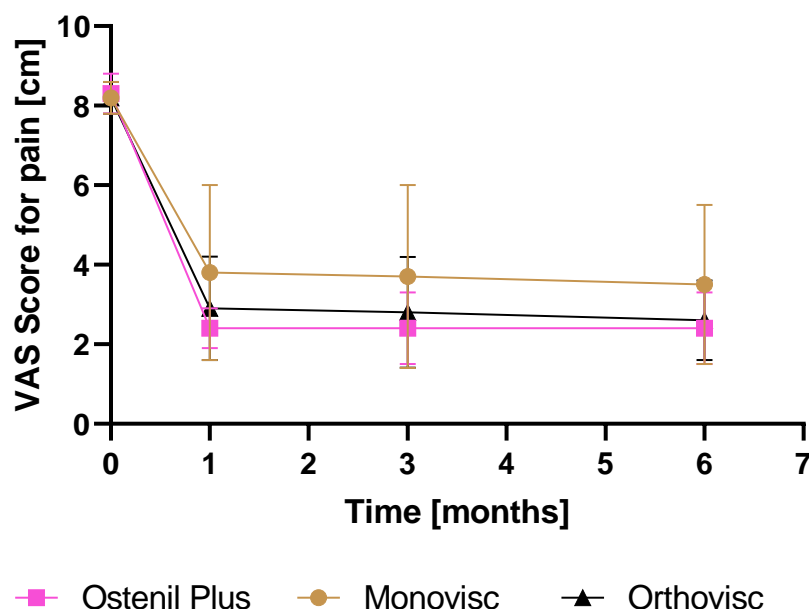


Figure 2: VAS score for pain. Data are presented as mean \pm SD.

AT SIX MONTHS, OSTENIL PLUS IS EQUIVALENT TO PLATELET-RICH PLASMA AND SUPERIOR TO OZONE TREATMENT TO MANAGE PAIN IN KNEE OSTEOARTHRITIS

- Study design: monocentric, prospective, randomized, controlled study comparing injections of Ostenil Plus, platelet-rich plasma (PRP) or ozone over a follow-up period of 12 months.
- Study population: patients aged 47-80 years, suffering from symptomatic knee osteoarthritis, with pain scoring ≥ 4 on a 10-cm VAS, Kellgren-Lawrence grade 2-3, with body mass index <30 , stable knees without malalignment. Exclusion criteria: recent history of knee trauma, rheumatic pathology, concomitant severe hip osteoarthritis, intra-articular corticosteroid injection within the previous 12 months, previous joint infection. N = 120
- At Month 1, VAS scores improved within each group compared to the initial scores. VAS scores increased then slowly until Month 12. When the VAS scores were compared between the groups at Month 1, no significant difference was observed between the Ostenil Plus and PRP groups, but the scores in both groups were better than those in the ozone group. Similar results were obtained at Month 3, 6 and 12 (Figure 3).
- Similar trends were observed for the WOMAC total score and the pain, stiffness and physical function subscores. A significant difference between ozone and the two other groups was identified from Month 3 onwards for the total score and the pain and physical function subscores, whereas the difference was significant at Month 6 and 12 for the stiffness subscore.
- In the total 12-month follow-up period, there were no statistically significant differences between PRP and Ostenil Plus during the first 6 months, and the VAS and WOMAC scores were similar between the two groups. At the end of month 12, there was a difference between the two groups, and the clinical efficacy had reduced, but some residual effect was seen. This reduction was more evident in the Ostenil Plus group, and at the end of Month 12, PRP was found to be significantly superior to Ostenil Plus.

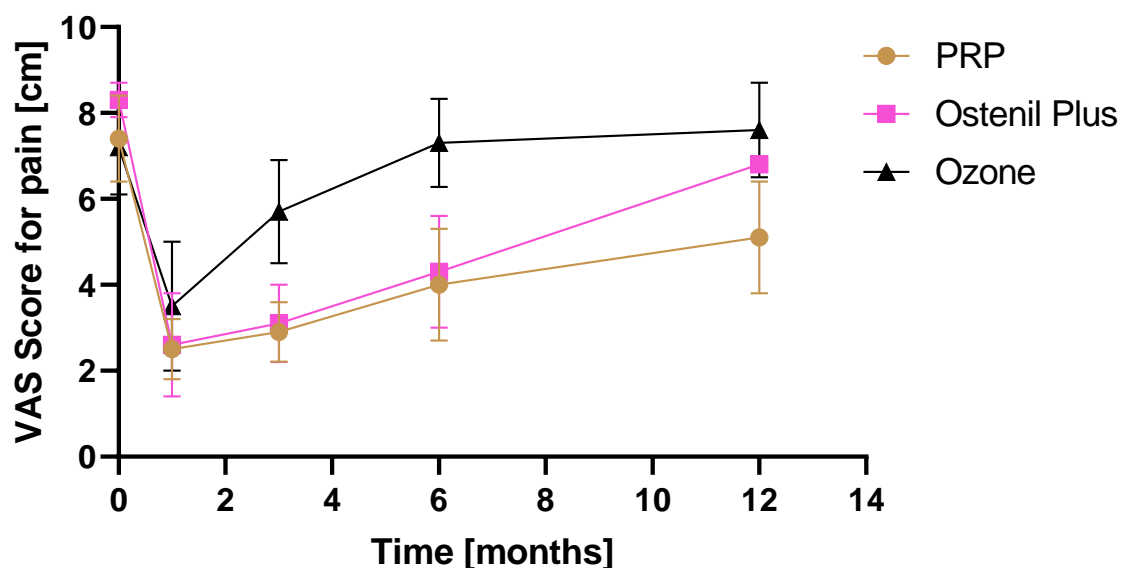


Figure 3: VAS scores pre- and post-treatment in the three groups.

