

# EARLY EFFICACY OF A NOVEL VISCOUSUPPLEMENT COMBINING HYALURONIC ACID AND SORBITOL, ANTI-OX-VS (SYNOLIS) IN PATIENTS WITH KNEE OSTEOARTHRITIS

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## ABSTRACT

**Title:** EARLY EFFICACY AND SAFETY OF A NOVEL VISCOUSUPPLEMENT COMBINING SODIUM HYALURONATE AND SORBITOL (ANTI-OX-VS) IN PATIENTS WITH SYMPTOMATIC KNEE OSTEOARTHRITIS.

**Objective(s):** ANTI-OX-VS is an innovative viscosupplement (VS) made of a high concentration (20 mg/ml) of a > 2MDa Sodium Hyaluronate (NaHA) from non animal origin, combined with a high concentration of an oxygen free radical (OFR) scavenger, the Sorbitol (40mg/ml). The high ability of Sorbitol to scavenge and neutralize OFR has already been proven to delay the degradation of the gel. We hypothesized the antioxidant effect of a Sorbitol may also play a role to reduce the time to onset of analgesia.

**Material and Methods:** 26 patients with symptomatic KOA were included in a 13 weeks prospective open pilot study. Treatment regimen consisted of 3 IA injections of 2 ml of ANTI-OX-VS on week apart. Pain and function (WOMAC scale, walking pain (WP), patient and physician global assessment (GA) using a 5 points Likert scale were obtained at W1, W2 and W13. Between W2 and W14 patients were asked to complete a weekly self evaluation questionnaire (WP, WOMAC A between W0 and W1, w2, W8, W13. The treatment efficiency was also evaluated at W13.

**Results:** Mean age was 71 ± 10, BMI 27.9 ± 3.9. KL grades 1,2,3,4 in 0, 6, 8, 12 cases respectively. At W0 mean WP was 2.1 and WOMAC A 8.3. At W3 mean WP to 1.5 (p<0.0003). As early as W1 WP was already reduced to 1.6 (p<0.0003) and decrease again 1.0 (p<0.0001) at W13. Variation of mean MP between W0 and W1, W2, W3, W8, W13 was resp. -0.5; -0.4; -0.5 and -1.1. Variation of mean WOMAC A between W0 and W1, W2, W8, W13 was resp. -2.1, -2.0, -2.0, -3.9. At W13, 82% of the patients considered ANTI-OX-VS treatment is moderately to extremely effective. There was no adverse related event reported.

**Conclusion(s):** This study suggests a quick and strong pain relief occurring immediately after the first injection on ANTI-OX-VS followed by continuous improvement until W13. Pain decreases much faster than what obtained with other VS probably because of the presence of a high concentration of Sorbitol through its antioxidant activity.

Viscosupplementation by intraarticular injections of hyaluronic acid (HA) reduces pain and improves function in patients with knee osteoarthritis (KOA) but the improvement is delayed and occurs usually 6 to 8 weeks after the injections.

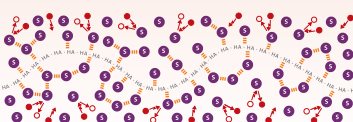


Figure 1

## Rationale

ANTI-OX-VS (Synolis™) is a new innovative viscosupplement made of a high concentration (20 mg/ml) of a 2MDa hyaluronic acid (HA) from non animal origin, combined with a high concentration of a free radical-scavenger, the sorbitol (40 mg/ml).



Figure 2

The high affinity between HA and sorbitol, stabilizes the complex through a very dense network of hydrogen bonds (figure 1).

Furthermore the high ability of sorbitol to scavenge and neutralize oxygen free radicals (OFR) has been demonstrated to delay the degradation of the gel, compared to linear and cross-linked HA viscosupplements (Figure 2).

## OBJECTIVES

**To evaluate the short term pain-relief effect of ANTI-OX-VS in patients suffering from knee osteoarthritis.**

## Study design

Prospective, open-label 13 week study 26 outpatients fulfilling the American College of Rheumatology clinical criteria for the diagnosis knee OA.

## Inclusion criteria

- Patients suffering from symptomatic knee OA and considered by the physician as requiring viscosupplementation
- 30 ≥ Age < 85 years
- Kellgren-Lawrence grade (KL) II to IV on standing AP view, Lyon schuss view, profile, skyline view of the patella.

## Main exclusion criteria

- Flare at any joint.
- VS of any knee within 6 months prior to the initiation of treatment.
- Intra-articular steroid injection of any knee within 3 months prior to the initiation of treatment.

## Treatment procedure

Three 2mL intra-articular injections of ANTI-OX-VS (Synolis™) were performed 1 week apart by an experienced rheumatologist.

## Authorized treatments

- Paracetamol < 4 g/jour
- NSAIDs if taken before inclusion
- SYSADOAs (*chondroitin sulfate, diacerhein, avocado/soja unsaponifiables, glucosamin, diacerhein*) if taken at stable doses at least 3 months before inclusion and during the whole follow-up period.

## Evaluation

At baseline, W1, W2 and W13: WOMAC A, WOMAC aggregate, walking pain (WP), patient and physician global assessment (PGA) using a Likert 5 points scale.

Between the third injection and end-point patients were asked to complete once a week a **self evaluation questionnaire** for WP, WOMAC A, patient GA and adverse events.

At W1, W2 and W13: Percentage of improvement since the first injection were obtained (figure 4).

Treatment satisfaction was also evaluated at the end of the follow up period (Likert 4 points scale).

**Primary criteria:** Variation of WP between first injection and W3.

**Secondary criteria:** Variation of WP, WOMAC A, PGA between baseline and W1, W2, W3, W8, W13. Variation of WOMAC between baseline and W13. Percentage of improvement between baseline and W1, W2, W13.

## RESULTS

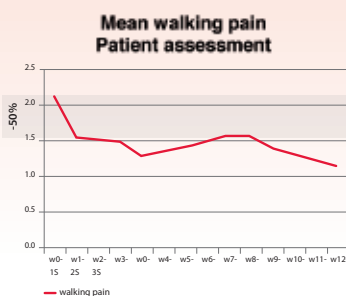


Figure 3

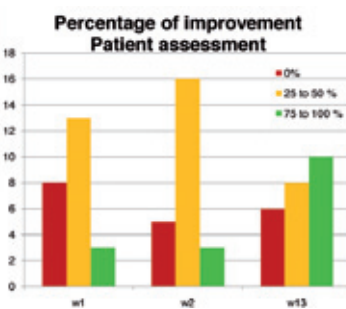


Figure 4

Mean age 71 ± 10  
Mean BMI 27.9 ± 3.9  
KL (grade /N): II/6; III/8; IV/12

At baseline:

- Mean WP = 2.1
- Mean WOMAC A = 8.3

At week 1:

- Mean WP 1.6 (p<0.0003)
- Mean WOMAC A = 6.2 (p<0.0000)

At week 3:

- Mean WP 1.5 (p<0.0003)
- Mean WOMAC A = 7.5 (p<0.05)

At week 13:

- Mean WP 1.0 (p<0.0001)
- Mean WOMAC A = 4.9 (p<0.0000)
- Variation of WP between baseline and W1, W2, W8 and W13 was respectively -0.5, -0.4, -0.5 and -1.1 (figure 3)
- Variation of WOMAC A between baseline and W1, W2, W8 and W13 was respectively -2.1, -2, -2 and -3.9. At W13, 82 % of the patients considered ANTI-OX-VS moderately to extremely effective.

No device-related adverse event was reported.

