OSTENIL
BOOK OF EVIDENCE

Published clinical data in osteoarthritis from 1995 to December 2022

Version 3.0/18-Jan-2023

Introduction

Osteoarthritis is the most common joint disease, especially in middle-aged and elderly people.[1] In patients suffering from this disease, the quality of the synovial fluid is reduced.[2] Visco-supplementation with exogenous hyaluronic acid aims to improve the viscoelastic properties of the synovial fluid and restore the mechanical properties of the cartilage.[3]
Ostenil 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 in osteoarthritis. Clinical trials publicly reported until December 2022 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 injections were performed more than one week apart, therefore not complying with Ostenil Instructions for Use. 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 as medical device. 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
ADR	Adverse device reactions
AE	Adverse event
BMI	Body mass index
CI	Confidence interval
HA	Hyaluronic acid
ITT	Intention-to-treat
KOOS	Knee Injury and Osteoarthritis Outcome Score
NSAID	Nonsteroidal anti-inflammatory drug
OMERACT-OARSI	Outcome Measures in Rheumatology Clinical Trials–Osteoarthritis Research Society International
PP	Per-protocol
SD	Standard deviation
SF-36	36-Item Short Form Survey
SYSADOA	SYSADOA
TA	Triamcinolone acetonide
TKR	Total knee replacement
TMJ	Temporomandibular joint
VAS	Visual analogue scale
WOMAC	Western Ontario & McMaster Universities Osteoarthritis Index

Overview of studies

Study name	Date of publication	Comparator	Pain score	Pain on movement	WOMAC score	Joint function	Functional impairment	Radiographic progression	Rescue medication use	Patient's global assessment	Physician's global assessment	Quality of Life	Safety
Braun et al.	2002*	-	**1**			2†							2
Pourbagher et al	2005	-	**1**	2									2
Tikiz et al	2005	Synvisc	**1**	2	2		2		2				2
Rehm et al.	2007	-	**1**	2			2			2			2
Karalezli et al.	2007	W/o fluoroscopy	**1**										
Von Eisenhart-Rothe et al.	2008	-	**1**		2			2		2	2		
Skwara et al.	2009	Triamcinolone	**1**				2					2	2
Penning et al.	2012	Triamcinolone	**1**			2	2						2
Krüger-Franke et al.	2021	-	**1**			2	2			2	2		2
Mathies et al	2004*	-		**1**	1	2			2	2	2	2	
Fraiman et al.	2002	Synvisc			**1**								2
Belenkiy et al.	2006	-			**1**					2	2		
Engelhardt	2008	-	2		**1**	2				2	2		2
Tsvetkova et al.	2010*	Lidocaine			**1**				2	2			2
Stoilov et al.	2011	Yaral forte Durolane			**1**		2			2			2
Dreiser et al.	2012*	Synvisc			**1**		2			2	2	2	2
Zoboli et al.	2013	-	2		**1**		2					2	
Berenstein et al.	2019	-	1			**1**				2			2
Möller et al.	2001	-	2				**1**	2		2			2
Funk L	2004*	-	2			2	**1**‡			2			
Uebelhart et al.	2003*	Synvisc									**1**		2
Almqvist et al.	2012	Betamethasone	2		2				2	2		**1**	2
SVISCOT-1	2007	Synvisc Orthovisc			1				2			2	**2**

*congress abstract only
†Harris hip score
‡Constant shoulder score
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.
VAS, visual analogue scale; WOMAC, Western Ontario & McMaster Universities Osteoarthritis Index

The following studies were not included in this overview:

- Iagel'skii et al., *Voen Med Zh* 2003: not enough information available
- Rehm & Wülle, *Orthop Prax* 2007: injection of 1 mL (not the entire syringe)
- Funk & Leftley, ICSES congress 2007: single injection of Ostenil (off-label)
- Yiasemidou et al., *J Knee Surg* 2016: Ostenil was injected biweekly (off-label)

FIVE INJECTIONS OF OSTENIL DEFERRED TOTAL HIP REPLACEMENT IN 80% OF PATIENTS

- Study design: prospective, open-label trial evaluating the efficacy of five weekly injections of Ostenil with a follow-up over one year.
- Study population: patients suffering from hip osteoarthritis, Kellgren-Lawrence grade ≥3, candidates for total hip replacement. Exclusion criteria not mentioned. N = 41
- Early results showed a mean relative pain reduction of 44.3% on the visual analogue scale (VAS) (52.98 ± 22.2 before therapy vs. 29.48 ± 26.27 points at Day 28, $p<0.0005$) and a statistically significant reduction of pain (19.13 ± 7.84 before therapy vs. 32.00 ± 10.00 points at Day 28, $p<0.0005$) and improvement of joint function (32.63 ± 9.95 before therapy vs. 39.43 ± 8.84 points at Day 28, $p<0.0005$) on the Harris hip score.
- After one year the mean relative pain reduction on the VAS had increased by 55.7% (52.98 ± 22.2 before therapy vs. 28.43 ± 22.93 points after 1 year, $p<0.0005$) (Figure 1). These results were confirmed by a significant reduction of pain on the Harris hip score (19.13 ± 7.84 before therapy vs. 28.47 ± 9.71 points after 1 year, $p<0.0005$). Function had not statistically significantly improved compared to the time before therapy.
- At the endpoint of this study total hip replacement could be deferred in 80% of the patients.
- There were no intra- or postoperative complications.

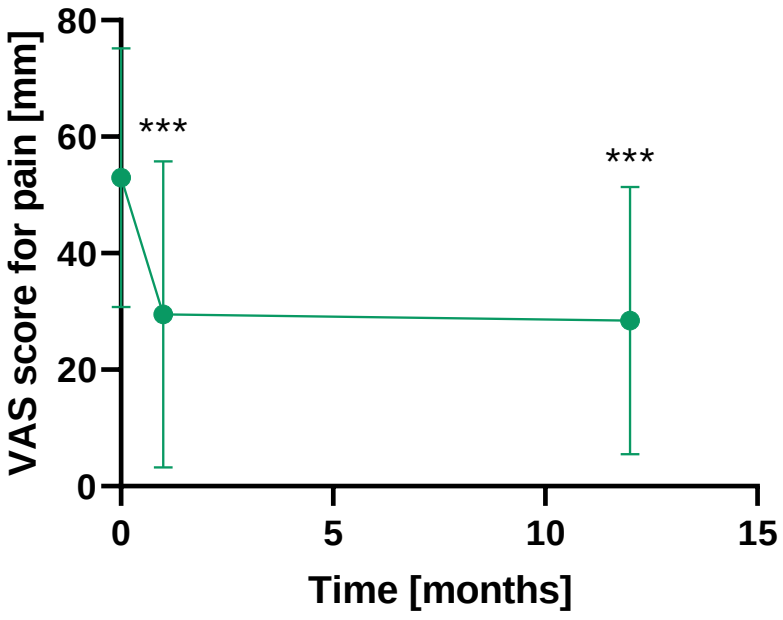
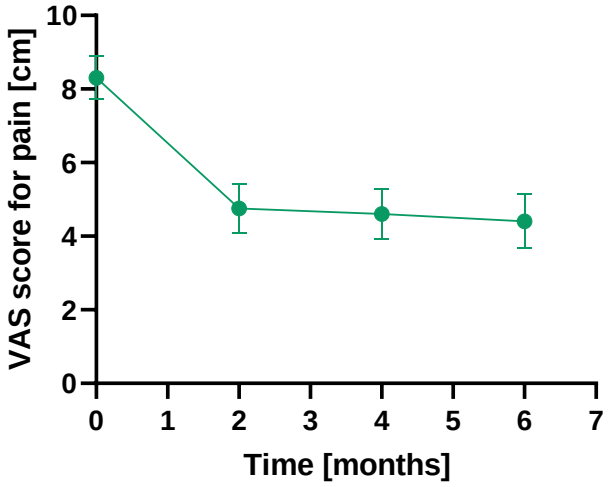


Figure 1: Evolution of VAS score for pain. Data are presented as mean ± standard deviation (SD). ***, $p<0.001$

Braun M, Groenemeyer DH, Schirp S. *Radiology*, 2002; 225(Suppl):557.

PAIN IN HIP OSTEOARTHRITIS DECREASES SIGNIFICANTLY FOLLOWING TREATMENT WITH OSTENIL

- Study design: monocentric, prospective, open-label trial evaluating the efficacy of three sonographically guided injections of Ostenil with a follow-up of at least 6 months.
- Study population: patients suffering from unilateral hip osteoarthritis (diagnosed on the basis of clinical and radiological findings). Exclusion criteria not mentioned. N = 10
- Based on VAS and Western Ontario & McMaster Universities Osteoarthritis Index (WOMAC) scores, pain was reduced in 80% of patients 6 months post-injection. The mean VAS score improved significantly from 8.3 cm at baseline to 4.4 cm at Month 6. The mean WOMAC score improved significantly from 41.6 at baseline to 20 at Month 6 (Figure 2).
- The WOMAC score identified 20% of patients as having excellent results (WOMAC 0-14), 60% good outcomes (WOMAC 15-28) and 20% fair results (WOMAC 29-38).
- No complication at the injection site, no joint infection, and no systemic side effects were reported. Most patients had mild pain during needle insertion but this resolved soon after the procedure was over.



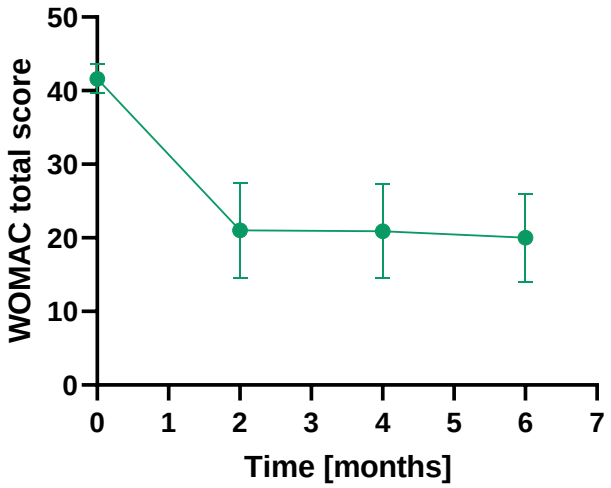


Figure 2: Evolution of VAS score for pain and WOMAC total score. Data are presented as mean ± SD

Pourbagher MA, Ozalay M, Pourbagher A. *J Ultrasound Med*, 2005; 24(10):1391-5.