OSTENIL PLUS WAS INFERIOR TO A COMBINATION OF HA AND PRP IN PATIENTS WITH KNEE OSTEOARTHRITIS

- Study design: monocentric, prospective, randomized, double-blind, controlled study comparing 3 weekly injections of Ostenil Plus, 3 weekly injections of ArthroVisc and 3 injections (one every second week) of CellularMatrix PRP-HA combination over a follow-up period of 12 months after the last injection.
- Study population: patients aged 30-80 years, suffering from chronic (≥ 4 months) pain or swelling of the knee, with pain scoring ≥ 50 on a 100-mm VAS, Kellgren-Lawrence grade up to 3. Exclusion criteria: major axial deviation, systemic diseases, hip osteoarthritis, history of intra-articular hyaluronic acid injection, corticosteroid treatment in the past two months. N = 53
- At Month 2, VAS pain score, WOMAC total score, Knee Injury and Osteoarthritis Outcome Score (KOOS) and International Knee Documentation Committee (IKDC) score improved in the three groups compared to baseline values. The improvement was significantly greater in the CellularMatrix group than in the Ostenil Plus and ArthroVisc groups. The superiority of CellularMatrix over Ostenil Plus and ArthroVisc was confirmed at Month 6 and Month 12.
- At Month 12, a deterioration of VAS, WOMAC, KOOS and IKDC scores was observed in the two HA groups (Ostenil Plus and ArthroVisc).
- No difference in cartilage thickness was observed in the Ostenil Plus and ArthroVisc groups. On the other hand, a significant thickening of cartilage compared to baseline was observed in patients treated with CellularMatrix at Month 2, 6 and 12.
- All treatments were well tolerated, with only mild, transient adverse events.

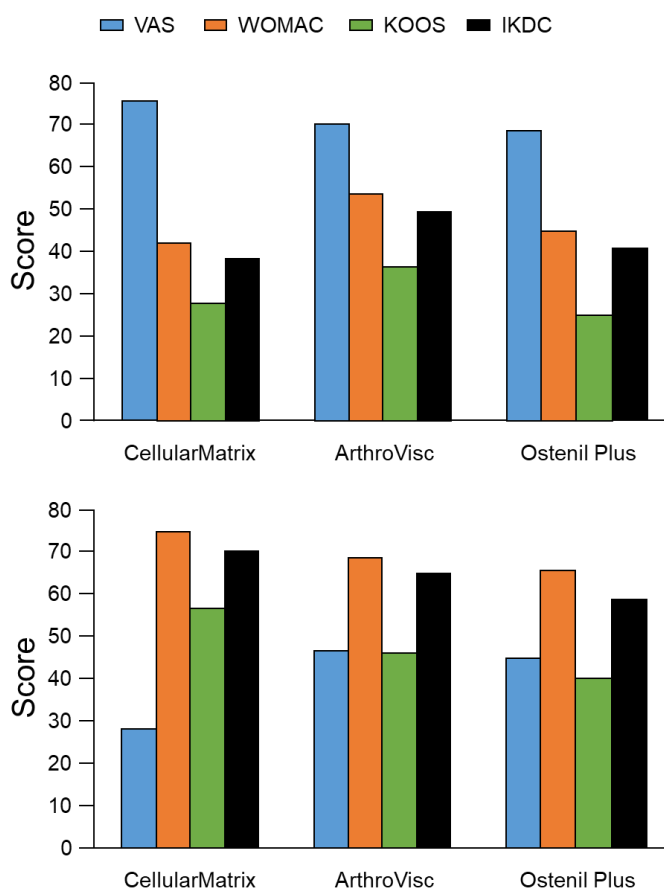


Figure 4: Disease scores at baseline (upper panel) and at Month 2 (lower panel) in the three treatment groups.

OSTENIL PLUS SIGNIFICANTLY REDUCES PAIN IN ATHLETES SUFFERING FROM PATELLOFEMORAL PAIN SYNDROME

- Study design: monocentric, prospective, randomized, controlled study comparing physiotherapy with or without a single injection of Ostenil Plus over a follow-up period of 12 weeks.
- Study population: patients aged 18-45 years, practicing physical activity ≥ 3 times per week, with good knee alignment, with anterior knee pain, physical examination suggestive of painful patellar syndrome and patellar lesions grade II-III according to the International Cartilage Repair Society (ICRS) classification. Exclusion criteria: increased trochlear groove angle, increased patellar deviation, abnormal patellar height, marked quadriceps hypotrophy, other associated knee injuries, previous surgery on the same knee, autoimmune or infectious diseases. N = 70
- Compared to baseline values, pain VAS score, Lysholm score and Kujala score were significantly improved at Month 3 and Month 6 in both treatment groups.
- Patients treated with Ostenil Plus were significantly improved compared to patients in the control group: at Month 3, the VAS score for pain was 3.8 ± 1.3 cm in the control group versus 2.8 ± 2.3 cm in the Ostenil Plus group ($p = 0.02$). At Month 6, the VAS score was 3.5 ± 0.9 cm versus 2.7 ± 2.1 cm ($p = 0.01$) in the control and Ostenil Plus groups, respectively. Significant differences between the two treatment groups were also identified at Month 3 and 6 for Lysholm and Kujala scores.
- At Month 6, the number of patients with positive Clarke's Test (Patellar Grind Test) was significantly lower in the Ostenil Plus group ($p = 0.02$).
- The occurrence of Rabot sign and the type of lesion determined by MRI (based on the ICRS classification) were not significantly different between the two treatment groups.