## CONCLUSION

This exploratory study demonstrates a **quick and strong pain relief occurring immediately after the first injection of ANTI-OX-VS, followed by a continuous improvement until the end of follow-up (W13).**

**Improvement was achieved much faster than that usually obtained with other commercial viscosupplements probably because of the presence of a high concentration of sorbitol acting through its antioxidant activity.**

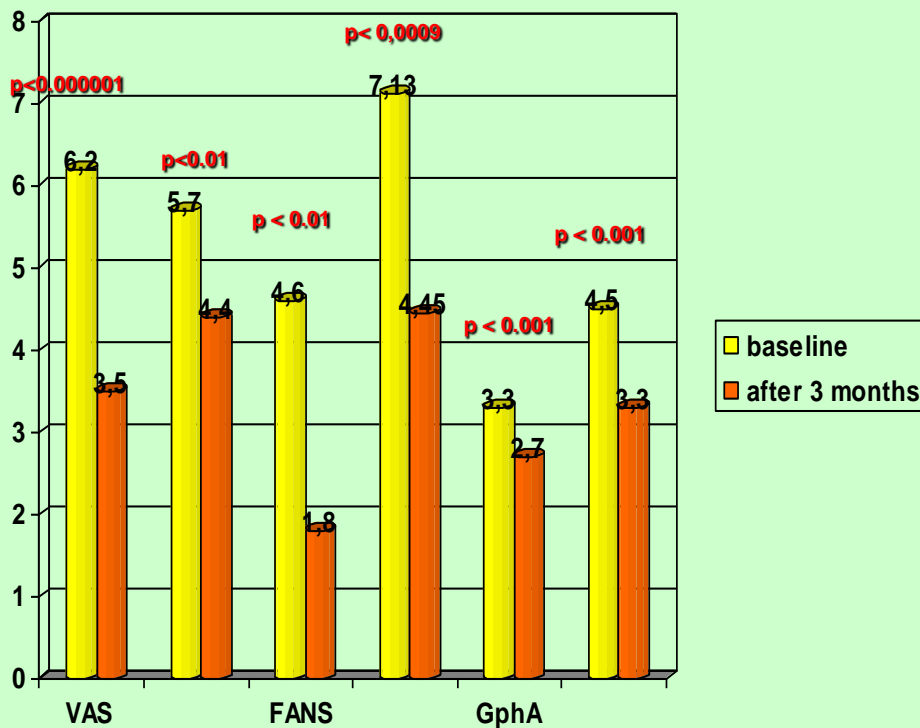
These data support the need for a large scale, prospective clinical trial comparing the safety and long term efficacy of Synolis™ to regular viscosupplement.

## Long term efficacy profile of Synolis V-A in patients affected by symptomatic hip osteoarthritis: The "SYCA" study. Preliminary data

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**Conclusions:** Our preliminary data evidenced a good efficacy and safety profile of Synolis V-A for the treatment of symptomatic hip osteoarthritis after 3 months follow-up

**Objective:** Osteoarthritis (OA) is one of the more frequent pathology in clinical practice; hip OA is less frequent than knee or hand OA but it is more frequently symptomatic than other localizations. Although this relevant impact in clinical practice, still not conclusive data about safety and efficacy of hip viscosupplementation are reported in litterature. This study investigated on the safety and efficacy profiles of ultrasound-guided intra-articular injections of Synolis V-A (2% sodium hyaluronate 4% sorbitol, 2 ml, Anteis) in hip osteoarthritis affected patients.

Synolis V-A is a new product for intra-articular treatment of osteoarthritis; it mixed sorbitol and sodium hyaluronate to improve analgesic effect of

hyaluronate and to maintain its effect until 12 months after one injection

**Design:** This is an open, spontaneous, prospective, monocentric, postmarketing study.

**Material and methods:** We enrolled adult outpatients affected by symptomatic hip OA; all patients has to show a radiographic grade 2, 3 or 4 according to Kellgren & Lawrence criteria; all patients underwent to one intra-articular (IA) injection of 4 ml (2 vials) of Synolis V-A under ultrasound guidance. Patients characteristics, such as gender, age, weight, height and BMI, smoking habit, unilateral or bilateral hip osteoarthritis involvement, radiological grade and duration of disease were evaluated. Patients were assessed at baseline and at every three months, during control visit; parameters evaluated were: Lequesne algo-functional index, Visuo Analogic Scale (VAS) for pain and NSAID consumption (calculated on the number of days patients assumed NSAID in the last month), Global patient assessment (GPA) and Global physician assessment (GPhA) and Health assessment questionnaire (HAQ). Drop out were recorded; distribution and causes of drop out were noted.

**Results:** We enrolled 50 patients in the study. All of them received one IA US-guided injection of Synolis V-A in the hip joint. We report preliminary data about three monts of follow-up A total of 2 drop outs were registered. A total of 50 injections was performed. Five patients were affected by bilateral hip OA (see tab 1)

No local or systemic infectious side effects were reported during the follow-up period.

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J. Heisel, C. Kipshoven

## Hyaluronic acid with sorbitol – efficacy and tolerability of intra-articular treatment for osteoarthritis of the knee

*Hyaluronsäure mit Sorbitol – Wirksamkeit und Verträglichkeit  
einer intraartikulären Behandlung der Gonarthrose*



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# Hyaluronic acid with sorbitol – efficacy and tolerability of intra-articular treatment for osteoarthritis of the knee

## *Hyaluronsäure mit Sorbitol – Wirksamkeit und Verträglichkeit einer intraartikulären Behandlung der Gonarthrose*

**Abstract:** In a non-interventional study under real-world conditions, 101 patients with long-standing osteoarthritis of the knee (mean age 58 years, ca. 55% female) were treated with three intra-articular (i.a.) injections at weekly intervals of a new medication (high-dose sodium hyaluronate [hyaluronic acid] and sorbitol [GO-ON matrix]\*). At the start of treatment, only 4% of the osteoarthritis patients were pain-free, while 21.8% of the patients complained of severe or very severe pain. The proportion of pain-free patients increased steadily after each of the three injections. After the first injection, 16.8% of the patients were pain-free, and 40.6% were pain-free 24 weeks after treatment was initiated. At the same time, the proportion of patients with moderate, severe or very severe pain decreased significantly during treatment. The proportion of patients with severe or very severe pain decreased from 21.8% to 5% after the first injection, and 74.3% of the patients reported that their pain was reduced at 24 weeks after the start of treatment. At the same time, the extent of functional impairment was also reduced. 14.9% of patients complained of severe or very severe impairment before treatment, but only 4% complained of this degree of impairment after the first injection. The proportion of patients with no functional deficit increased from 31.7% to 51.5%. 24 weeks after the start of the injection treatment, 45.5% of patients reported an improvement with respect to baseline values. The patients and their treating doctors assessed the overall efficacy of the injections in a very similar way. The proportion of patients who reported improvement increased from 64.4% one week after the first injection to 87.1% a week after the third injection, while assessment by the doctors improved from 57.4% to 82.2%. There were no local or systemic adverse effects.

**Keywords:** Osteoarthritis of the knee, hyaluronic acid, sorbitol, intra-articular injection therapy

**Zusammenfassung:** In einer nicht-interventionellen Studie unter Praxisbedingungen wurden 101 Patienten mit langjährig bestehender Gonarthrose (ca. 55% weiblich) im Durchschnittsalter von 58 Jahren mit 3 in wöchentlichen Abständen applizierten intraartikulären (i.a.) Injektionen eines neuen Präparates (hochdosiertes Natriumhyaluronat [Hyaluronsäure] und Sorbitol [GO-ON matrix]\*) behandelt.