OSTENIL AND SYNVISC HAVE A SIMILAR EFFICACY TO REDUCE PAIN AND INCREASE ACTIVITIES IN HIP OSTEOARTHRITIS

- Study design: prospective, randomized, single-blind study comparing three injections of the low molecular weight hyaluronic acid (HA) Ostenil 1% with three injections of the high molecular weight HA Synvisc 0.8% over a 6 month period.
- Study population: patients suffering from primary hip osteoarthritis (American College of Rheumatology [ACR] criteria), Kellgren-Lawrence grade ≤3, with pain scoring ≥50 mm on a 100-mm visual analogue scale, Lequesne index >6, persistence of pain for ≥3 months despite conservative methods. Key exclusion criteria: inflammatory joint disease, erythrocyte sedimentation rate >40 mm/h, recent intra-articular injection of corticosteroids or HA, previous hip surgery. N = 48
- Pain measured by VAS score decreased significantly in both groups at Month 1 and this effect persisted until Month 6 (Ostenil: 38% reduction; Synvisc: 40% reduction). No significant difference between the groups was identified (Figure 3).
- WOMAC score improved significantly in both groups at Month 1 and this effect persisted until Month 6 (Ostenil: 43% reduction; Synvisc: 40% reduction). No significant difference between the groups was identified. Similar results were obtained for the Lequesne index.
- Walking time for 30 m, time to sit and stand up 10 times, and time to go up and down 20 stairs were reduced in both groups at Month 1 and stayed stable until Month 6. No significant difference between the groups was identified.
- The intake of nonsteroidal anti-inflammatory drugs (NSAID) was significantly reduced in both groups at the end of the follow-up period (Ostenil: 60% reduction; Synvisc: 56% reduction).
- No systemic adverse event (AE) was reported. Local AEs consisted of pain and/or swelling and were noted in 9% of Ostenil and 12.5% of Synvisc patients.

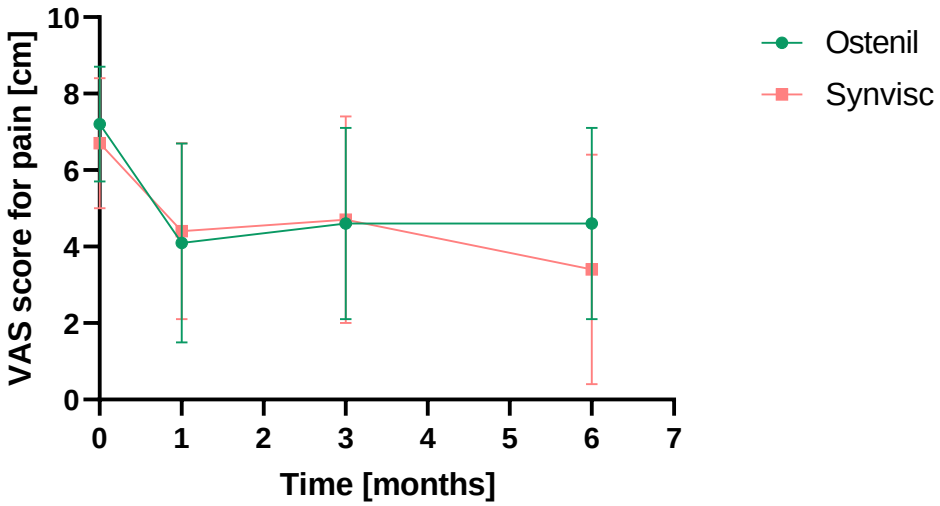


Figure 3: Pretreatment values and the changes in VAS score for pain after treatment. Differences between the two groups were not statistically significant. Data are presented as mean ± SD.

Tikiz C, Ünlü Z, Sener A, Efe M, Tüzün C. *Clin Rheumatol*, 2005; 24(3):244-50.

THREE INJECTIONS OF OSTENIL LEAD TO IMPROVEMENT OF PAIN AND OF DAILY ACTIVITIES

- Study design: prospective trial evaluating the efficacy of three injections of Ostenil at a rate of one injection per week with a follow-up of approximately three weeks.
- Study population: patients suffering from knee osteoarthritis, Kellgren-Lawrence grade I-IV. Exclusion criteria not mentioned. N = 50
- The majority of patients (70%) suffered from Kellgren-Lawrence grade II-III osteoarthritis, but 8% had a severe knee osteoarthritis (Kellgren-Lawrence grade IV).
- Resting pain, pain on movement and impairment in activities of daily life were all improved at the end of the follow-up period. Most patients noticed this improvement already after the second injection.
- The WOMAC score improved significantly from 52.1 points at baseline to 35.5 points at the end of the follow-up period ($p<0.05$). Similar results were obtained for the Lequesne index which improved from 12.7 to 9.2 points. The Tegner & Lysholm activity score also improved significantly from 2.3 to 3.7 points (Figure 4).
- No AE was reported during the study.

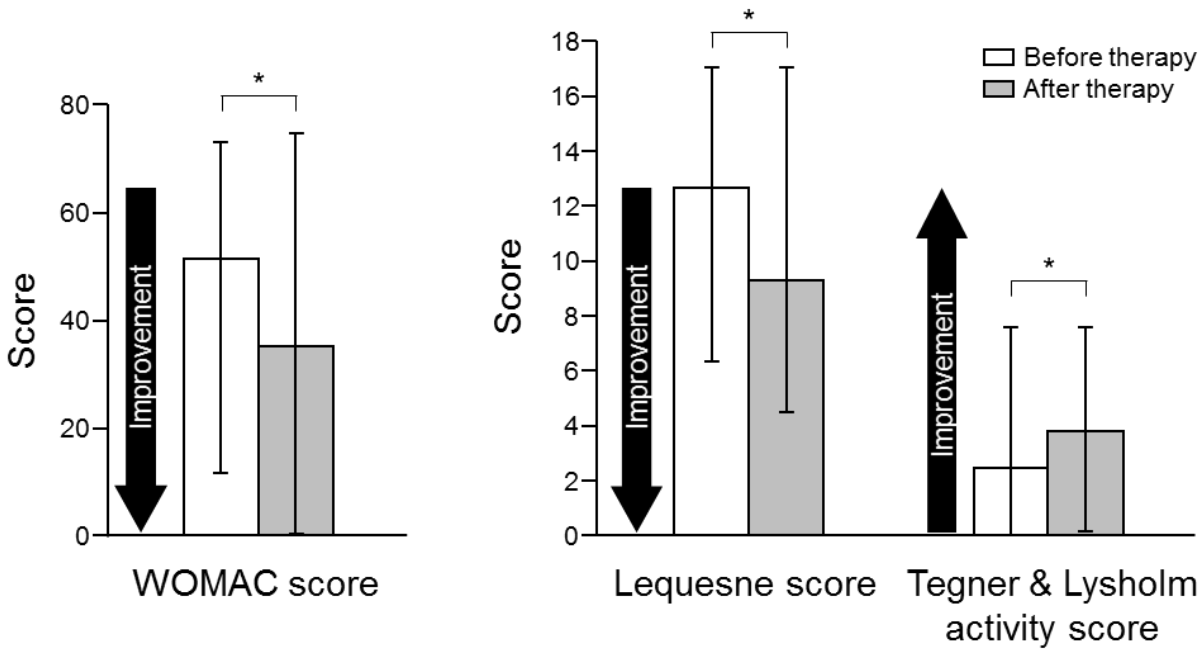


Figure 4: Evolution of WOMAC, Lequesne, and Tegner & Lysholm scores between baseline and the end of the follow-up period. *, $p<0.05$

Rehm S, Wulle EL. *Orthop Prax*, 2007; 43(7):370-3.

USING FLUOROSCOPY DURING INJECTION REDUCES PAIN IN PATIENTS RECEIVING OSTENIL TO TREAT HAND OSTEOARTHRITIS

- Study design: prospective trial comparing the pain induced by three injections of Ostenil with (group A) and without (group B) fluoroscopy control with a follow-up period of one month after the first injection.
- Study population: patients suffering from radiographic painful osteoarthritis of the first carpometacarpal joints. Key exclusion criteria: psychotic disorders, mental retardation, infection or any skin conditions at the injection site, non-osteoarthritic joint disease, malignant disease, use of anticoagulants. N = 16
- All patients complained of pain and discomfort during the injections. The mean VAS scores of the pain in groups A and B were 4.1 (range 3–6) and 5.6 cm (range 3–7), respectively (Figure 5). The difference of the VAS scores between the two groups was statistically significant ($p<0.005$).
- The tolerability of the treatment was evaluated as moderate to good by the patients of both groups.
- No complications were reported following the intra-articular injections.

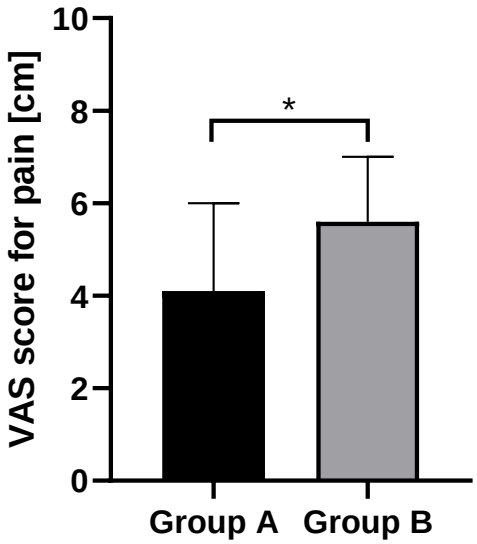


Figure 5: VAS score for pain during injection. *, $p<0.005$

OSTENIL MIGHT PREVENT LOSS OF CARTILAGE VOLUME IN THE PATELLAR REGION

- Study design: prospective, randomized, controlled trial comparing the efficacy of 5 injections of Ostenil with conventional treatment over 24 weeks.
- Study population: patients suffering from knee osteoarthritis, Kellgren-Lawrence grade II-III. Exclusion criteria not mentioned. N = 33
- Statistical analysis demonstrated that VAS score for pain and Range of Motion over 24 weeks were significantly improved in the Ostenil group compared to the control group.
- After 24 weeks, WOMAC pain subscore decreased by an average of 45.0% and the total WOMAC score by 29.2% in the Ostenil group. These differences were statistically significant versus control group (Figure 6).
- 23.5% of patients in the control group and 86.7% of patients in the Ostenil group evaluated the treatment effects as positive. The inter-group difference was statistically significant.
- Quantitative magnetic resonance tomography did not identify any significant difference between the two groups. A numerical decrease of retropatellar parameters was observed in the control group (-16.1 mm^3) whereas these parameters were stable in the Ostenil group (0.91 mm^3), indicating a trend to a smaller loss of volume in the patellar region of the cartilage with Ostenil. The difference was not statistically significant (p = 0.2).