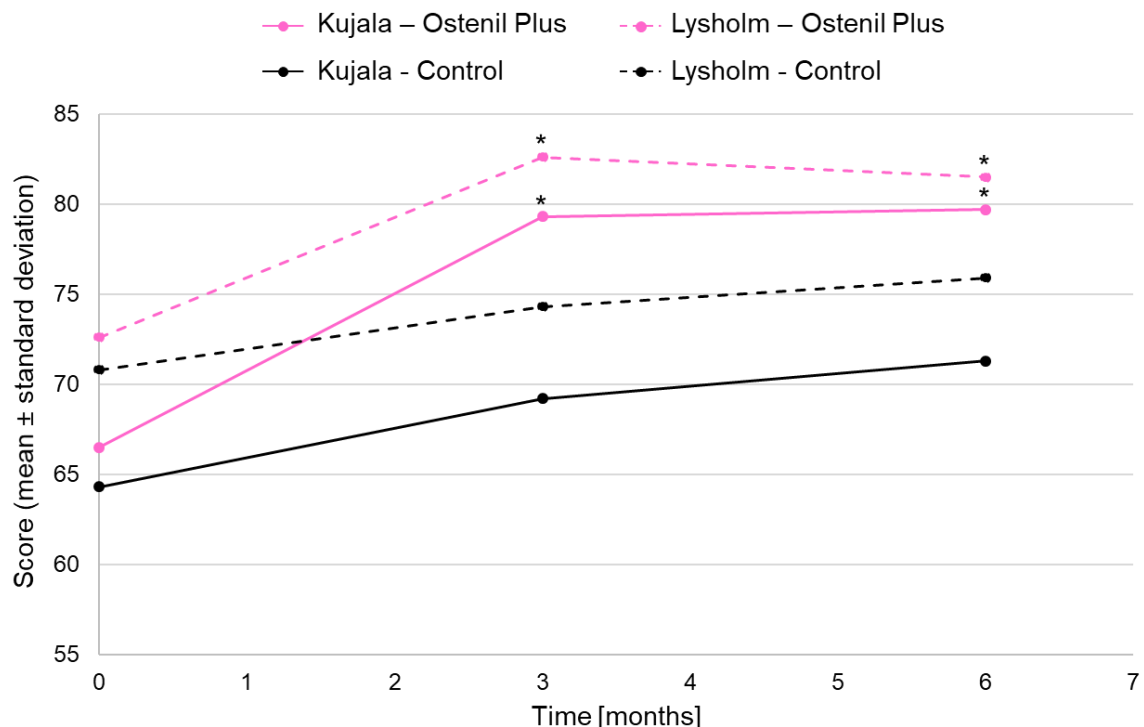


Figure 5: Evolution of Kujala and Lysholm scores in the two treatment groups. *, $p < 0.05$ versus control group.

OSTENIL PLUS IS A SAFE AND EFFICIENT OPTION IN THE MANAGEMENT OF HIP AND KNEE OSTEOARTHRITIS

- Study design: monocentric, prospective, open-label trial evaluating the efficacy of 1 (hip osteoarthritis) or 3 (knee osteoarthritis) injections of Ostenil Plus over 3 months. In case of knee osteoarthritis, the injections were made every 2 weeks.
- Study population: patients suffering from radiographic osteoarthritis of the knee or of the hip, with substantial pain since ≥ 3 months. N = 25 (N = 6 hip osteoarthritis, N = 19 knee osteoarthritis).
- A statistically significant improvement of WOMAC score was observed, from 36.81 at baseline to 15.56 3 months after the last injection. Similar results were obtained for the WOMAC pain ($\Delta 23.27$), physical function ($\Delta 20.40$) and stiffness ($\Delta 23.40$) subscores (Figure 6).
- The number of patients suffering from crepitus improved but not in a statistically significant way. Similar results were obtained for the presence of morning stiffness.
- A statistically significant improvement of the number of patients suffering from pain on movement was observed: at baseline, 7 patients were pain-free whereas 3 months after the last injection, 15 patients did not have any pain and 8 patients had only mild pain on movement. Similar results were obtained for pain on charge.
- Global assessment of the treatment by patients and physicians was very good, good or satisfying for 87.5% of patients, whereas 12.5% evaluated that the treatment was not successful. No worsening of the condition was reported.
- The tolerance of the treatment was evaluated as very good by 94.7% of patients and as good by the remaining patients. Similar results were obtained when the tolerance was evaluated by physicians. No AE related to the product was reported.