Bei Therapiebeginn waren bezüglich der Gonarthrose nur 4% der Patienten schmerzfrei, während 21,8% der Patienten über starke oder sehr starke Schmerzen klagten. Der Anteil schmerzfreier Patienten nahm nach jeder der 3 Injektionen stetig zu. Schon nach der ersten Injektion waren 16,8% der Patienten schmerzfrei, 24 Wochen nach Therapiebeginn waren es 40,6%. Gleichzeitig nahm der Anteil der Patienten mit mäßiggradigen, starken oder sehr starken Schmerzen unter der Therapie deutlich ab. So fiel bereits nach der ersten Injektion der Anteil an Patienten mit starken und sehr starken Schmerzen von 21,8 auf 5%. 24 Wochen nach Therapiebeginn beurteilten 74,3% der Patienten ihre Beschwerden als gelindert. Zeitgleich verbesserte sich auch das Ausmaß der funktionellen Beeinträchtigung: Nach der ersten Injektion klagten, von anfänglich 14,9%, nur noch 4% der Patienten über starke und sehr starke Beeinträchtigungen. Der Anteil der Patienten ohne funktionelles Defizit nahm von 31,7 auf 51,5% zu. 24 Wochen nach Beginn der Injektionstherapie berichteten 45,5% der Patienten über eine Verbesserung gegenüber dem Ausgangsbefund.

Patienten und behandelnde Ärzte beurteilten die globale Wirksamkeit der Injektionen sehr ähnlich. Der Anteil der Patienten mit berichteter Besserung stieg von 64,4% eine Woche nach der ersten auf 87,1% eine Woche nach der dritten Injektion, die positive Bewertung der behandelnden Ärzte von 57,4 auf 82,2%. Unerwünschte Nebenwirkungen lokaler oder systemischer Art traten nicht auf.

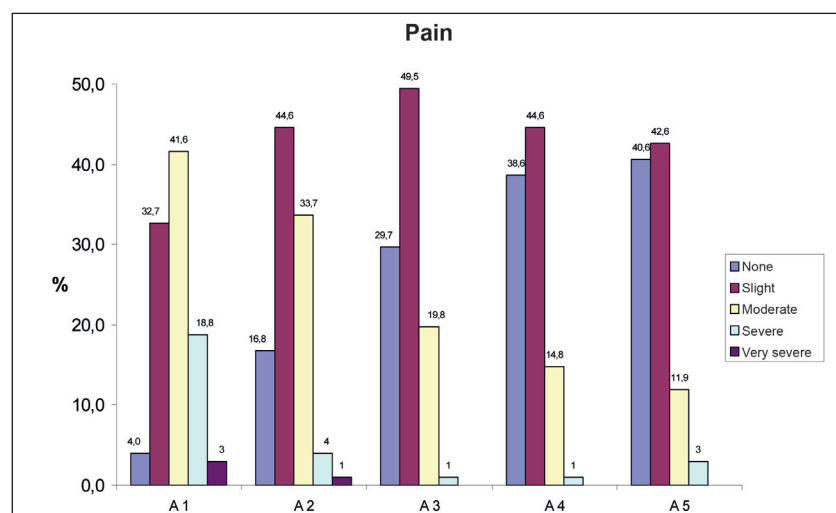
**Schlüsselwörter:** Gonarthrose, Hyaluronsäure, Sorbitol, intraartikuläre Injektionstherapie

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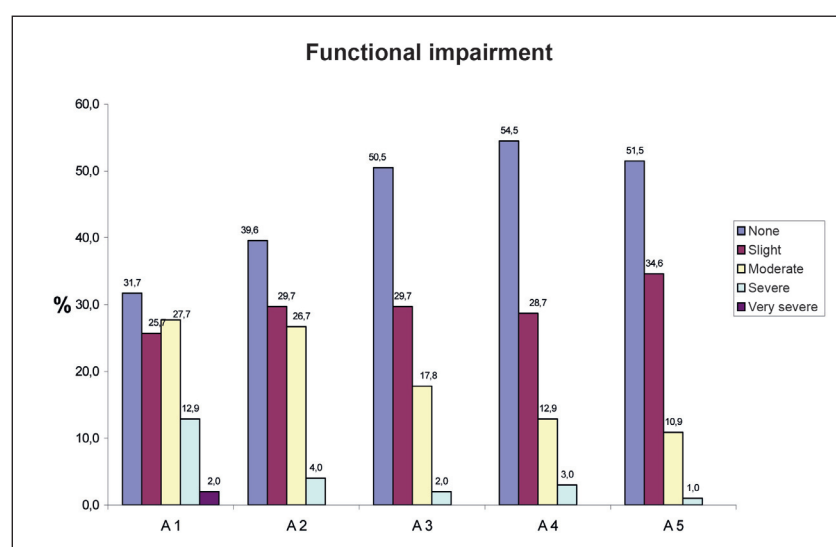
<sup>2</sup> Rottapharm/Madaus GmbH, Köln

\* GO-ON matrix distributed by Rottapharm Madaus GmbH is the same product as Synolis V-A developed and manufactured by Anteis SA (Switzerland).

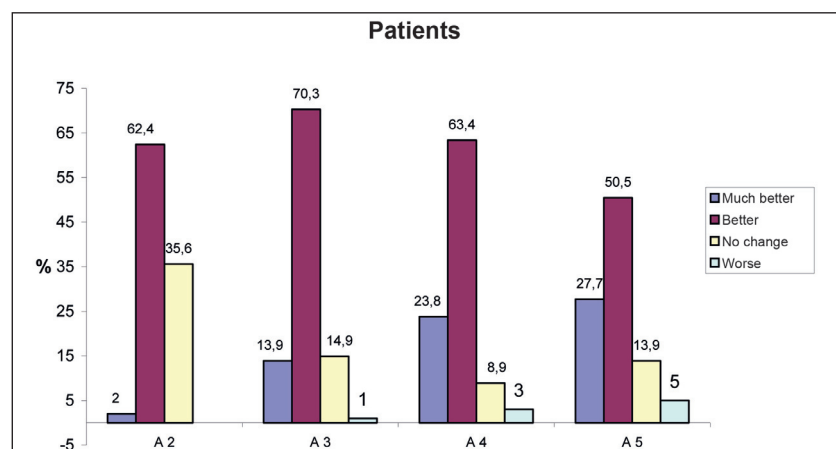
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**Figure 1** Pain symptoms during the course of treatment. A2: One week after the first injection.



**Figure 2** Functional impairment of the affected knee joint during the course of treatment. A2: One week after the first injection.



**Figure 3** Overall assessment by patients of the efficacy of the intra-articular injection treatment.

## Introduction

Osteoarthritis results in progressive and irreversible degenerative changes in synovial joints, starting with the articular cartilage, then attacking the structure of the articulating bones and finally affecting all components of the joint. It occurs most frequently in the knee joint. The most important risk factors for development of osteoarthritis are advanced age and excess biomechanical load due to overweight. Experts estimate that about 10% of people over the age of 50 have clinical osteoarthritis of the knee [1]. A study in the U.S. rated the lifetime risk of symptomatic knee osteoarthritis at 45% [2].

In osteoarthritis, both the viscosity and the quantity of synovial fluid are reduced. This increases friction between the sliding components of the joint and reduces their ability to cushion axial forces, leading to further joint damage. The clinical results are pain and eventually functional impairment of the knee joint.

Hyaluronic acid is a major component of synovial fluid and determines its ability to lubricate the joint. In addition to its viscoelastic properties, pre-clinical and clinical studies have reported that hyaluronic acid also has chondroprotective [3–6] and anti-inflammatory [5, 7, 8] properties in the joint.

Current trials and recent observational studies on intra-articular injection of various hyaluronic acid preparations (without sorbitol) have demonstrated their clinical efficacy in osteoarthritis of the knee in terms of both pain reduction and functional improvement [9–18]. These positive effects have been confirmed by meta-analysis [19, 20]. Other studies have shown that this treatment is safe and well tolerated [9–11, 14, 16–19]. Intra-articular application of hyaluronic acid is now a recognised treatment option for osteoarthritis of the knee.