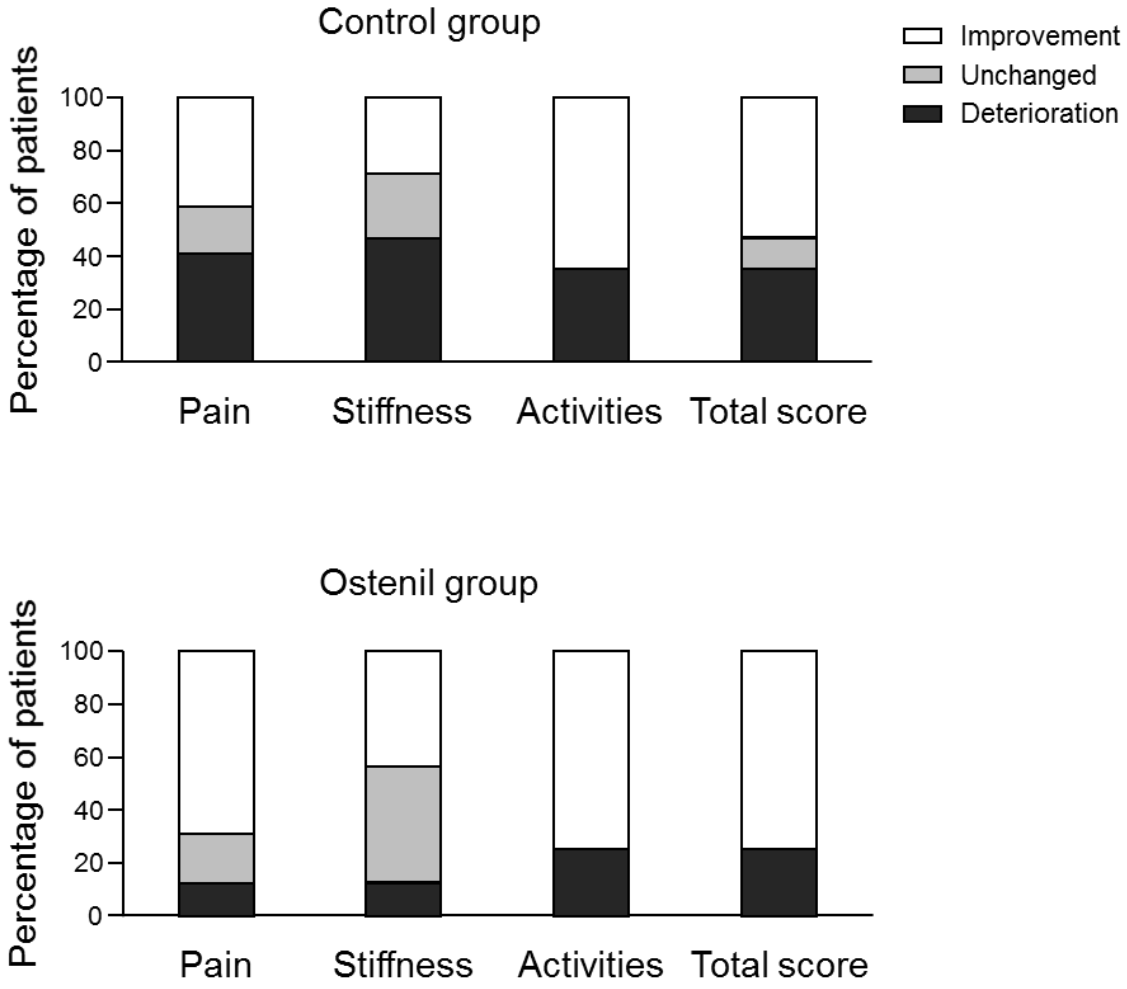


Figure 6: Change in the WOMAC score in the Ostenil and control groups over 24 weeks.

Von Eisenhart-Rothe R et al. *MedReview*, 2008; 9(1):10-1.

OSTENIL REDUCES PAIN AND IMPROVES KNEE FUNCTION IN A SIMILAR WAY TO TRIAMCINOLONE ACETONIDE

- Study design: monocentric, prospective, randomized, double-blind trial comparing five injections at weekly intervals of Ostenil and triamcinolone acetonide (TA, Volon A10) with a follow-up until 12 weeks after the last injection.
- Study population: patients aged 50-75 years, radiographically verified unilateral degenerative osteoarthritis of the knee, Kellgren-Lawrence grade II-III, with pain scoring ≥40 mm on a 100-mm visual analogue scale, persisting pain for ≥6 months, Lequesne score ≥10 points. Key exclusion criteria: non-degeneratively induced osteoarthritis, rheumatoid arthritis, ligamentous instability or complete resection of the meniscus, operations of the affected knee within the last three months, intra-articular therapy with HA within the last 6 months and/or with corticosteroids within the last three months, anti-thrombotic medication or regular medication with NSAID/psychiatric pharmaceuticals, infectious diseases, acute hemarthros or joint effusion. N = 42
- The VAS score for pain decreased significantly in both groups between baseline and one week after the last injection (Ostenil: Δ29.9 mm; TA: Δ37.4 mm). The improvement was maintained 12 weeks after the end of the treatment (Ostenil: Δ19.5 mm; TA: Δ25.9 mm). The intergroup differences were not statistically significant (Figure 7). Similar results were obtained for the Lequesne score and the Knee Society Score.
- The evaluation of the 36-Item Short Form Survey (SF-36) health questionnaire in both groups showed an improvement of the mean values for all parameters. In the Ostenil group, significant improvement was found only for the parameter physical function whereas in the TA group, significant improvement was shown only for the parameter social role function.
- In the computer-assisted gait analysis of the Ostenil group, small improvements of the mean values were observed, but a significant difference was only evident for the second maximum of the Knee Abduction Moment 12 weeks after the last injection. In the analysis of the TA group, no significant differences for any evaluated parameters at any time point could be demonstrated.
- In both groups there was no significant difference between Week 12 and baseline regarding muscle activity measured by electromyographic examination and no significant difference between the groups was identified.
- No complication or AE were reported in any of the groups.

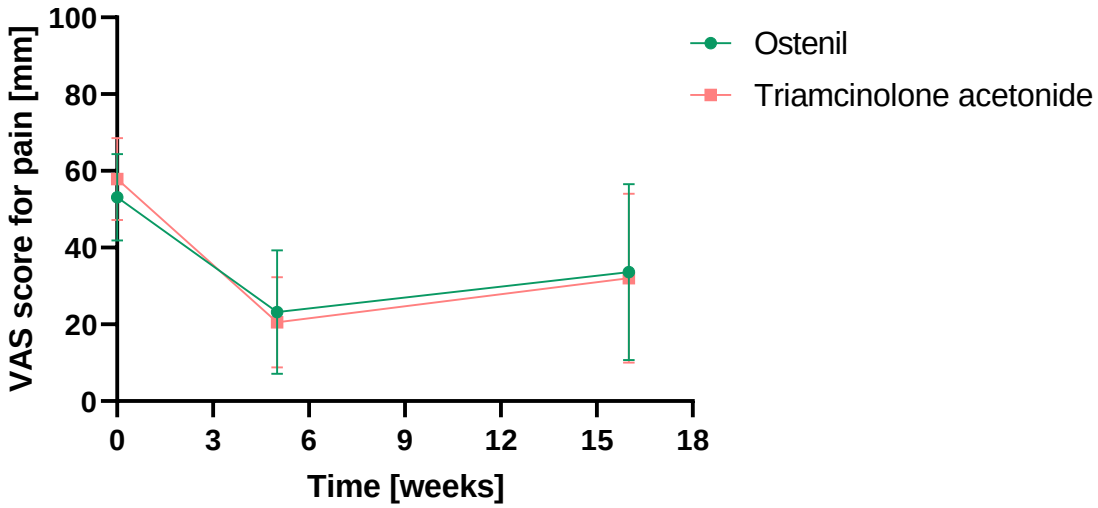


Figure 7: Evolution of the VAS score for pain. The differences between the two groups were not statistically significant. Data are presented as mean ± SD.

Skwara A, Peterlein CD, Tibesku CO, Rosenbaum D, Fuchs-Winkelmann S. *Knee*, 2009; 16(6):466-72.

OSTENIL WAS NOT BETTER THAN PLACEBO TO DECREASE PAIN IN PATIENTS SUFFERING FROM SHOULDER OSTEOARTHRITIS

- Study design: monocentric, prospective, randomized, double-blind trial comparing Ostenil, triamcinolone acetonide (TA) and NaCl 0.9% as placebo over 26 weeks. Lidocaine 1% was injected concomitantly with the tested product. Injections were repeated, if necessary, after three and six weeks. In case of complete resolution of pain, no further injections were given.
- Study population: patients aged ≥18 years suffering from pain in the shoulder either at rest or on movement, presenting with a painful arc with or without abnormal scapulohumeral movement. Key exclusion criteria: pain for <6 weeks, corticosteroid injection in the preceding three months, prior infection of the shoulder joints, previous fracture or surgery of the shoulder, osteoporosis, rheumatoid arthritis, ankylosing spondilitis. N = 159
- A reduction of the VAS score for pain was observed in all groups, with no significant difference between the three groups at baseline and at Week 26. TA was significantly superior to Ostenil at Week 3, 6 and 12. Placebo was superior to Ostenil at Week 12 and TA was significantly better than Placebo only at Week 6 (Figure 8).
- The mean reduction of pain at Week 12 versus baseline was 7% with Ostenil, 28% with TA and 23% with placebo. At Week 26, the mean reduction was 15% in the Ostenil group, 20% in the TA group and 21% in the placebo group. A reduction of pain versus baseline was observed in 63% of Ostenil patients, 72% of TA patients and 69% of placebo patients at Week 26.
- Similar trends were observed for the other secondary endpoints (Constant score, functional mobility test, shoulder disability questionnaire, shoulder pain score).
- Most adverse reactions encountered were local and mild and concerned prolonged pain after injection; there were no allergic reactions or infections.

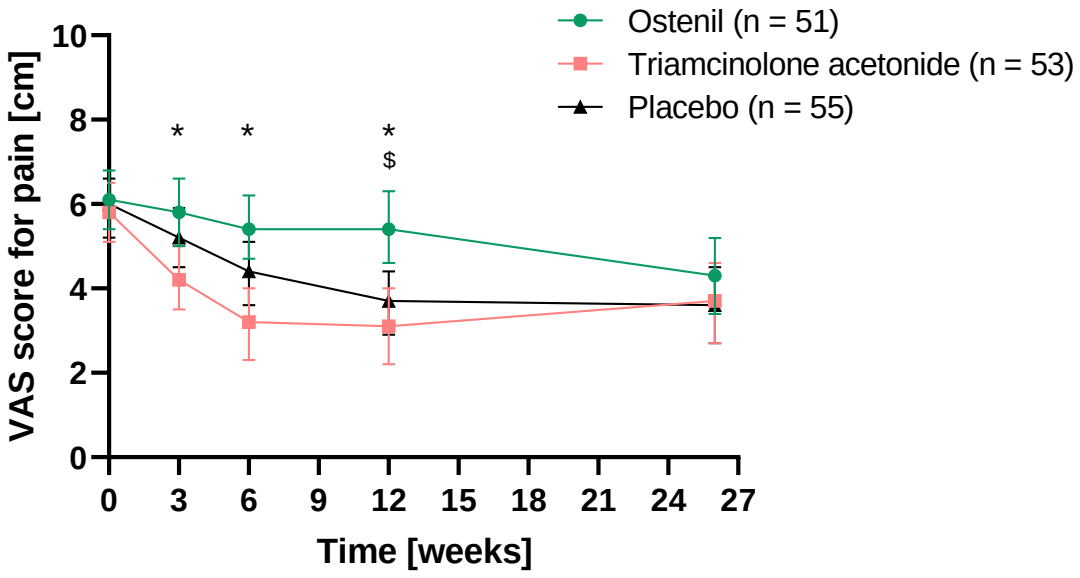


Figure 8: Mean VAS score for pain (95% confidence intervals) over the follow-up period adjusted for significant prognostic baseline variables. *, significant difference between TA and Ostenil group ($p < 0.005$); $, significant difference between placebo and Ostenil ($p = 0.001$)

Penning LI, de Bie RA, Walenkamp GH. *J Bone Joint Surg Br*, 2012;94(9):1246-52.