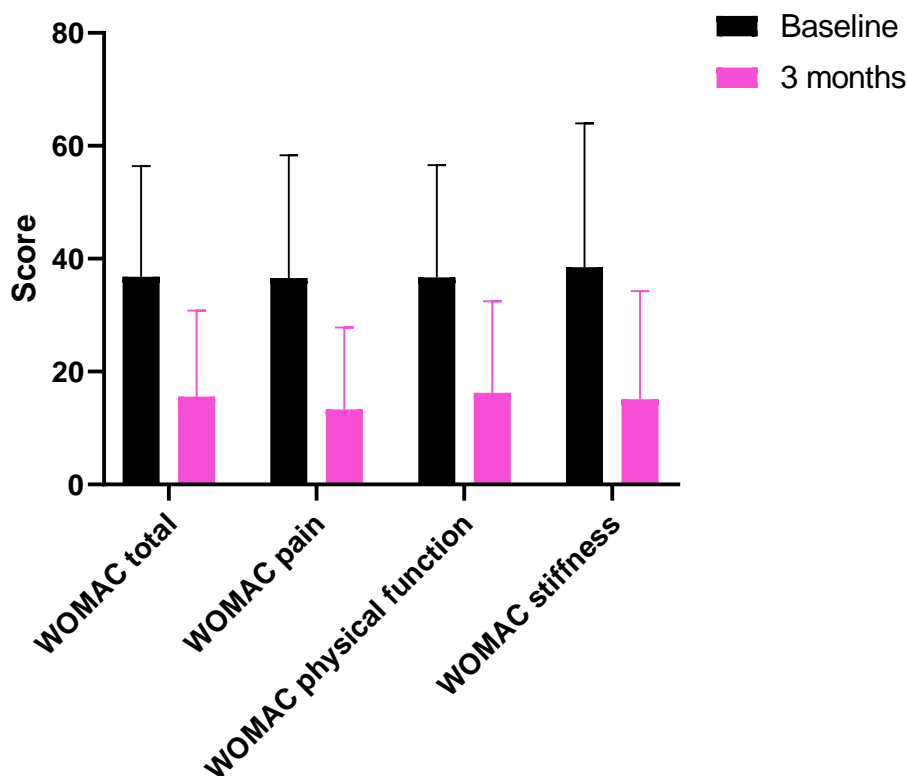


Figure 6: WOMAC scores at baseline and 3 months after the last injection. Data are presented as mean \pm SD.

OSTENIL PLUS REDUCES PAIN UP TO 18 MONTHS AFTER THE THERAPY IN PATIENTS WITH KNEE OSTEOARTHRITIS

- Study design: prospective study comparing intra-articular therapies with Ostenil, Ostenil Plus, Yaral Forte and Durolane over a 72-week follow-up period.
- Study population: patients suffering from knee osteoarthritis, Kellgren-Lawrence grade I-III. Exclusion criteria not mentioned. N = 268
- A significant proportion of patients in the Ostenil (30%), Ostenil Plus (33.1%), Yaral Forte (28.9%) and Durolane (27.1%) groups achieved a reduction of pain at Week 12 versus baseline as measured by the WOMAC pain subscore. This tendency was confirmed at Week 24, 48 and 72 (Figure 7).
- A significant proportion of patients in the Ostenil (28%), Ostenil Plus (31%), Yaral Forte (30%) and Durolane (%) groups achieved an improvement of physical function at Week 12 versus baseline as measured by the Lequesne index. This tendency was confirmed at Week 24, 48 and 72.
- Patients from all treatment groups reported rapid and significant improvement of disease activity assessed by a VAS score.
- No statistically significant difference was identified between the four treatment groups in terms of efficacy and safety.
- The medications were well tolerated, with no unexpected safety issues. Most AEs were mild or moderate.

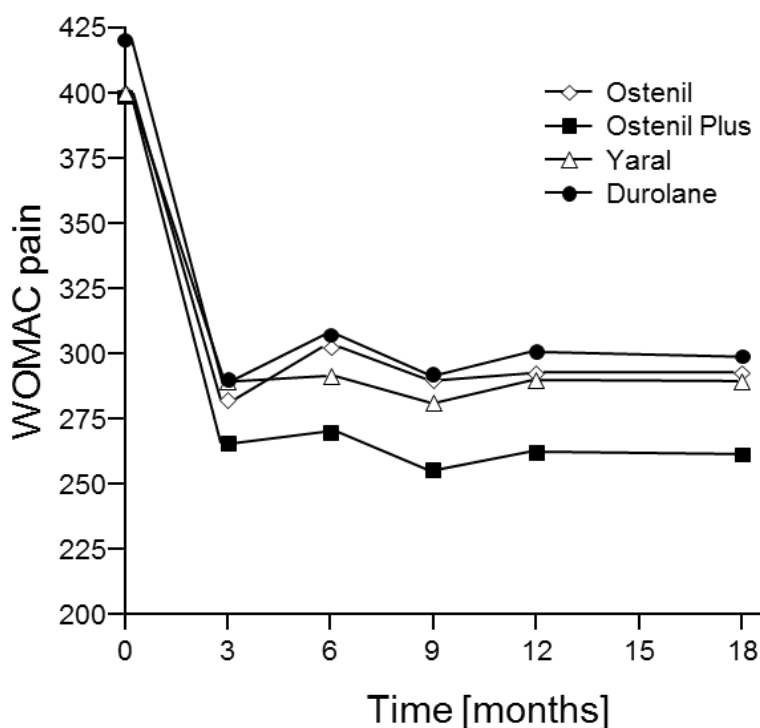


Figure 7: WOMAC pain score measured on a VAS.