Biochemical studies have shown that free radicals have destructive effects on tissues and stimulate inflammatory processes [21, 22]. In the joint, these substances convert hyaluronic acid directly to oligosaccharides, leading to a reduction in viscosity and molecular weight of the synovial fluid [23].

<b>A 1</b> (Start of study)	<ul style="list-style-type: none"> <li>• collection of demographic data, duration of osteoarthritis symptoms, concomitant treatment, previous therapeutic measures</li> <li>• self-assessment of current pain and functional impairment by the patients themselves</li> <li>• <b>first i.a. injection of the preparation</b></li> </ul>
<b>A 2</b> (1 week after A 1)	<ul style="list-style-type: none"> <li>• self-assessment of current pain and functional impairment by the patient</li> <li>• overall evaluation of treatment by patient and doctor</li> <li>• records of any other recent treatment for osteoarthritis</li> <li>• questions regarding side effects and their documentation</li> <li>• <b>second i.a. injection of the preparation</b></li> </ul>
<b>A 3</b> (1 week after A 2)	<ul style="list-style-type: none"> <li>• as for A 2</li> <li>• <b>third i.a. injection of the preparation</b></li> </ul>
<b>A 4</b> (1 week after A3)	<ul style="list-style-type: none"> <li>• as for A 2 (no injection)</li> </ul>
<b>A 5</b> (24 weeks after first injection)	<ul style="list-style-type: none"> <li>• as for A 2 (no injection)</li> <li>• records of any change in dosage of NSAIDs and analgesics</li> </ul>

**Table 1** Protocol of the observational study

Pain	A 1	A 2	A 3	A 4	A 5
None (%*)	4	16.8	29.7	38.6	40.6
Slight (%)	32.7	44.6	49.5	44.6	42.6
Moderate (%)	41.6	33.7	19.8	14.8	11.9
Severe (%)	18.8	4	1	1	3
Very severe (%)	3	1	–	–	–
No data (%)	–	–	–	1	2
* Percentage of patients					

**Table 2** Pain symptoms during the course of treatment

Sorbitol is known to be an effective scavenger of free radicals. In combination with hyaluronic acid, it acts at two levels. Firstly, sorbitol protects hyaluronic acid from direct attack by free radicals, so that hyaluronic acid stays intact longer as an active agent. Secondly, reducing the concentration of free radicals decreases the migration of macrophages into the synovial membrane, resulting in reduced inflammation and less pain [24].

### Materials and Methods

In this prospective non-randomised, non-interventional observational study without a control group, we documented for the first time the clinical course of patients with symptomatic osteoarthritis of the knee who received i.a. injections of high-dose sodium hyaluronate (hyaluronic acid) and sorbitol. The longitudinal study was carried out in a real-world setting. The aim of the

study was to gain further knowledge on the efficacy and tolerability of this new preparation in clinical practice. The investigators decided on the indications and patient selection for this treatment. Diagnostic and other therapeutic measures were not affected.

The hyaluronic acid preparation used in this study was 'GO-ON matrix'\* (Rottapharm Madaus GmbH). This consists of high doses of sodium hyaluronate with an average molecular

Functional impairment	A 1	A 2	A 3	A 4	A 5
None (%*)	31.7	39.6	50.5	54.5	51.5
Slight (%)	25.7	29.7	29.7	28.7	34.6
Moderate (%)	27.7	26.7	17.8	12.9	10.9
Severe (%)	12.9	4	2	3	1
Very severe (%)	2	–	–	–	–
No data (%)	–	–	–	1	2
* Percentage of patients					

**Table 3** Functional impairment of the affected knee during the course of treatment

Change from baseline	A 2	A 3	A 4	A 5
<b>Patients</b>				
Much better (%*)	2	13.9	23.8	27.7
Better (%)	62.4	70.3	63.4	50.5
No change (%)	35.6	14.8	8.9	13.9
Worse (%)	–	1	3	5
<b>Doctors</b>				
Much better (%*)	4	16.8	25.7	29.7
Better (%)	53.5	55.4	56.4	50.5
No change (%)	42.6	27.7	13.9	14.8
Worse (%)	–	–	3	3
* Percentage of patients				

**Table 4** Overall assessment by patients and doctors of the efficacy of the intra-articular injection treatment

weight (two million Da) and sorbitol. A 2 ml pre-filled syringe contains 40 mg hyaluronic acid (2% gel), 80 mg of sorbitol and buffered saline. Sorbitol is a free radical scavenger, which not only helps to stabilise hyaluronic acid, but may also accelerate the effects of treatment.

All participants in the study received three intra-articular injections of the preparation into the affected knee joint at intervals of one week. Orthopaedic

patients had to be at least 18 years old and have radiologically confirmed osteoarthritis of at least grade I (Kellgren-Lawrence) to be included in the study. Prior indication for treatment with intra-articular hyaluronic acid was required in each case, independent of the planned observational study. Patients were not included in the study if they were receiving (or had received immediately beforehand) another intra-articular treatment (e.g. corticosteroids).

The protocol of the observational study specified five contacts with doctors (A1–A5; Table 1).

The data were analysed using descriptive statistical methods. The mean, median, standard deviation and interquartile ranges were calculated for quantitative variables. Absolute and relative frequencies were calculated for qualitative variables. The principal results are presented graphically.

## Results

101 patients with osteoarthritis of the knee (55% women, 45% men) with a mean age of 58.4 years (min.: 15, max.: 88, SD: 12.83) participated in the study. Their mean body weight was 81.7 kg (min: 47, max.: 135, SD: 17.12). Degenerative changes had been present in the knee joints of the patients for an average of 7.5 years (data from 86 patients). The efficacy and tolerability of the treatment were evaluated for all patients.

The most common osteoarthritic complaints or findings at the start of treatment were pain after periods of inactivity in 90.1% of cases, retropatellar pain in 80.2% and a positive Zohlen sign (patellar inhibition) in 75.2%. 41.6% of patients had some joint malposition (mainly misalignment), while 19.8% had joint contracture.

Patients reported physiotherapy (63.4%), NSAID administration (62.4%), topical measures (51.5%) and analgesics (29.7%) as the most common prior treatments. During the course of intra-articular treatment, 12.9% of patients received additional physiotherapy and 6.9% received other forms of non-medicinal therapy.

At the start of the study, only a very small number of patients reported that they had no significant pain, while about one in five patients complained of severe or very severe pain. During treatment with three i.a. injections of hyaluronic acid/sorbitol, the proportion of patients without joint pain increased steadily and continued to increase significantly until 24 weeks after the first injection. At the same time, the proportion of patients with moderate, severe or even very severe pain decreased significantly during treatment. The number of patients in this clinically important group had already decreased significantly after the first injection. Twenty-four weeks after the start of treatment, three quarters of the patients evaluated their pain as alleviated; deterioration was only reported in two cases. The time course of joint pain is shown in Table 2 and Figure 1. Given these results, it is not surprising that concomitant administration of NSAIDs or analgesics could be reduced in 30.7% of patients during the course of treatment.

The proportion of patients without functional impairment of the affected knee joint also increased steadily during

the course of treatment. At the same time, the proportion of patients with moderately, severely or very severely restricted movement decreased significantly. Twenty-four weeks after the start of injection treatment, nearly half of the patients showed an improvement compared with baseline parameters. The time course of functional impairment is documented in Table 3 and Figure 2.

Assessments of the overall efficacy of the i.a. hyaluronic acid/sorbitol treatment during the study were quite similar for the treating doctors and the patients. 57.5% of doctors and 64.4% of patients already found an improvement one week after the first injection. By the fourth time point, i.e. one week after the third injection, this percentage had increased to 82.1% of doctors and 87.2% of patients. Six months after the start of treatment, i.e. 22 weeks after the last injection, 80.4% of doctors and 78.3% of patients still reported a sustained improvement. Detailed results of the overall assessment of efficacy are summarised in Table 4. The patients' assessment is also shown in Figure 3.