OSTENIL IS EFFECTIVE AND SAFE IN REAL-LIFE CONDITIONS, WITH LONG-LASTING EFFECTS UP TO 9 MONTHS AFTER THE INJECTIONS

- Study design: multicentric, prospective, open-label, post-marketing clinical follow-up evaluating the efficacy of 3 to 5 injections of Ostenil, over 9 months.
- Study population: patients aged ≥18 years, in good health condition, with an existing recommendation of using Ostenil for the treatment of knee osteoarthritis. Key exclusion criteria: presence of effusion in the joint. Objective: n = 250. Results reported here are those of a planned interim analysis performed after the inclusion of 47 patients.
- In this real-life cohort, the majority of patients suffered from Kellgren-Lawrence grade II knee osteoarthritis, but patients from grade 0 to III were included. Most patients had been suffering from osteoarthritis symptoms for > 6 months. 41 patients received 5 injections and 6 patients 4 injections.
- VAS score for pain decreased from 50.0 mm (median) at baseline to a median of 10.0 mm at Month 6. The pain decreased continuously from baseline to Week 4 and then remained stable up to Month 6. The reduction of pain versus baseline was significant at all time points. At Month 6, the median reduction of pain was -34.0 mm. The mean change from baseline of VAS pain score always exceeded the minimal clinically important difference for this parameter (10 mm). One week after the first injection, 61.7% of patients reported an improvement of pain compared to baseline. This proportion increased continuously to reach 93.9% of patients at Month 6.
- The range of motion increased from 130° (median) to 140° at Month 6. The change was statistically significant from Week 2 onwards. At baseline, 75% of patients already had a normal range of motion (between 120° and 150°) and only 7 patients had a limited flexion range. At Month 6, all patients except one were within the normal range.
- The four categories (quality of life, activities of daily living, pain and stiffness) of the Knee Injury and Osteoarthritis Outcome Score (KOOS) improved significantly from baseline to Month 3. The improvement was maintained up to Month 6 (Figure 9).
- After six months, 87.9% of patients and 84.8% of investigators reported an improvement of osteoarthritis symptoms.
- The rate of responders was analysed based on the Outcome Measures in Rheumatology Clinical Trials–Osteoarthritis Research Society International (OMERACT-OARSI) criteria. Three months after the first injection, 82.1% of patients were classified as responders.
- In the telephone survey performed nine months after the first injection, 90% of patients (18/20) rated their knee problems as very improved/improved.
- Five adverse events in four patients were reported during the study, none of them assessed as related to Ostenil treatment.

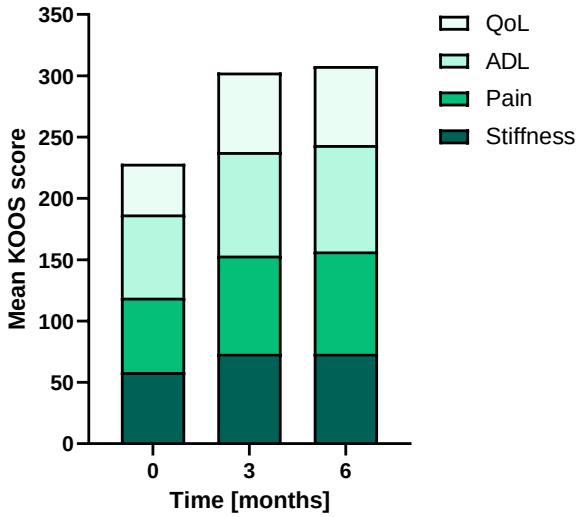


Figure 9: Mean KOOS score per category over the follow-up period.

Krüger-Franke M, Gillesberger F, Rucker A. *OUP*, 2022; 11: 169–173.

A TREATMENT CYCLE WITH OSTENIL DELAYS TOTAL KNEE REPLACEMENT BY UP TO 12 MONTHS

- Study design: monocentric, prospective, open-label, pilot, phase III trial evaluating the efficacy of five injections of Ostenil at weekly intervals with a follow-up up to 12 months after the first injection
- Study population: patients suffering from painful advanced knee osteoarthritis, candidate to receive total knee replacement (TKR) within three months (based on Kellgren-Lawrence scale and severe clinical scores), continuous treatment with NSAIDs. Key exclusion criteria: accompanying osteoarthritis of the hip interfering with the assessment of the knee, known or suspected infection of the joint, painful knee conditions other than osteoarthritis, severe obesity (body mass index [BMI] >40), treatment with symptomatic slow-acting drug for osteoarthritis (SYSADOA) or intra-articular corticosteroid within the last three months. N = 24
- The VAS score for pain on walking improved significantly from 43.67 mm at baseline to 16.67 mm before the last injection (61.8% reduction) and then stayed stable during the treatment-free follow-up period.
- The WOMAC pain subscore improved significantly from 6.86 at baseline to 2.43 mm at the last visit. Similar results were obtained for the WOMAC stiffness (45.7% reduction after 2 injections) and physical impairment (34.9% reduction after 2 injections) subscores.
- Of the 21 patients evaluated, three underwent TKR between 4.5 and 6 months after the start of treatment while the other 18 did not require TKR in the 12-month period after the start of treatment (end of study). TKR was delayed by a mean of 7.5 ± 2.3 months after a treatment cycle with Ostenil.
- Quality of life measured by the SF-36 score improved significantly up to three months after the first injection, with a 22% improvement in the median score (Figure 10).
- Knee effusion, which was present in 80% of the patients at baseline, was found in 57.1% of the patients at the last visit.
- Consumption of analgesics or NSAIDs did not change during the study period.
- Patients judged treatment as ‘good’ or ‘excellent’ in 53% of the cases at Month 3. At the end of the study, 43% of the patients judged the treatment as ‘good’ or ‘excellent’. The efficacy judgements expressed by the investigator showed a similar trend.
- The dynamic elasticity, the dynamic viscosity and the steady state viscosity of the synovial fluid all increased from baseline to Month 3.
- One AE (impaired joint function, of moderate intensity, due to effusion occurring one day after the second injection and lasting more than 1 day but resolving spontaneously) was reported in one patient.

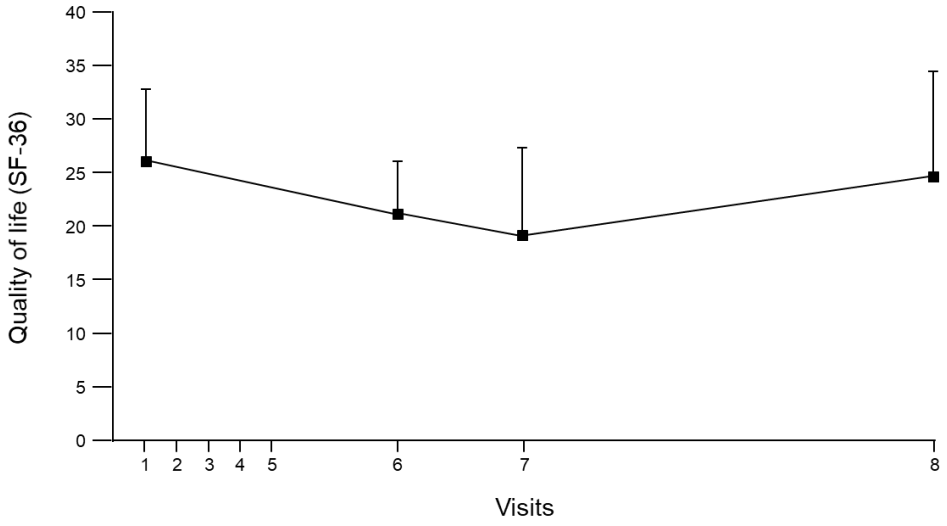


Figure 10: Quality of life measured by the SF-36 score.

Mathies B, Berger J, Siegfried C, Gurny R. *ICRS Abstract Book*, 2004. Abstract No.: 397.

OSTENIL IS AS EFFICIENT THAN SYNVISC BUT HAS A BETTER SAFETY PROFILE

- Study design: prospective, randomized, controlled trial comparing three weekly injections of Ostenil or Synvisc with a follow-up over 150 days.
- Study population: patients suffering from radiologically confirmed primary osteoarthritis of the knee, Larsen grade I-III, persistent pain of the target knee despite analgesic use, erythrocyte sedimentation rate <40. Key exclusion criterion: effusion in the target joint. N = 50
- The WOMAC pain score improved in both groups, reaching statistical significance from Day 28 to Day 150 (Figure 11). The improvement was similar in both groups, e.g. at Day 150: Δ17.8 for Ostenil (-74.9%), Δ18.29 for Synvisc (-59.2%).
- The WOMAC joint function score improved in both groups, reaching statistical significance from Day 21 to Day 150. The improvement was similar in both groups, e.g. at Day 150: Δ61.3 for Ostenil (-75.4%), Δ66.9 for Synvisc (-63.9%).
- Except for the baseline values of the functional assessments (where the Synvisc group was a bit more severe), there were no statistically significant differences between the groups.
- Adverse events were reported in 0% of Ostenil patients and in 16.7% of Synvisc patients and mostly concerned pain at the injection site. The rate of drop-outs was also significantly higher in the Synvisc group, with 25% of drop-outs versus 3.8% in the Ostenil group (p = 0.045).

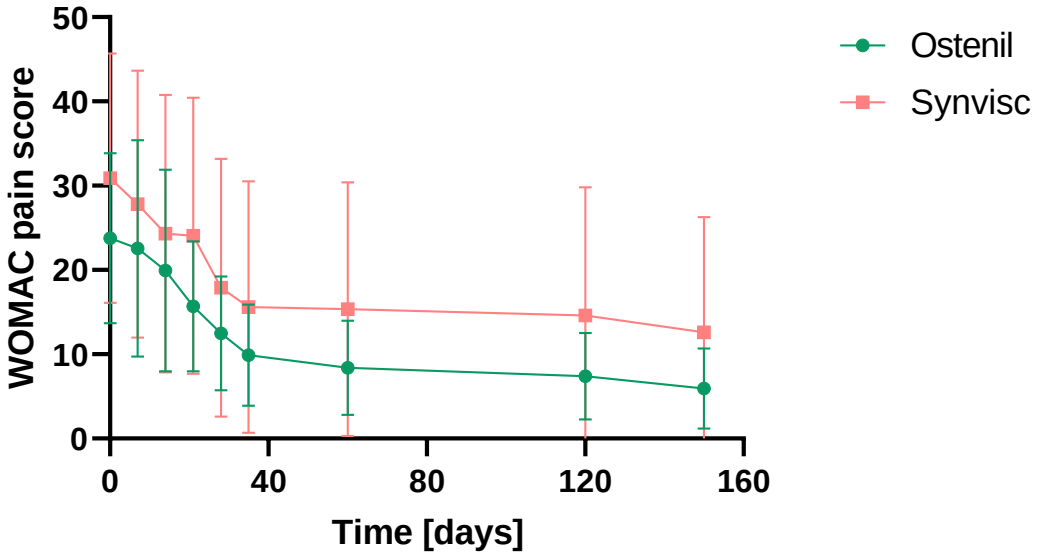


Figure 11: Overall evolution of WOMAC pain score. Data are presented as mean ± SD.