A SINGLE INJECTION OF OSTENIL PLUS IS AS EFFICIENT AS SYNVISC-ONE TO REDUCE PAIN IN KNEE OSTEOARTHRITIS

- Study design: multicentre, prospective, randomized, double-blind, controlled, non-inferiority study comparing a single injection of Ostenil Plus or of hylan G-F 20 (Synvisc-One) over a follow-up period of 6 months.
- Study population: patients aged 40-85 years, suffering from painful tibiofemoral osteoarthritis (ACR criteria), Kellgren-Lawrence grade Ib-III, with pain scoring ≥ 40 mm on the VAS of WOMAC A pain. N = 292
- In the per-protocol (PP) population, the mean WOMAC A score improved by 34.3 ± 1.8 mm and 36.2 ± 2.1 mm at Day 180 versus baseline in the Ostenil Plus and Synvisc-One groups, respectively. The mean intergroup difference was -1.9 mm, with a two-sided 95% confidence interval of [-7.3; 3.5 mm]. The lower bound of the confidence interval lays above the non-inferiority margin (-8 mm), demonstrating the non-inferiority of Ostenil Plus versus Synvisc-One in this population. Results were similar for the intention-to-treat (ITT) population.
- The WOMAC subscores for stiffness and function improved in both groups during the follow-up period, with no statistically significant difference between the two arms (Figure 8). Similar results were obtained for the Lequesne index (at Month 6: Ostenil Plus -4.3 points, Synvisc-One -4.7 points).
- The evaluation by patients of their global health condition on a VAS improved between baseline and Day 180 in both groups in a similar manner (Ostenil Plus -25.4 mm; Synvisc-One -27.0 mm).
- The rate of responders in the ITT population as defined by the Outcome Measures in Rheumatology Clinical Trials–Osteoarthritis Research Society International (OMERACT-OARSI) criteria was similar in both groups (Ostenil Plus 83.0%, Synvisc-One 85.7%).
- No serious reaction related to the injection was reported. Local reaction was observed in 8.5% of Ostenil Plus patients and 13.0% of Synvisc-One patients. The rate of flare up was numerically higher in the Synvisc-One group (3.4%) than in the Ostenil Plus group (0.7%).

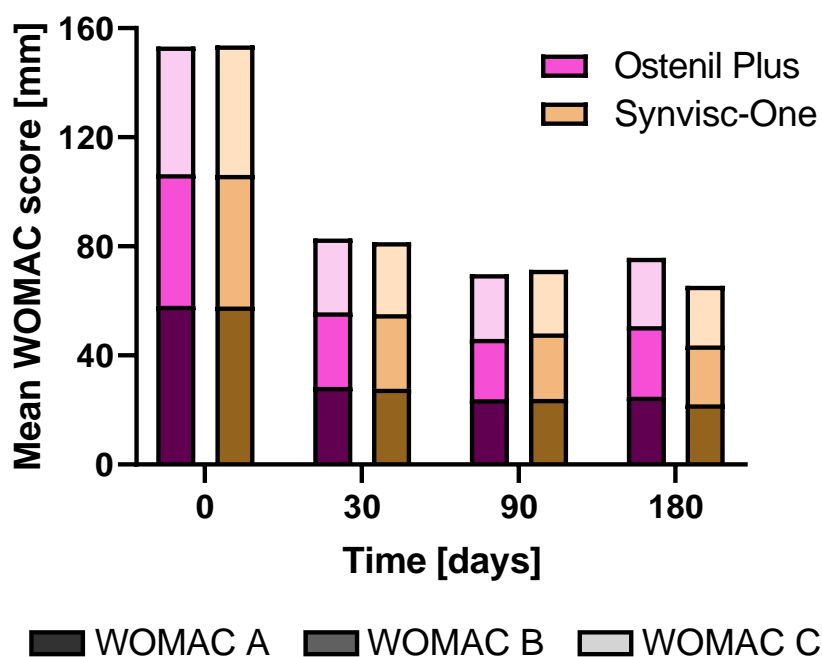


Figure 8: WOMAC pain subscores measured on a VAS. No statistically significant difference was observed between Ostenil Plus and Synvisc-One.