## Safety

At each contact with the doctors, patients were asked specifically about adverse events. Any changes in the general condition of the patients, any symptoms and complaints that occurred after the start of injection therapy, and any changes in lab values were noted, and their correlation with the treatment was assessed. There were no findings that could be regarded as undesirable side effects, either as a local reaction at the injection site or as a systemic disorder.

## Summary

After three intra-articular injections of the hyaluronic acid/sorbitol preparation, the osteoarthritic knee pain reported by patients (including those with grade 3 osteoarthritis on the Kellgren-Lawrence scale) was significantly reduced in comparison with baseline values. The proportion of pain-free patients was already significant after the first application, and increased steadily after each subsequent dose. At the same time, the proportion of patients with moderate pain decreased continuously after

each injection. The number of patients with severe or very severe pain decreased significantly, especially after the first injection. A clear beneficial effect of treatment was still measurable 24 weeks after the first injection.

Function of the affected knee improved in parallel with the pain relief reported by patients.

The efficacy of the intra-articular hyaluronic acid/sorbitol injections was assessed positively by patients and treating doctors in a similar way. The proportion of patients who reported an improvement one week after the third injection was 87%, while the corresponding assessment of the trial doctors was 82%.

No adverse effects of the i.a. hyaluronic acid/sorbitol injections were found during the study.

## Conclusion

This observational study was carried out on patients with mostly long-term, symptomatic osteoarthritis of the knee, and demonstrated the efficacy of three intra-articular injections of hyaluronic acid/sorbitol (GO-ON matrix)\* in terms of subjective symptoms and impairment of joint function, often after the first injection. Almost nine out of ten patients experienced an improvement after three injections. No adverse effects were reported, either at the injection site or of a systemic nature. In the majority of patients, a positive effect of treatment was still observed six months after the start of therapy. Further prospective studies should be undertaken on a larger patient population to determine the efficacy of this treatment strategy in knee joints with varying degrees of degenerative changes. OUP

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Synolis V-A is developed and  
manufactured by Anteïs S.A. (Switzerland).

[www.anteis.com/orthopaedics](http://www.anteis.com/orthopaedics)

# SYNOLIS V-A

SODIUM HYALURONATE & SORBITOL VISCO-ANTALGIC





# IMPROVED PREDICTABILITY, EARLY EFFICACY AND SAFETY OF A NOVEL VISCO-ANTALGIC COMBINING HYALURONIC ACID AND SORBITOL (SYNOLIS V-A) IN PATIENTS WITH SYMPTOMATIC KNEE OA

Dr. Mauro Bausani  
Piazza Matteotti, Sienna, Italy

Viscosupplementation by intra-articular injections of hyaluronic acid (NaHA) reduces pain and improves function in patients with knee OsteoArthritis (OA) but the improvement is delayed and occurs usually 6 to 8 weeks after the first injection.

### RATIONALE

Synolis V-A is an innovative viscosupplement made of a high concentration (20 mg/ml) of a 2mDa Hyaluronic Acid (HA) from non animal origin, combined with a high concentration of a free radical scavenger, the sorbitol (40 mg/ml).

The high affinity between HA and sorbitol, stabilizes the complex through a very dense network of hydrogen bonds (figure 1).

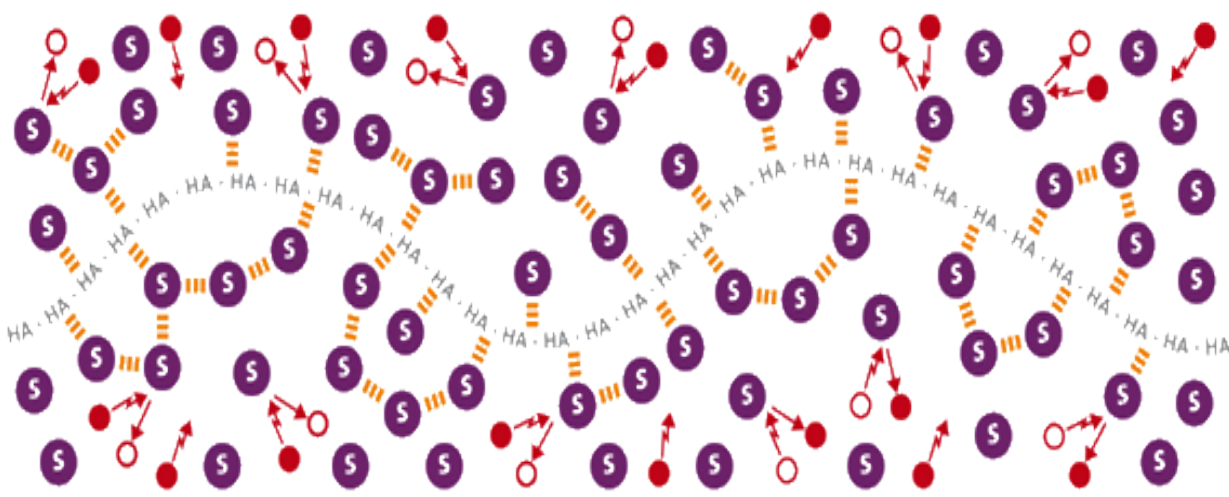


Figure 1

Furthermore the high ability of sorbitol to scavenge and neutralize Oxygen Free Radicals (OFR) has been demonstrated to delay the degradation of the gel compared to linear and cross-linked HA viscosupplements (VS); conserving viscosity properties for a longer period (figure 2).