Fraiman S, Aparicio R. *Rev Argent Gerontol Geriatr*, 2002; 22:15-20.

BOTH 3-INJECTION AND 5-INJECTION COURSES OF OSTENIL DEMONSTRATE EFFICACY UP TO 12 MONTHS AFTER THE FIRST INJECTION

- Study design: multicentre, prospective, randomized, masked-observer study comparing 3 injections of Ostenil plus 2 injections of lidocaine (3X) with 5 injections of Ostenil (5X) over 48 weeks.
- Study population: patients aged 50-70 years, suffering from knee osteoarthritis (ACR criteria), Kellgren-Lawrence grade I-III. Exclusion criteria not mentioned. N = 140
- WOMAC pain subscore decreased from baseline in a statistically significant manner in both groups between baseline and week 5 ($p<0.001$): from 40.3 mm to 16.3 mm in the 3X group and from 41.7 mm to 17.5 mm in the 5X group. The pain subscores remained at a stable level until Week 48. No statistically significant intergroup difference was found (Figure 12). Similar results were obtained for the WOMAC stiffness and function subscores. None of the intergroup differences reached statistical significance.
- At Week 5, 88.5% of 3X patients and 87.1% of 5X patients evaluated the treatment as moderately to very effective. This number decreased slowly to reach 68.5% (3X) and 68.6 (5X) of patients at Week 48. The overall judgment of efficacy by the investigators followed a similar trend.
- Response to treatment was defined as a ≥20% improvement of WOMAC score compared with baseline. At Week 5, 70.0% of 3X patients and 65.7% of 5X patients were identified as responders whereas this was the case of 50.0% and 44.2% at week 48 for 3X and 5X, respectively.
- Ostenil was well tolerated by the patients. Local AEs (synovitis) were reported in two patients (one in each group). No serious AE occurred in this study.
- The authors propose that the absence of difference between the 3-injection and the 5-injection courses can be explained in part by the presence of patients with more severe radiological grade in the 5X group.

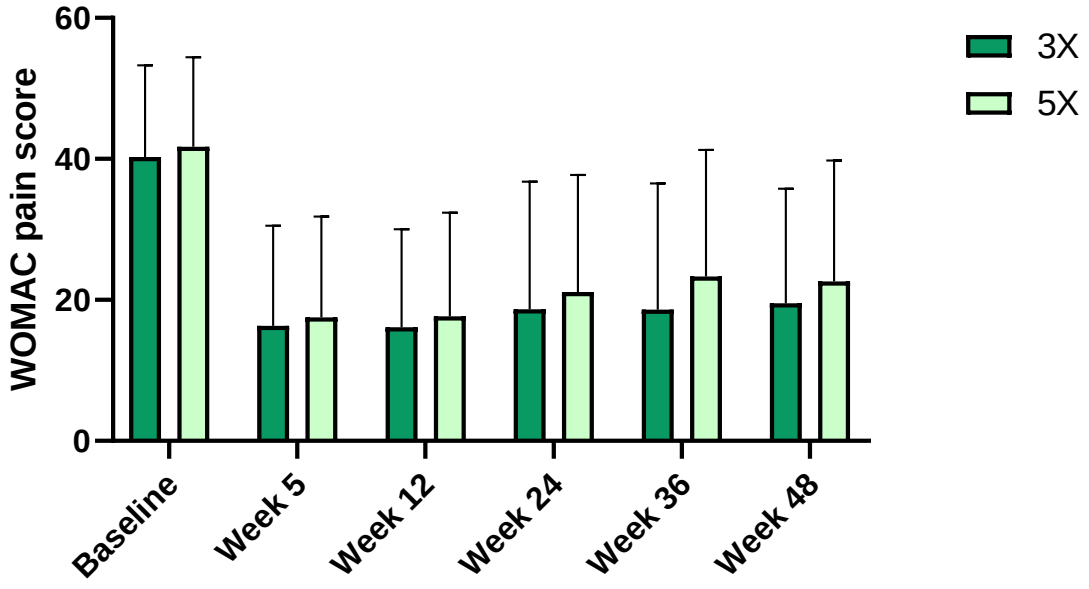


Figure 12: WOMAC pain subscore. Data are presented as mean ± SD.

Belenkiy A, Denisov L, Lila A, Shmidt EI, Panasyuk E, Ionichenok N, et al. *Ann Rheum Dis*, 2006;65 (Suppl 2):223-4. Abstract No.: THU0351.

OSTENIL SHOWS A GREATER EFFICACY IN PATIENTS WITH KELLGREN-LAWRENCE GRADE <4

- Study design: monocentric, observational study evaluating the efficacy of three to five injections of Ostenil over 8 weeks.
- Study population: patients suffering from osteoarthritis of any synovial joint. Exclusion criteria not mentioned. N = 154
- The majority of enrolled patients (n = 140) suffered from knee osteoarthritis; other affected joints were the hip, the ankle and the shoulder. Osteoarthritis was mainly (62.4%) of grade II-III on the Kellgren-Lawrence scale.
- The mean WOMAC total score improved during the study period from 58.5 ± 20.9 points before treatment to 69.6 ± 19.8 points at one week (Visit 6) and 77.6 ± 19.1 points at four weeks (Visit 7) after the last injection (Figure 13).
- The results of the individual subscores showed a similar improvement: the WOMAC pain subscore improved from 58.8 at baseline to 70.5 (Visit 6) and 78.7 (Visit 7) points, the WOMAC stiffness subscore from 56.7 to 67.7 and 76.2 points and the WOMAC daily activities subscore showed mean values of 58.6, 69.6 and 77.4 points.
- A stratification analysis of the WOMAC total score based on the Kellgren-Lawrence scale showed an improvement in 100% of patients with grade 0, 95.2% of patients with grade 1, 100.0% of patients with grade 2, 96.7% of patients with grade 3 and 75.0% of patients with grade 4 osteoarthritis.
- The number of patients who had no functional limitations increased from a baseline value of 7.3% to 50.0% four weeks after the last injection. The most significant improvement in joint function in the total patient population occurred from Visit 5 (time of final injection) to Visit 6, i.e. from 29.3% to 45.3% of the patients. Following stratification of the treatment results in accordance with the radiographic findings of the joint, there was an improvement in joint mobility in 83.3% (grade 0), 61.9% (grade 1), 62.2% (grade 2), 75.9% (grade 3) and 45.5% (grade 4) of the patients. No patient experienced a worsening of joint mobility.
- While at baseline only 6.4% of patients had “no” pain or “mild” pain, this value increased to 47.7% at Visit 6 and 74.3% at Visit 7. The proportion of patients who rated their pain as “severe” or “unbearable” decreased, from a baseline value of 51.4% to 10.1% (Visit 6) and 8.3% (Visit 7).
- Four weeks after the end of treatment, 75.7% of the patients had a “good” to “very good” global impression of the treatment and only 11.2% judged that the treatment was unsuccessful. Similar results were obtained for the physician’s overall assessment. The most favourable global assessment was observed in patients with Kellgren-Lawrence grade 2 and the least favourable one in grade 4 patients.
- 91.7% and 94.5% of patients had no AEs at Visit 6 and Visit 7, respectively. No causal relationship was identified for the AEs observed in the remaining patients.

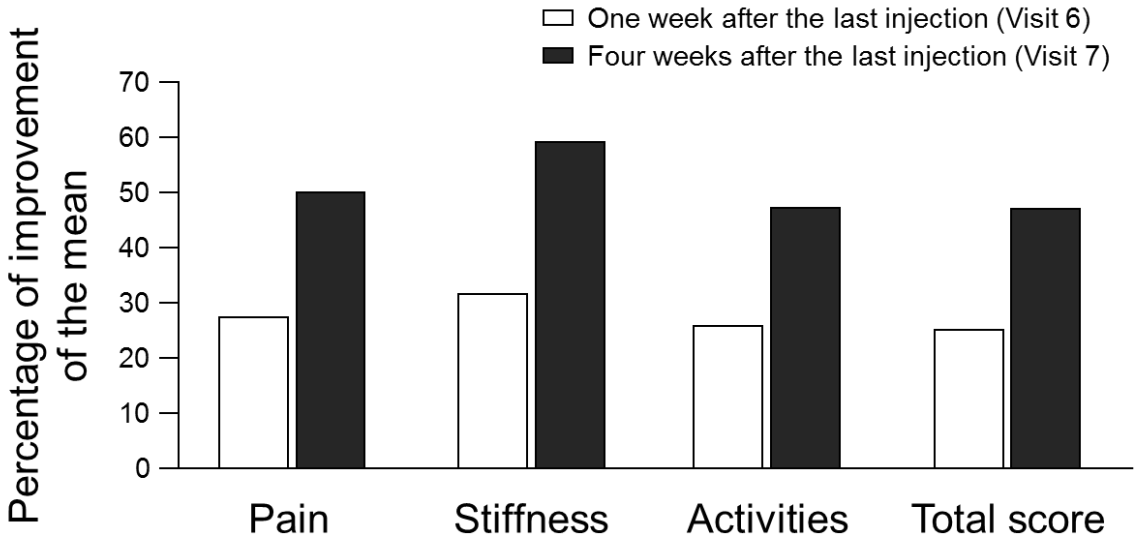


Figure 13: Improvement of WOMAC score and subscores versus baseline.

Engelhardt M. *Osteoporose & Rheuma aktuell*. 2008; 3:36-40, 2, 4-5.

OSTENIL IS SUPERIOR TO LIDOCAINE AND HAS A 12-MONTH EFFECT IN PATIENTS SUFFERING FROM HIP OSTEOARTHRITIS

- Study design: multicentre, prospective, randomized, double-blind trial comparing three injections at weekly intervals of Ostenil or lidocaine 20 mg/2 mL. Lidocaine patients were followed for 6 months whereas patients receiving Ostenil were followed for 12 months.
- Study population: patients aged 40-75 years, suffering from hip osteoarthritis (ACR criteria), Kellgren-Lawrence grade I-III, with pain scoring ≥40 mm on the WOMAC A pain subscale visual analogue scale. Key exclusion criteria: inflammatory rheumatology disease, accompanying knee osteoarthritis of sufficient severity to interfere with hip function assessment, trauma or arthroscopic procedures in the past, necrosis of the femoral head, severe concomitant disease. N = 74
- The WOMAC pain subscore decreased in both groups between baseline and Month 1. It then increased gradually in the lidocaine group while remaining stable in the Ostenil group, leading to a significantly better reduction of pain in the Ostenil group at Month 6 (Figure 14). Similar results were obtained for the total WOMAC score, the WOMAC stiffness subscore and the WOMAC function subscore, although the intergroup difference did not reach statistical significance for the last two scores.
- Global assessment of their condition by patients improved in both groups during the 6-month follow-up period, with no significant intergroup difference.
- The consumption of rescue medication (paracetamol) decreases significantly in the Ostenil group after the end of the treatment and stayed stable until Month 6 whereas in the lidocaine group, the reduction was not statistically significant versus baseline.
- The long term analysis of the Ostenil group showed that the WOMAC total score and the pain, stiffness, and function subscores all stayed stable and low until 12 months after the first injection.
- Five patients in the lidocaine group (versus none in the Ostenil group) had to stop the study due to the inefficacy of the treatment.
- No local or systemic AE was reported in any of the groups during the study.