OSTENIL PLUS REDUCES PAIN, STIFFNESS AND RESCUE MEDICATION USE WHILE IMPROVING PHYSICAL FUNCTION COMPARED TO CONTROL GROUP

- Study design: monocentric, prospective, randomized, open-label, controlled study comparing a single injection of Ostenil Plus with no injection (control) over a follow-up period of 24 weeks. Diclofenac 25 mg was used as rescue pain medication in both groups.
- Study population: patients aged 40-70 years, suffering from primary tibiofemoral osteoarthritis (ACR criteria), with pain scoring ≥ 4 on a 10-point scale for ≥ 2 of 5 subscales of WOMAC pain subscore, Kellgren-Lawrence grade II-III. Exclusion criteria: secondary osteoarthritis, clinical signs of acute flare, painful knee condition other than osteoarthritis, concomitant rheumatic disease, varus or valgus misalignment >15 degrees, significant injury of the target knee within the last 6 months, intra-articular corticosteroid within the last 6 months, intra-articular hyaluronic acid injection within the last 3 months. N = 20
- A significant improvement of WOMAC score versus baseline was observed in both groups at Week 24 (Figure 9). The improvement was significantly higher in the Ostenil Plus group than in the control group at Week 4 ($\Delta -61.2$ versus $\Delta -13.8$), 8 ($\Delta -66.8$ versus $\Delta -22.9$), 12 ($\Delta -57.9$ versus $\Delta -28.7$) and 16 ($\Delta -60.2$ versus $\Delta -31.8$).
- Similar trends were observed for the WOMAC pain, stiffness and physical function subscores. The intervention group had a significantly better WOMAC pain, stiffness and physical function subscores than the control group up to Week 20, 12, and 16, respectively. No significant improvement was observed for the stiffness subscore in the control group.
- Daily consumption of rescue medication was significantly lower over the 24-week follow-up period in the Ostenil Plus group than in the control group: at Week 24, the daily amount of rescue medication was 27.2 mg in the Ostenil Plus group and 64.5 mg in the control group.
- No serious AEs were reported in the Ostenil Plus group; however, one patient in the control group developed enterocolitis. 6 AEs occurred in 5 patients of the control group and 9 AEs occurred in 6 patients of the Ostenil Plus group. None of the AEs in either group were found to be related to study treatment.

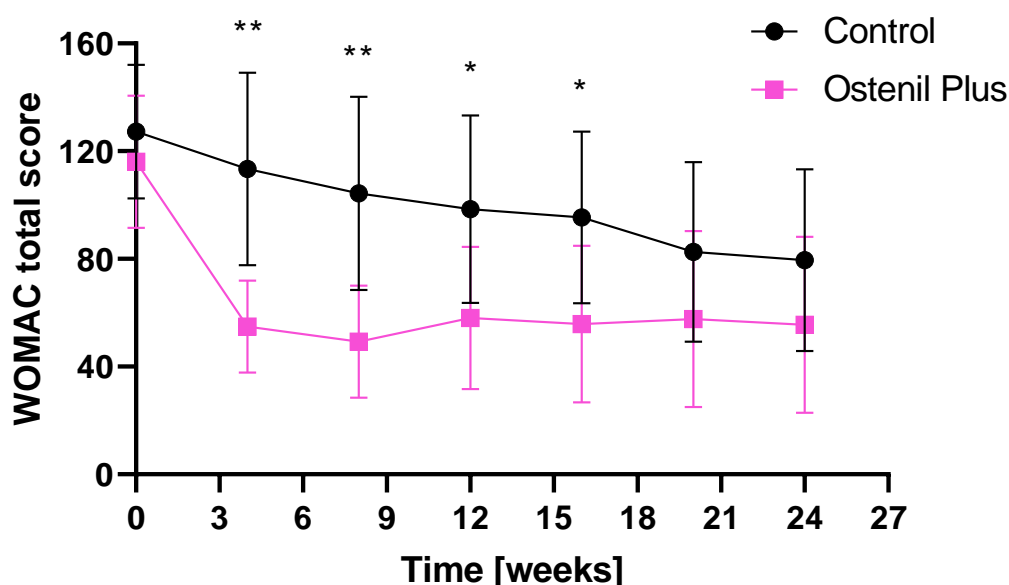


Figure 9: WOMAC total score. Data are presented as mean \pm SD. *, $p < 0.01$; **, $p < 0.001$

OSTENIL PLUS IMPROVES JOINT FUNCTION AND REDUCES PAIN IN YOUNG PATIENTS WITH SHOULDER OSTEOARTHRITIS

- Study design: monocentric, retrospective, single-arm, interventional study evaluating the efficacy and safety of a single injection of Ostenil Plus over a follow-up period of 26 weeks.
- Study population: patients aged 18-55 years, suffering from clinically and radiologically confirmed glenohumeral osteoarthritis. Exclusion criteria: surgical intervention within the last 12 months. N = 55
- Patients included in the study had a median age of 44.5 years. Their glenohumeral osteoarthritis was classified as mild in 11 (20%) patients, moderate in 21 (38%) patients and severe in 23 (42%) patients.
- The mean Oxford Shoulder Score (OSS) increased significantly versus baseline six weeks after the injection (from 23.9 to 28.8) and remained then stable up to Week 26. A subgroup analysis based on modified Samilson-Prieto classification was performed and identified a statistically significant improvement of the OSS at Week 6 in patients with moderate or severe osteoarthritis but not in patients with mild osteoarthritis (Figure 10).
- The median Single Assessment Numeric Evaluation scores evaluating the function of the shoulder joint improved significantly between baseline (38.3) and Week 6 (47.2). At Week 12 and 26, the difference was not statistically significant. Subgroup analyses demonstrated again a significant improvement in patients with moderate or severe osteoarthritis but not in patients with mild osteoarthritis. Similar results were obtained for the Western Ontario Osteoarthritis Scores.
- Pain evaluated on a 0-10 Numeric Rating Pain Scale decreased significantly between baseline and Week 6 from 6.4 to 4.6. At Week 12 (5.1) and 26 (5.5), the difference was not statistically significant. Subgroup analyses demonstrated again a significant improvement in patients with moderate or severe osteoarthritis but not in patients with mild osteoarthritis.
- No complications were reported during the study.