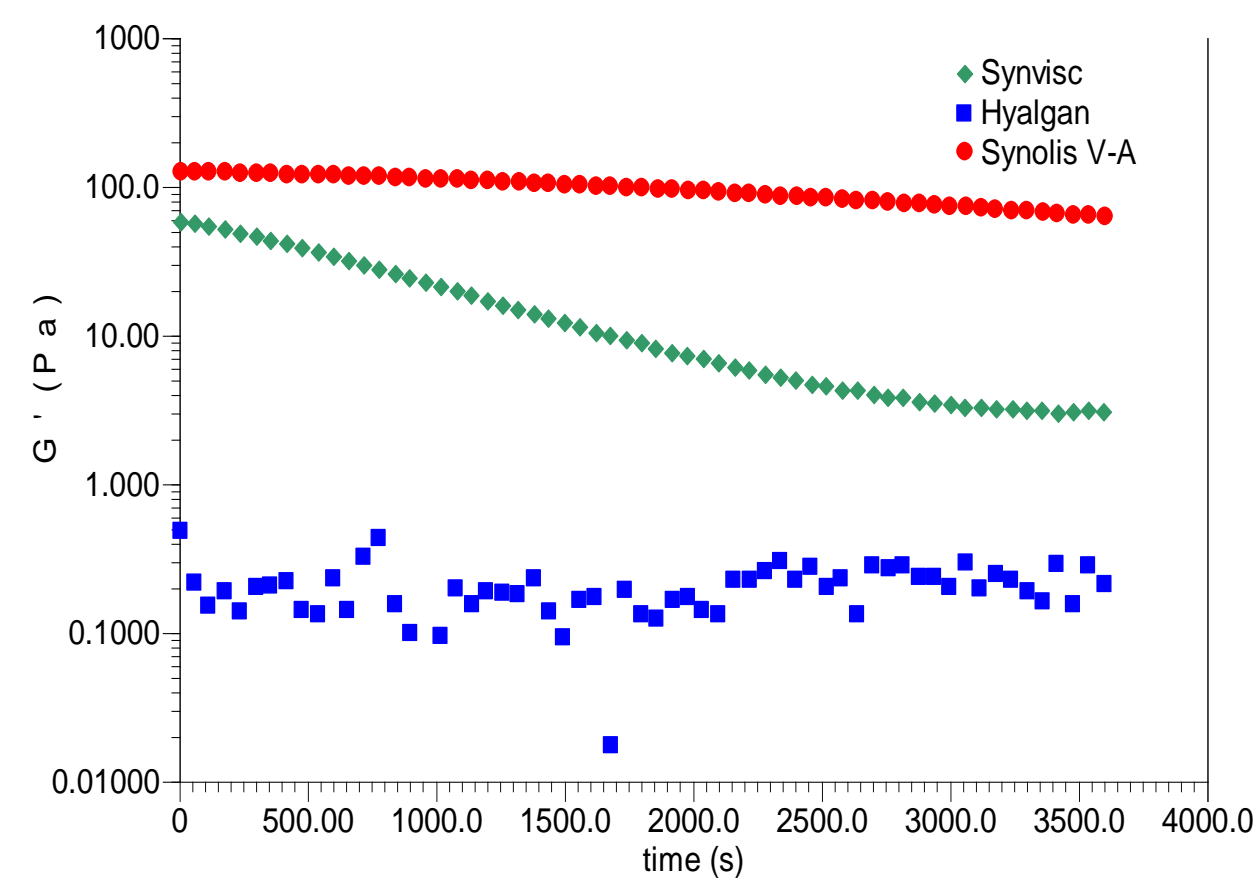


Figure 2

### OBJECTIVES

To show evidences of quick pain relief and mobility recovery in the days following the 1<sup>st</sup> injection, whatever the disease Kellgren-Lawrence (K-L) grade (ranging from II to IV); and of long-term efficacy (up to 6months)

### METHODS

#### Study design

Prospective, open-label 26 weeks study including 29 patients fulfilling the American College of Rheumatology clinical criteria for the diagnosis knee OA.

#### Inclusion criteria

- Patients suffering from symptomatic knee OA and considered by the physician as requiring viscosupplementation
- 30 ≤ Age ≤ 85 years
- K-L grade II to IV on standing AP view, Lyon-schuss view, profile, skyline view of the patella.

#### Main exclusion criteria

- Flare or significant effusion at any joint.
- Viscosupplementation of any knee within 6 months prior to the initiation of treatment.
- Intra-articular steroid injection of any knee within 3 months prior to the initiation of treatment.
- Know hypersensitivity to NaHA and/or sorbitol

#### Treatment procedure

Three 2ml intra-articular injections of Synolis-VA were performed 1 week apart by an experienced rheumatologist.

#### Authorized treatments

- Paracetamol ≤ 4 g/jour
- NSAIDs if taken before inclusion
- SYSADOAs (*chondroitin sulfate, diacerhein, avocado / soja unsaponifiables, glucosamin, diacerhein*) if taken at stable doses at least 3 months before inclusion and during the whole follow-up period.

#### Evaluation

At baseline, week (W)1, W2, W13 and W26: WOMAC A (pain) with score from 0 to 20 (figure 3), WOMAC stiffness with score from 0 to 8 (figure 5), Patient Global Assessment (PGA) in % (figure 6) using single or multi-criteria Likert 5 points scale.

All end-points for Walking Pain (WP) with score 0 to 4, WOMAC A, WOMAC stiffness, PGA and adverse events were collected by the physician during patient's visits.

At W1, W2, W13 and W26: Percentage of improvement vs. baseline were obtained (figure 6)

#### Study criteria

- Primary criteria was the variation of mean WP between baseline and W26
- Secondary end points were variations of WP, WOMAC A, WOMAC stiffness and PGA between baseline and W1, W2, W3, W13, W26; percentage of improvement vs. baseline for all those criteria, and safety and tolerance quantitative assessment (number of side effects / number of treatments)