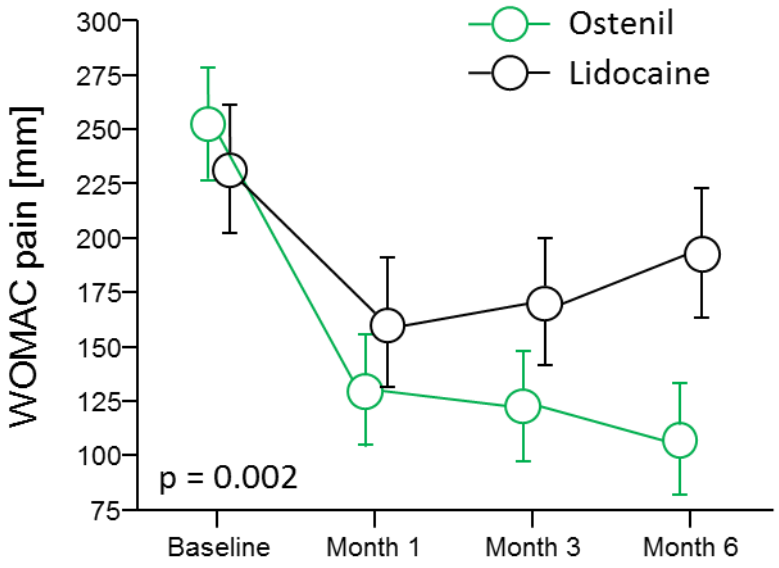


Figure 14: Pain dynamics according to WOMAC index. P = 0.002

Tsvetkova ES, Denisov L, Shmidt EI, Ryabitseva O, Anikin S. *Ann Rheum Dis*, 2010; 69(Suppl 3):281. Abstract No.: THU0411.

OSTENIL 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 (Figure 15). This tendency was confirmed at Week 24, 48 and 72.
- 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.

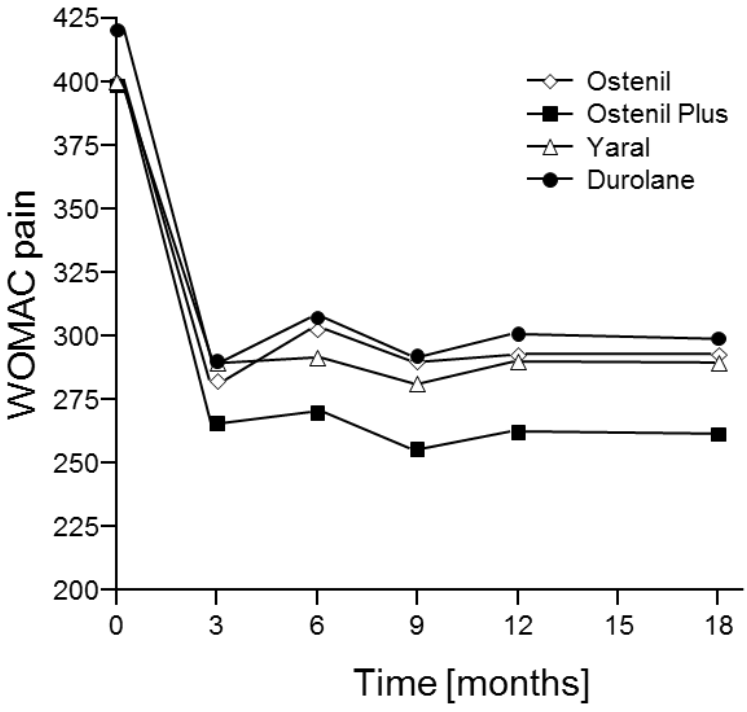


Figure 15: WOMAC pain score measured on a VAS.

Stoilov R, Goycheva M, Garbeva K, Marinova N, Manolova I. *Osteoporos Int*. 2011; 22(Suppl 1):S361. Abstract No.: P585.

THREE QUARTERS OF PATIENTS WITH KNEE OSTEOARTHRITIS RESPOND TO OSTENIL TREATMENT

- Study design: multicentre, prospective, randomized, double-blind, controlled, non-inferiority study comparing three injections at weekly intervals of Ostenil or hylan G-F 20 (Synvisc) over a follow-up period of 6 months.
- Study population: patients aged 40-80 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. Exclusion criteria not mentioned. N = 269
- In the PP population, the mean WOMAC A improved by 28.9 ± 20.8 mm and 27.8 ± 22.9 mm at Day 180 versus baseline for Ostenil and Synvisc, respectively (Figure 16). The mean observed difference between groups was 1.0 mm, with a two-sided 95% confidence interval (CI) of [-5.0; 7.1 mm]. The lower bound of the confidence interval was above the non-inferiority margin (-8 mm), indicating the non-inferiority of Ostenil versus Synvisc in this population. Results were similar for the intention-to-treat (ITT) population.
- The WOMAC stiffness subscore improved in both groups between baseline and Day 180 (Ostenil: Δ23.2, Synvisc: Δ17.5), with no statistically significant intergroup difference. Similar results were obtained for the WOMAC function subscore (Ostenil: Δ22.8, Synvisc: Δ18.5) and for the Lequesne index (Ostenil: Δ4.2 points, Synvisc: Δ3.5 points).
- The SF-12 physical score and the SF-12 mental health score which reflect the quality of life of the patients improved in both groups between baseline and day 180, with no statistically significant intergroup difference.
- The rate of responders as defined based on the OMERACT-OARSI criteria in the per protocol (PP) population was numerically higher in the Ostenil group (75.7%) than in the Synvisc group (70.2%) but the difference did not reach statistical significance. Similar results were obtained when the ITT population was analysed.
- AEs included local inflammatory reaction (3 occurrences), effusion (1), burning sensation (1) in the Ostenil group and effusion (2), headache (3) in the Synvisc group.

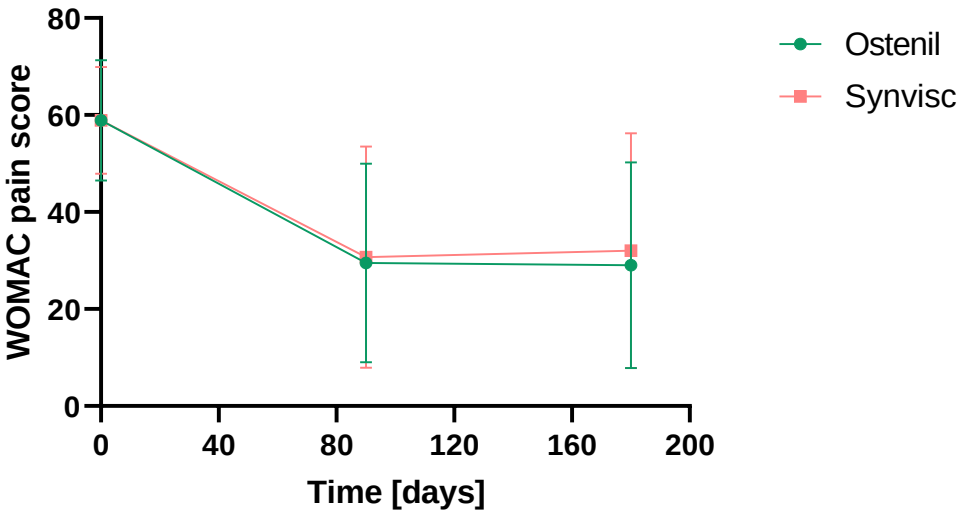


Figure 16: Evolution of WOMAC pain score. The differences between the groups were not statistically significant. Data are presented as mean ± SD.

Dreiser RL, Avouac B, Bardin T. *Ann Rheum Dis*, 2012; 71(Suppl 3):584-5. Abstract No.: SAT0333.

3 INJECTIONS OF OSTENIL ARE REQUIRED TO OBSERVE AN IMPROVEMENT OF WOMAC SCORE AND OF PAIN

- Study design: monocentric, prospective, randomized trial comparing a single injection of 6 mL Ostenil (1X) with 3 weekly injections of 2 mL Ostenil (3X) over 12 weeks. 1 ml of triamcinolone hexacetonide was added to the first dosage in both groups.
- Study population: patients suffering from knee osteoarthritis (ACR criteria), absence of history of previous surgery and/or fracture of the studied knee, no infiltration in the studied knee for at least 6 months. Key exclusion criteria: severe reaction to the procedure, development of active infection in the studied knee joint during the study, use of non-hormonal anti-inflammatory drugs at any time. N = 108
- An improvement of total WOMAC score and of WOMAC pain subscore was observed only in the 3X group (Figure 17). Even though this improvement was statistically significant versus baseline in the 3X group only ($p<0.001$), it was not possible to differentiate between the groups in relation to the WOMAC and WOMAC pain scales at any time ($p>0.05$).
- The VAS score for pain presented reduction in both groups, with a statistical decrease from baseline to one month only in the 3X group ($p<0.001$). At no time was there any statistically significant difference in the mean values of pain between the groups ($p>0.05$).
- Lequesne score improved in both groups after one month and returned close to the initial value after three months. Both groups present an improvement in the physical component of the SF-36 quality of life questionnaire.

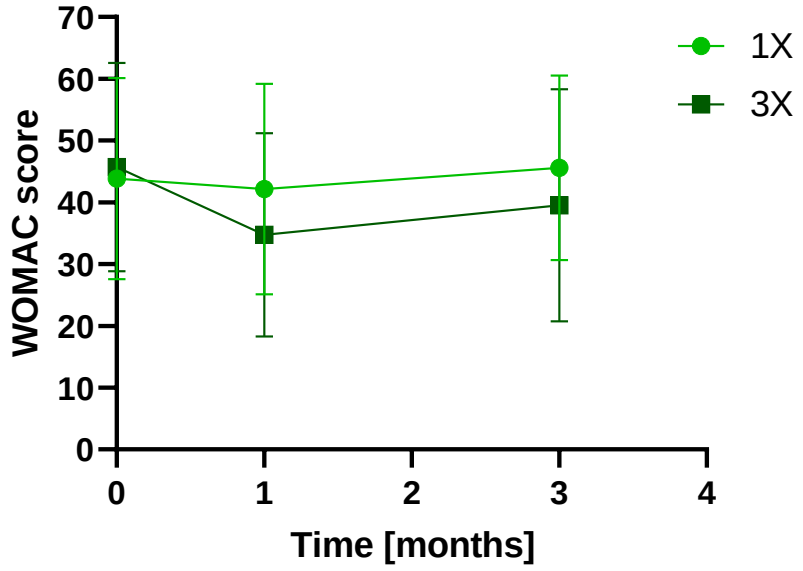


Figure 17: Evolution of WOMAC pain score. Data are presented as mean ± SD.

Zoboli AA, de Rezende MU, de Campos GC, Pasqualin T, Frucchi R, de Camargo OP. *Acta Ortop Bras*, 2013;21 (5):271-5.