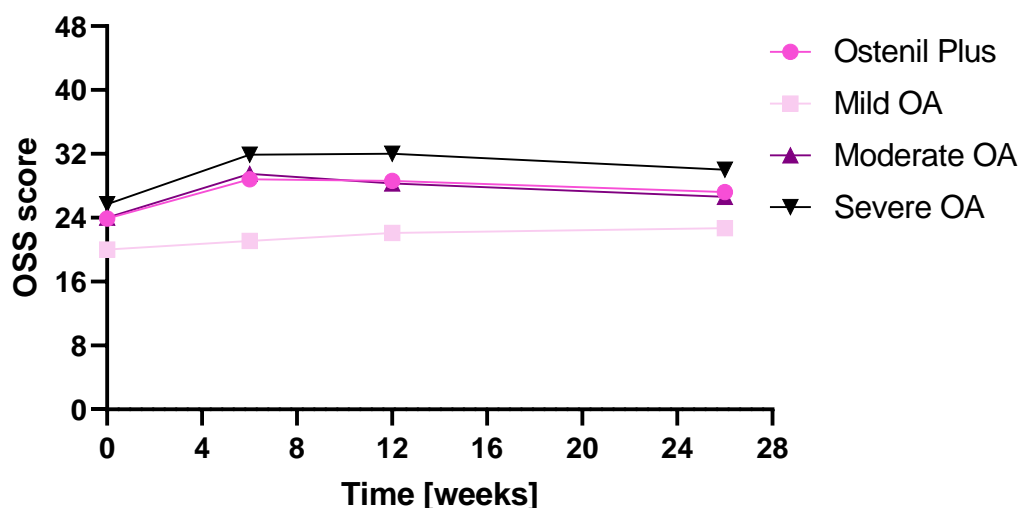


Figure 10: Evolution of OSS over the 26-week study period. Data are presented as mean for the overall population and for each subgroup.

PRP WAS SUPERIOR TO OSTENIL PLUS TO IMPROVE KNEE'S FUNCTIONAL ABILITIES IN A RETROSPECTIVE, REAL-LIFE STUDY

- Study design: monocentric, retrospective study comparing injections of Ostenil Plus with PRP over a follow-up period of 6 months.
- Study population: patients aged 47-80 years, suffering from symptomatic knee osteoarthritis, Kellgren-Lawrence grade I-II, treated with intra-articular PRP or with Ostenil Plus. Exclusion criteria: rheumatoid disease, major lower extremity axis disorder, anti-inflammatory drugs until 5 days before blood sampling. N = 132
- While there was no difference between the groups in terms of pre-treatment Knee Society's Knee Scoring System (KSS) score, the PRP group had significantly higher KSS scores at Month 2 and Month 6 post-treatment (Figure 11). The change in KSS score over time and the intergroup difference in terms of change in KSS score over time were significant in favour of PRP.
- VAS score for pain improved significantly versus baseline values in both groups at Month 2 and 6. Pre-treatment and post-treatment VAS scores at Month 2 and 6 were significantly lower in the PRP group than in the Ostenil Plus group. The decrease of VAS score from baseline to Month 2 was higher with PRP than with Ostenil Plus (difference between the scores in the Ostenil Plus group: - 1.83 versus in the PRP group: - 3.01). Decrease of VAS score from Month 2 to Month 6 was significant in both groups and did not differ between the two groups.
- No intra-articular injection-related major complication was detected in any of the patients over the course of treatments. Temporary swelling occurred in 5 knees in the PRP group and in 8 knees in the Ostenil Plus group.