### RESULTS

Mean age 68 ± 9  
K-L (grade/N): II/12; III/16; IV/1

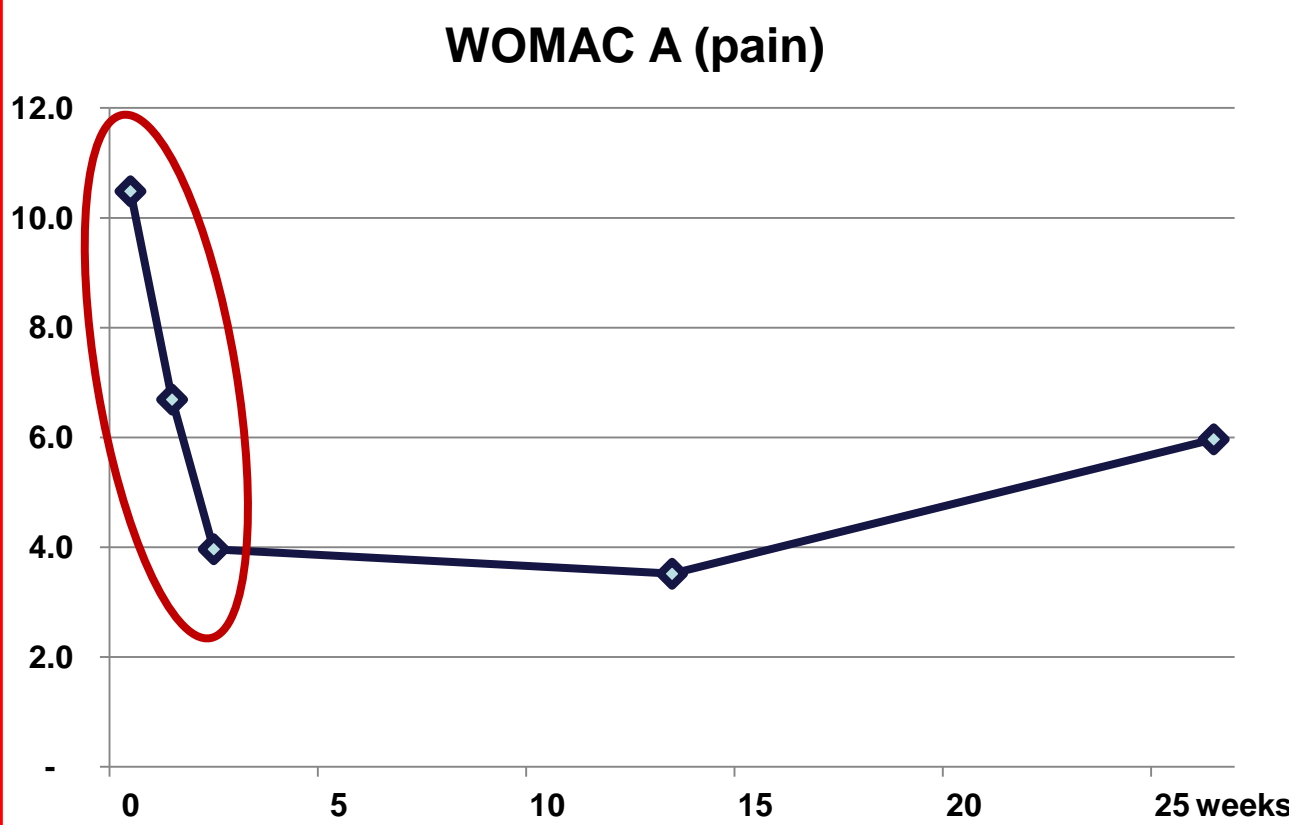


Figure 3

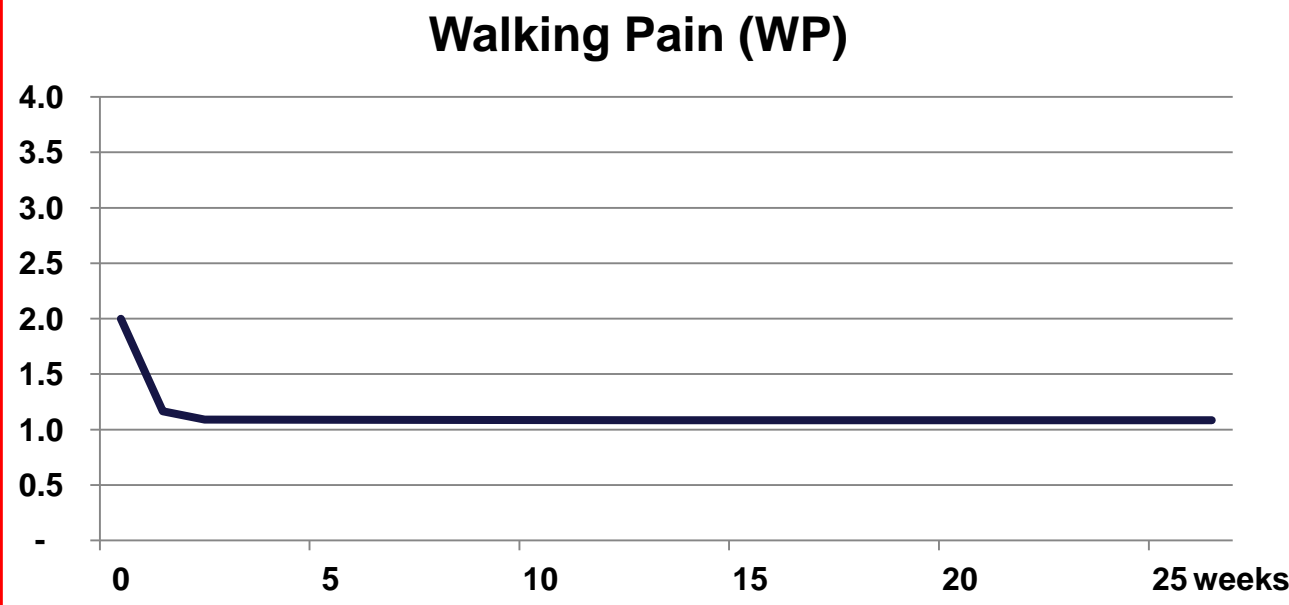


Figure 4a – K-L grade II

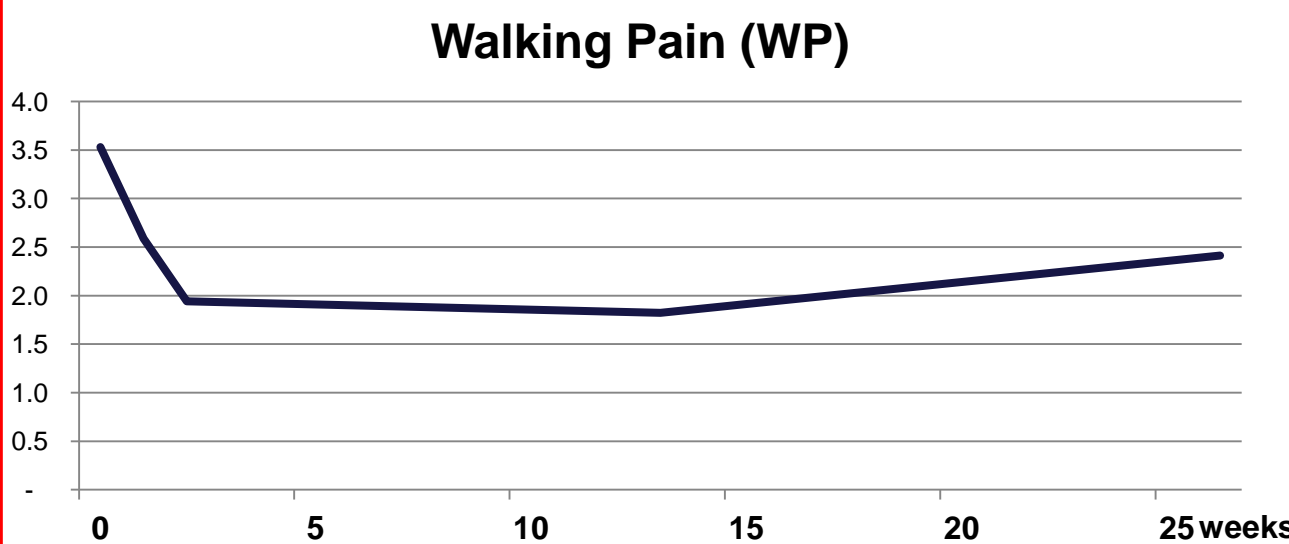


Figure 4b – K-L grades III & IV

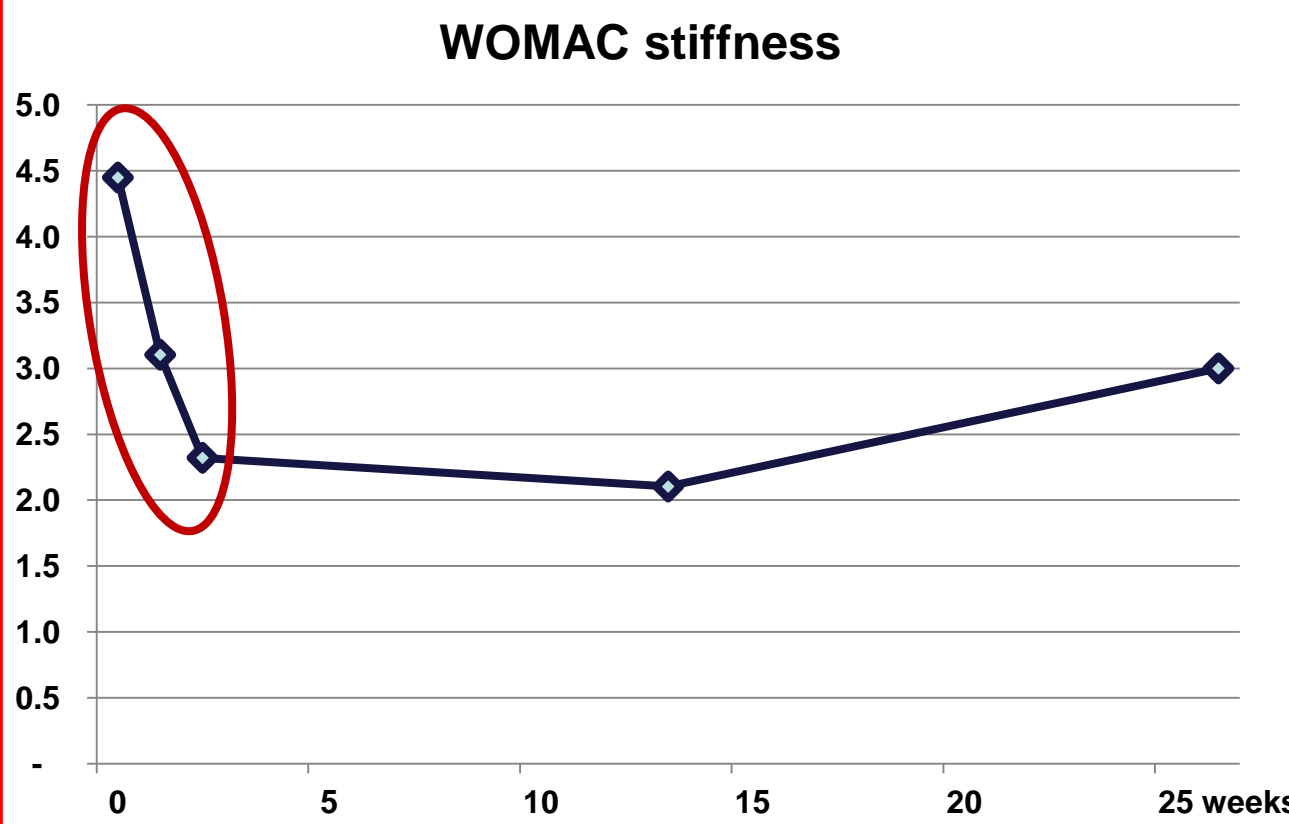


Figure 5

At W26, 100 % of the patients considered Synolis-VA moderately to extremely effective (figure 6).