IN REAL LIFE CONDITIONS, 75% OF OSTENIL PATIENTS RATED THEIR OVERALL IMPROVEMENT AS GOOD TO VERY GOOD

- Study design: sub-study of a multicentric, retrospective, observational registry evaluating the usual clinical use of Ostenil and Ostenil Plus in Argentina.
- Study population: patients with a diagnosis of knee osteoarthritis, who received intra-articular hyaluronic acid, with a follow-up visit at six months documented in the clinical history. N = 1227
- The total number of injections was significantly higher in the Ostenil (5.7 ± 3.1 injections) than in the Ostenil Plus (3.7 ± 2.1 injections) group.
- Efficacy was evaluated by the researchers before starting treatment (baseline) and at six months, using a 5-point Likert scale, which assessed pain and functional limitation (scores from 1 = asymptomatic to 5 = very severe). The median Likert score improved significantly from baseline to six months in both groups: from 3.77 ± 0.69 to 1.99 ± 0.76 in the Ostenil group, and from 3.65 ± 0.65 to 1.86 ± 0.72 in the Ostenil Plus group (Figure 18).
- 61% and 66% of patients had an improvement of ≥50% of the symptom score in the Ostenil and Ostenil Plus groups, respectively. Patients who achieved an improvement of 50% or more were younger, had shorter disease progression and a higher baseline Likert score than non-responders.
- 75% of Ostenil patients and 81% of Ostenil Plus patients rated their overall improvement as good or very good.
- The most common treatment-related adverse events reported were mild or moderate injection-site reactions: 11/953 (1.2%) in the Ostenil group and 1/274 (0.36%) in the Ostenil Plus group.

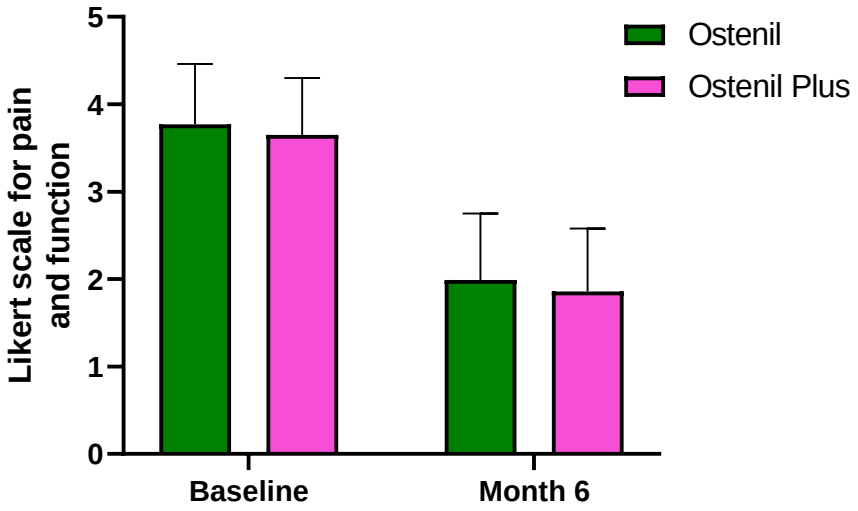


Figure 18: Evolution of Likert scale for pain and functional limitation. Data are presented as mean ± SD.

Berenstein M, Tacus L, Kobrinsky P, Vaineras D. Rev Asoc Argent Ortop Traumatol. 2019;84(2):122-8.

OSTENIL DRAMATICALLY IMPROVES THE ABILITY OF PATIENTS WITH KNEE OSTEOARTHRITIS TO PERFORM DAILY ACTIVITIES

- Study design: monocentric, prospective, open-label study evaluating the efficacy of five weekly injections of Ostenil with a 6-month follow-up.
- Study population: patients aged 37-75 years, suffering from knee osteoarthritis, Kellgren-Lawrence grade II-III, BMI 18-30. Key exclusion criteria: other inflammatory diseases, any other joint problems, treatment such as intra-articular corticosteroids, NSAIDs, SYSADOA or osteoporosis treatment during the 3 months prior to the study. N = 40
- A statistically significant improvement of the Lequesne index was observed at Week 4 (-72.7%). The Lequesne index further improved one month after the end of the treatment and stayed stable six months after the end of the treatment (reduction of 89.9% versus baseline) (Figure 19). At the end of the study, an absolute improvement was observed in 97.5% of the patients.
- The VAS score for pain improved significantly during the study, with a reduction from 5.67 cm at baseline to 2.38 cm at Week 4, decreasing further until 0.88 cm one month after the last injection and staying stable at 0.83 cm 6 months after the end of the treatment.
- Six months after the end of the treatment, 95% of patients evaluated the efficacy of the treatment as very good or excellent, which was statistically significantly more than at Week 4.
- No radiological changes were noted 6 months after the end of the treatment when the treated and the non-treated knees were compared (all patients had bilateral osteoarthritis).
- The tolerability of the treatment was excellent. There were no changes in the laboratory safety parameters between baseline and the end of the study.

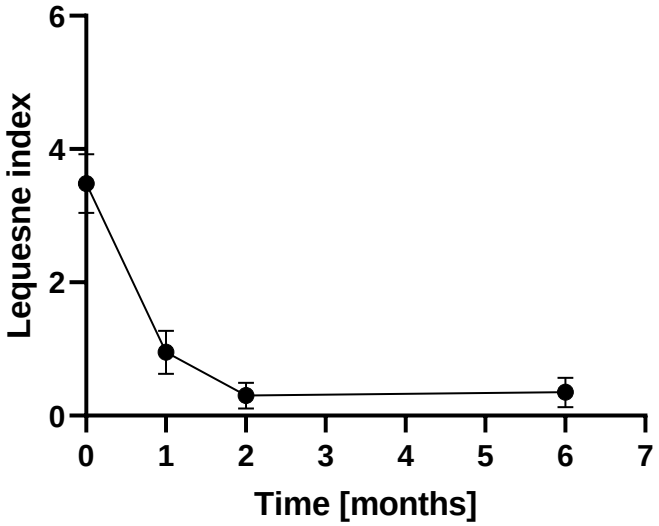


Figure 19: Evolution of the Lequesne index. Data are presented as mean ± 95% CI

Möller I, Moragues C, Marti N, Alegre JJ. *Osteoarthritis Cartilage*, 2001; 9(Suppl B):S51. Abstract No.: PB22.

OSTENIL REDUCES PAIN AND IMPROVES PATIENT SATISFACTION IN ADVANCED ARTHRITIS OF THE SHOULDER

- Study design: case series evaluating the efficacy of three injections of Ostenil at weekly intervals with a follow-up three months post-injection
- Study population: patients suffering from disabling arthritis of the shoulder, who were not suitable for shoulder arthroscopy as they were too medically unfit or refused shoulder replacement surgery. Exclusion criteria not mentioned. N = 7
- The mean patient age was 83 years (range 72 to 93), including six females and one male. Five patients had osteoarthritis, one rheumatoid arthritis and one cuff arthropathy.
- The mean Constant score improved post injection, from 15.5 (10-25) at baseline to 49.5 (25-84) at three months.
- Pain was evaluated on a 15-cm visual analogue scale and improved significantly from 11.6 cm (10-14) at baseline to 4.7 cm (0-9) after three months, corresponding to a 59.5% reduction.
- All patients had their sleep disturbed by pain prior to the injections. Only three had some disturbance of sleep at three months post-injection, with none having their sleep disturbed at all times after the injections.
- Subjective shoulder elevation improved from chest level to hand above head, whilst objectively it improved from 61.8 degrees (30-90) to 92.1 degrees (60-130).
- Patient satisfaction (on a scale of 0 to 10) improved from 1.3 (0-2) pre-injection to 8.4 (4-10) following the injections.
- The safety of the therapy has not been reported.

	Baseline	**3 months**
Constant score	15.5 (10-25)	49.5 (25-84)
Pain score (VAS)	11.6 (10-14)	4.7 (0-9)
Subjective range of motion	Chest level	Above head
Shoulder elevation	61.8° (30-90)	92.1° (60-130)
Patient satisfaction in %	13 (0-20)	84 (40-100)

Table of results. Data are presented as mean (range).

Funk L. *Osteoarthritis Cartilage*, 2004; 12(Suppl B):S140. Abstract No.: P338.

IN REAL-LIFE CONDITIONS, OSTENIL WAS MORE EFFICIENT AND SAFER THAN A CROSS-LINKED HA OF AVIAN ORIGIN

- Study design: multicentre, retrospective survey to collect tolerability, safety and efficacy data following intra-articular injections of hyaluronic acid in Switzerland.
- Study population: patients suffering from knee osteoarthritis, treated with intra-articular hyaluronic acid within the previous 15-month period. Exclusion criteria not mentioned. N = 436
- Ostenil and Synvisc were the main products used in the centres participating to the study. A total of 2022 intra-articular injections were made: 1753 with Ostenil (86.7%) and 264 with Synvisc (13.1%).
- Investigators judged global efficacy as "good" to "moderate" in 92.3% of the Ostenil treated cases and 79.0% of the Synvisc treated cases ($p<0.001$), and "poor" or "insufficient" in 7.7% and 21.0% of the cases, respectively. Efficacy was significantly better ($p<0.001$) in the Ostenil group compared to the Synvisc group. When the comparison was performed for patients having received 3 injections, the efficacy remains significantly better for the Ostenil group ($p=0.03$).
- The investigator's judgement of tolerability was good to moderate in 98.7% of the patients treated with Ostenil and in 92.6% of the patients treated with Synvisc.
- The incidence of adverse device events in the Synvisc treated cases was 7.7% compared to 2.1% in the Ostenil group ($p<0.0001$). The incidence of events classified as at least probably related to study treatment (adverse device reactions, ADR) was 5.1% in the Synvisc group and 0.7% in the Ostenil group ($p<0.0001$). Inflammatory reactions were more frequent with Synvisc (swelling 6.5%; inflammation 8.7%) than with Ostenil (swelling 1.1%; inflammation 0.2%).
- In the Synvisc group, the incidence of ADRs increased with additional injections: 4.3%, 5.7% and 6.3% after the 1st, 2nd and 3rd injection, respectively, compared to 0.6%, 1.1% and 0.7% in the Ostenil group (Figure 20).
- In total, ADRs were found in 2.8% of Ostenil patients versus 20.8% of Synvisc patients ($p<0.0001$) and their severity was greater with Synvisc ($p=0.03$).