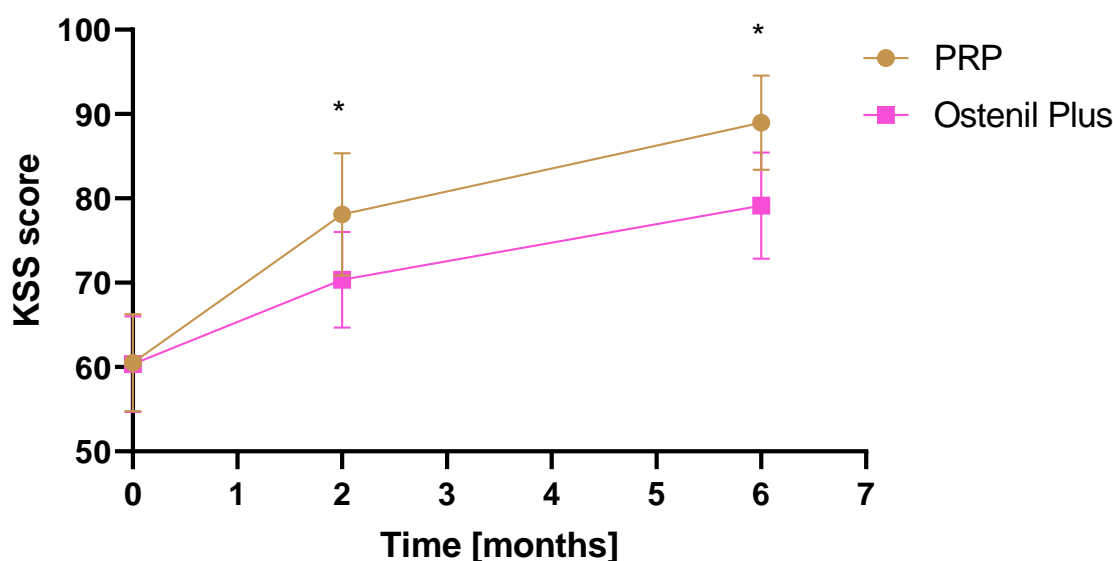


Figure 11: KSS scores in the knees of the treatment groups. Data are presented as mean \pm SD. *, $p < 0.001$

OSTENIL PLUS LEADS TO AN IMPROVEMENT OF GAIT PARAMETERS AND IS SUPERIOR TO SYNOLIS IN PATIENTS WITH KNEE OSTEOARTHRITIS

- Study design: monocentric, prospective, randomized, double-blind, controlled, pilot study comparing a single injection of Ostenil Plus (HA + mannitol), Synolis (HA + sorbitol) or saline over a follow-up period of 4 weeks.
- Study population: patients with a diagnosis of primary knee osteoarthritis, Ahlbäck grade II-III. Exclusion criteria: recent history of infection, diabetes, neurological impairment, chronic venous or lymphatic stasis, HA or corticosteroid injections within the last 6 months. N = 22
- At Week 4, a significant change versus baseline of walking speed and stride length was reported in patients treated with Ostenil Plus, with a median increase of 0.076 m/s ($p = 0.039$) and 0.055m ($p = 0.027$), respectively. Changes in cadence and swing phase duration were not significantly different versus baseline (Figure 12).
- No significant change from baseline to Week 4 of any of the gait parameters was identified in the Synolis or in the saline group.
- Clinical outcomes were evaluated using the KSS score, VAS for pain, VAS for stiffness, WOMAC score and EuroQol questionnaire. At week 4, a significant increase of the KSS score was observed in the Ostenil Plus group, with a median increase of 15 points ($p = 0.047$). None of the changes in other clinical scores for the Ostenil Plus group and in all scores for the two treatment groups were reported as statistically significant.
- All treatments were well tolerated and no adverse events were reported.

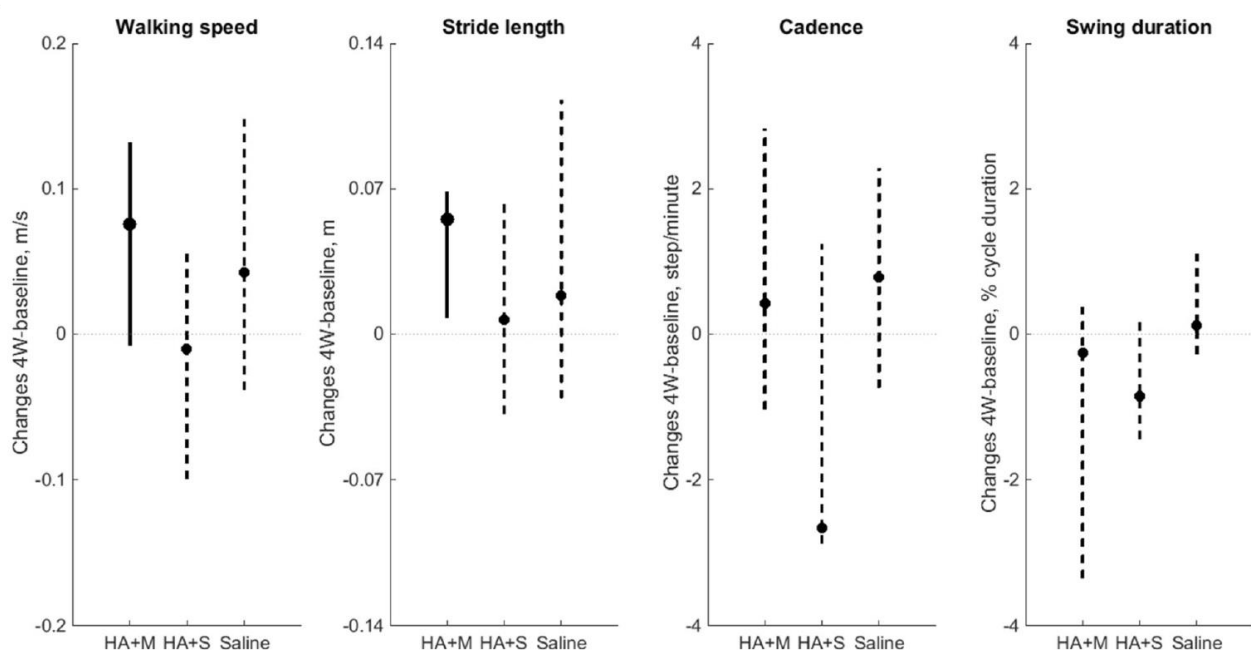


Figure 12: Changes in gait parameters from baseline to Week 4. Data are presented as median and interquartile ranges. Significant changes are indicated with solid lines. HA+M, Ostenil Plus; HA+S, Synolis.