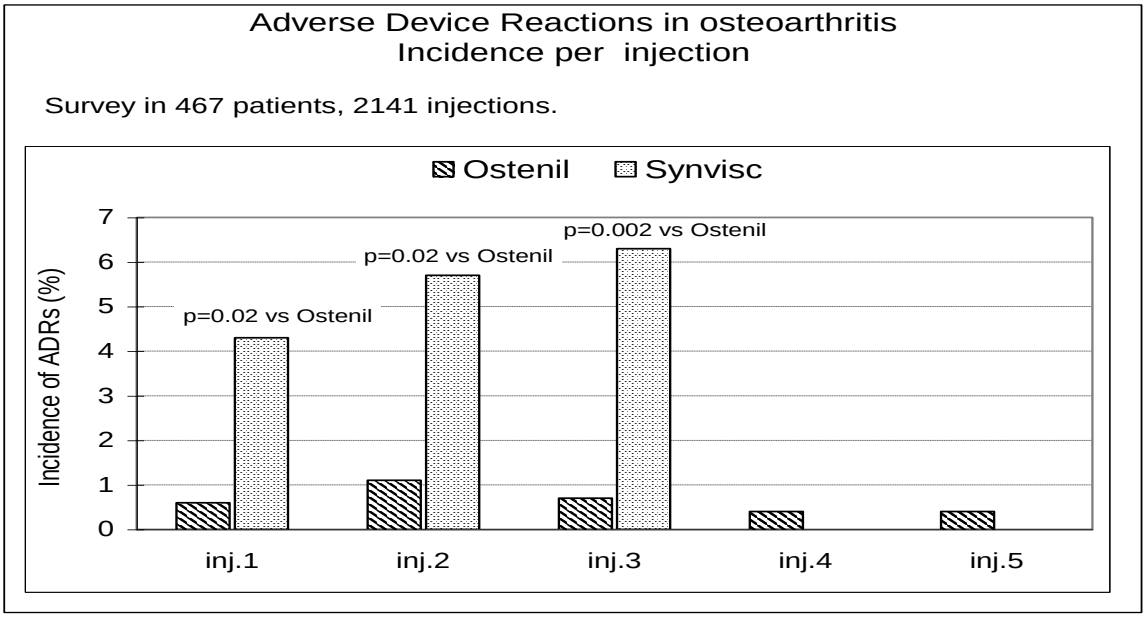


Figure 20: Adverse device reactions incidence following intra-articular injection of Ostenil or Synvisc.

Uebelhart D, Berz S. *Osteoarthritis Cartilage*, 2003; 11(Suppl A):S80. Abstract No.: P223.

PATIENTS TREATED WITH OSTENIL WAIT A MEDIAN OF 350 DAYS BEFORE REQUESTING A SECOND TREATMENT CYCLE

- Study design: two-centre, prospective, randomized, masked-observer, cross-over study comparing 3 injections of Ostenil with one injection of betamethasone plus 2 injections of sham (Diprophos) over 48 weeks. The patients were injected either one of the two medications during a first treatment cycle. Results were evaluated up to 48 weeks post the first cycle. The cross-over was triggered through request of the patient to initiate a second treatment cycle of injections followed by evaluations up to 48 weeks post the last injection. The second cycle terminated when the patient demanded further treatment.
- Study population: patients aged 30-80 years, suffering from symptomatic knee osteoarthritis confirmed by radiography, Kellgren-Lawrence grade II-III, with pain scoring ≥40 on a 100-mm VAS, chronic pain for ≥3 months prior to study entry. Key exclusion criteria: knee joint arthroscopy in the prior six months, known or suspected infection of the joint to be treated, intra-articular treatment with any product within 3 months or with a sodium hyaluronate-based product within 6 months prior to study start. N = 80
- The median time to recurrence was 350 days in the Ostenil group and 339 days in the Diprophos treatment (Figure 21). The difference was not statistically different when the two treatments were compared (p = 0.5065). Similar results were obtained for the mean time to recurrence (432 days in the Ostenil group versus 418 days in the Diprophos group).
- The total WOMAC score decreased from 35.0 to 17.0 in the Ostenil group and from 41.0 to 24.0 in the Diprophos group. In terms of percent change, the improvement was maximal at Day 270 in the Ostenil group and at Day 14 and 21 in the Diprophos group. At Day 7 and 14, a proven superiority of Diprophos was observed whereas from Day 180 to Day 360 a small to medium superiority of Ostenil was observed but not proven.
- Several of the secondary outcome measures (VAS pain score, percentage of patients with pain reduction, morning stiffness, clinical global impression) exhibited proven or observed superiority for the Ostenil group, especially at the latest visits.
- There were no target knee serious AEs and no serious AE related to the study treatment or the study procedure. The incidence of AEs resulting in a drop-out was slightly higher in the Ostenil group (9.8%) than in the Diprophos group (7.7%), but this was not statistically significant.

Comment: the poster of this study was finally not presented at the mentioned congress due to lack of time of the principal investigator. The Clinical Study Report is however available upon request.

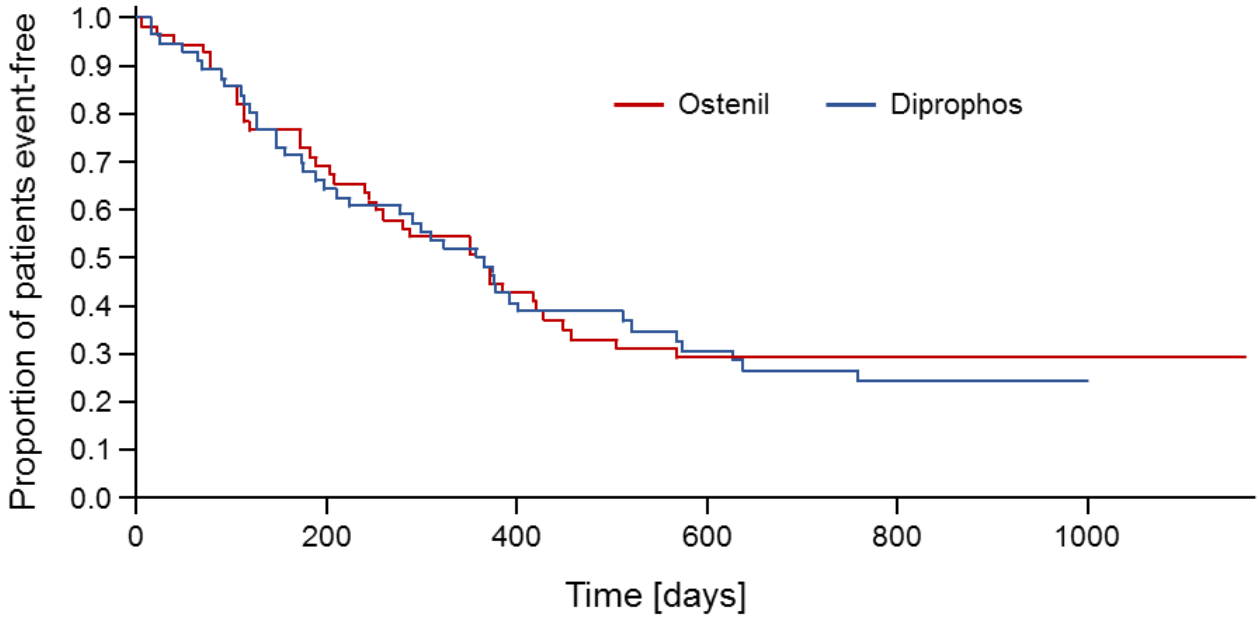


Figure 21: Kaplan-Meier function of time to recurrence (pooled data from the first and second cycles).

Almqvist KF, van Lauwe J, van der Bracht H, Verdonk R, Luyten F. *Knee Surg Sports Traumatol Arthrosc*, 2012; 20(Suppl 1):S258. Abstract No.: P26-172.

OSTENIL IS AS EFFICIENT THAN SYNVISC BUT HAS A BETTER SAFETY PROFILE AND IS CHEAPER

- Study design: multicentre, prospective, randomized, patient-blind study comparing 3 injections of Ostenil (bacterial HA), Orthovisc (avian HA) and Synvisc (avian cross-linked hylan). One cycle per knee was allowed during the first 6 months, a second cycle was offered between month 7 and 12. Industry-independent trial.
- Study population: patients suffering from radiographically confirmed knee osteoarthritis (ACR criteria), Kellgren-Lawrence grade ≥2, symptomatic for ≥6 months, with pain on most days for the previous 3 months, not responding sufficiently to or not tolerating paracetamol or NSAIDs taken regularly. Key exclusion criteria: inflammatory joint disease, chondrocalcinosis, replacement surgery in the study knee, receiving anticoagulant therapy, previous viscosupplementation treatment within the last 6 months. N = 660
- A reduction of WOMAC pain subscore was observed at month 3 and 6 versus baseline in all groups, but there was no significance intergroup difference at any time point. A stratified analysis by subgroup did not highlight any subpopulation benefiting from hylan over HA or vice versa. Similar results were obtained for the total WOMAC score.
- There was little evidence for a difference between groups on the Euro-Qol VAS (0.1 [95% CI -0.2, 0.4]) and health state index (0.2 [95% CI -0.1, 0.4]).
- No differences were observed in the number of patients receiving intra-articular steroid injections in the 4 weeks before the 6-month assessment. There was no statistical evidence for differences between groups in the use of pain medication or other disease-specific treatments, including surgical interventions.
- Median direct costs were CHF 1,824 ($1,459) in the Synvisc group, CHF 1,548 ($1,238) in the Orthovisc group, and CHF 1,271 ($1,017) in the Ostenil group (p<0.001).
- During the first cycle, 9.5% of patients in the Synvisc group and 7.3% of patients in the HA groups (Orthovisc + Ostenil) experienced a local AE. This trend was due to more flares in the Synvisc group (difference 3.3%), while effusions appeared equally distributed between groups. During the second cycle of treatment (n=330), local AEs occurred more frequently in the Synvisc group than in the HA groups (difference 6.4% [95% CI 0.6, 12.2]). This difference was apparent for all outcome measures, but was most pronounced for flares (difference 6.4% [95% CI 1.8, 10.9]), leading to a number needed to harm of 8 when based only on treated patients.
- Serious AEs occurred in 6.8% of SYN patients and in 5.7% of HA patients (Orthovisc + Ostenil). There was little evidence for a difference between groups. Two serious AEs were judged to be probably related to the evaluated intervention: 1 episode of septic arthritis, which occurred after injection of Orthovisc, and 1 episode of anaphylactic shock, which occurred after injection of Synvisc.

	First cycle			Second cycle		
	SYN n=222	HAs n=438	Difference (95% CI)	SYN n=110	HAs n=220	Difference (95% CI)
Local AE	21 (9.5)	32 (7.3)	2.2 (-2.4, 6.7)	10 (9.1)	6 (2.7)	6.4 (0.6,12.2)
Type of local AE Effusion Flare	 7 (3.2) 19 (8.6)	 14 (3.2) 23 (5.3)	 0.0 (-2.9, 2.8) 3.3 (-0.9, 7.5)	 8 (7.3) 7 (6.4)	 6 (2.7) 0 (0.0)	 4.6 (-0.8, 9.9) 6.4 (1.8, 10.9)
Corticosteroid injection because of local AE	5 (2.3)	5 (1.1)	1.2 (-1.1, 3.3)	4 (3.6)	0 (0.0)	3.6 (0.1, 7.1)
Treatment stopped because of local AE	2 (0.9)	6 (1.4)	-0.5 (-2.1, 1.2)	5 (4.5)	0 (0.0)	4.5 (0.7, 8.4)

Patients experiencing local AEs during the first cycle (months 0-6) and the second cycle (7-12). Data are presented as number of patients (%). CI, confidence interval; HAs, hyaluronic acids (Orthovisc + Ostenil); SYN, Synvisc.

Jüni P, Reichenbach S, Trelle S, Tschannen B, Wandel S, et al. *Arthritis Rheum*, 2007; 56(11):3610-9.