No device-related adverse event was reported.

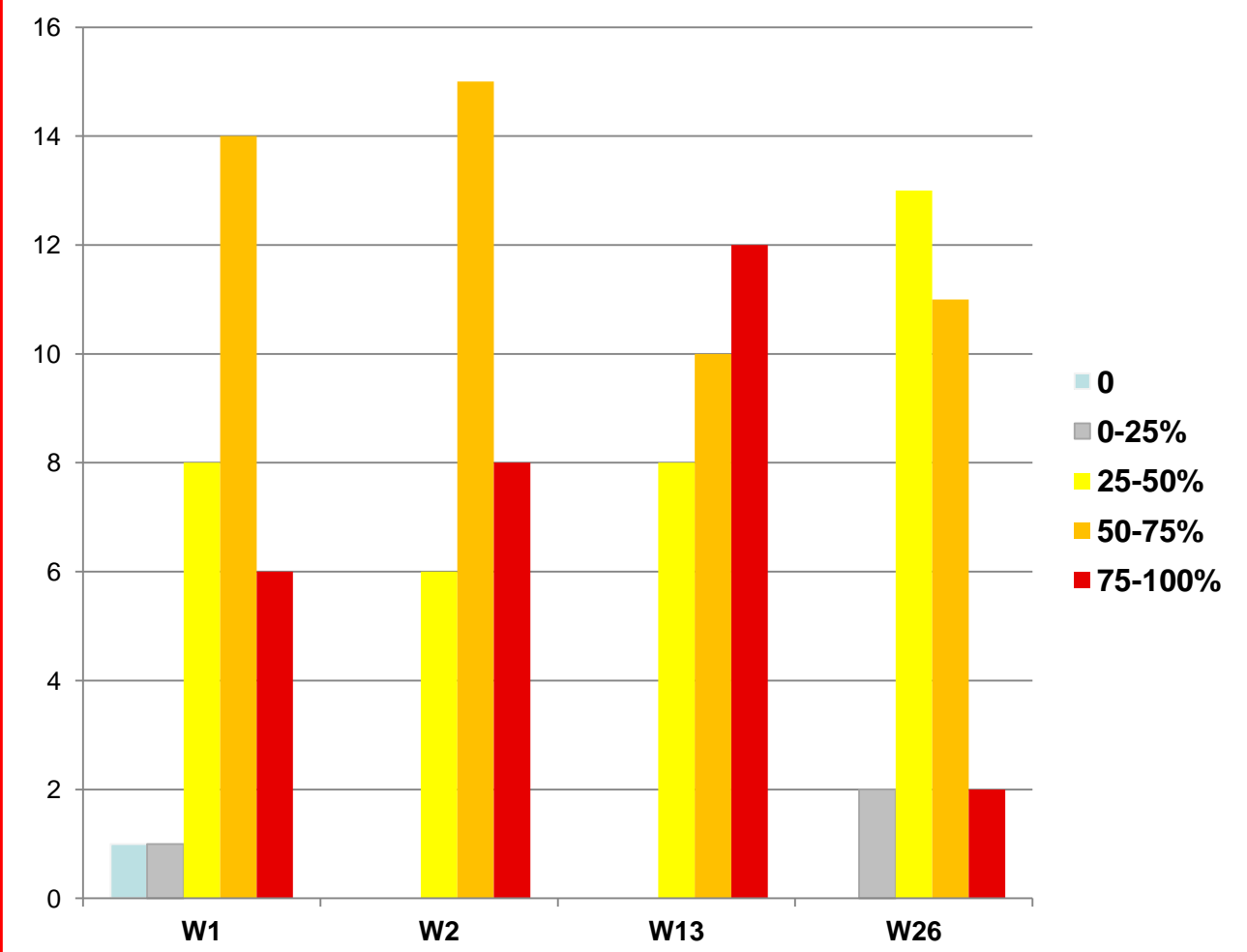


Figure 6 – Level of improvement

### RESULTS

At baseline:  
- Mean WOMAC A = 10.5  
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At week 1:  
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At week 2:  
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At week 13:  
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At week 26:  
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- Variation of WOMAC A between baseline and W1, W2, W13 and W26 was respectively -3.8, -6.5, -7.0 (-66%) and -5.5 (-43%) (figure 3).

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- For KL Grade II patients, average WP at baseline was 2.0, down to 1.2 (-40%) with 10 responders at W1 and remaining flat to 1.1 at W26 (-55%) with 11 responders (92% of responders) (figure 4a).

- For Grades III & IV, average WP at baseline was high at 3.5, down to 2.6 (-28%) with 13 responders at W1, with a minimum of 1.8 (-49%) at W13, and rising to 2.4 (-31%) at W26 with 16 responders (94% of responders) (figure 4b)

### CONCLUSION

This exploratory study demonstrates a quick and strong pain relief occurring immediately after the first injection of Synolis V-A, followed by a continuous improvement until week 13 and a sustainable effect up to week 26.

The high concentration of sorbitol combined with a high concentration of Hyaluronic acid is believed to both stabilize the structure of the gel for prolonged mechanical benefits but more importantly to neutralize the oxidative stress responsible for the appearance of OA symptoms

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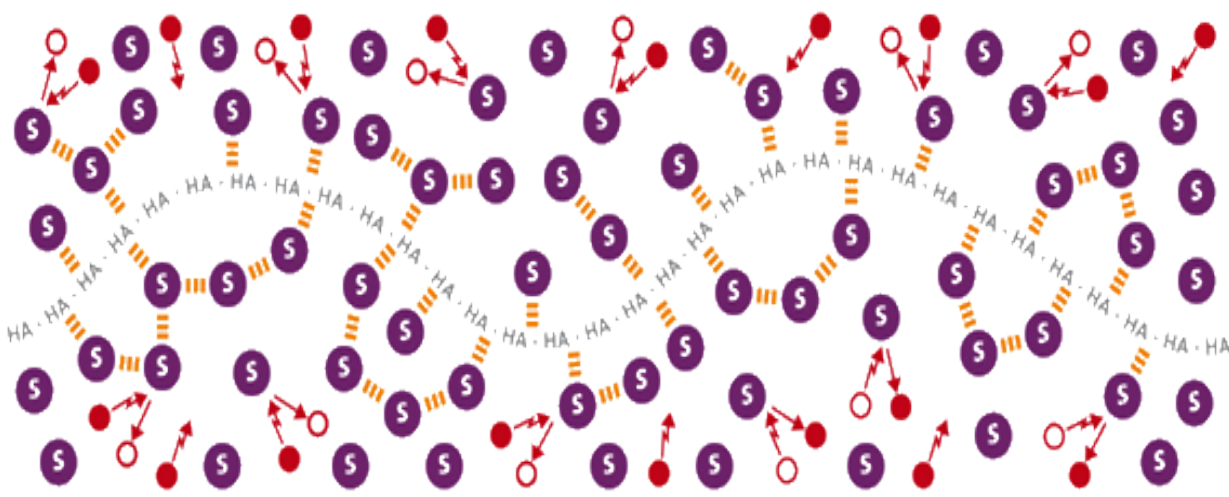


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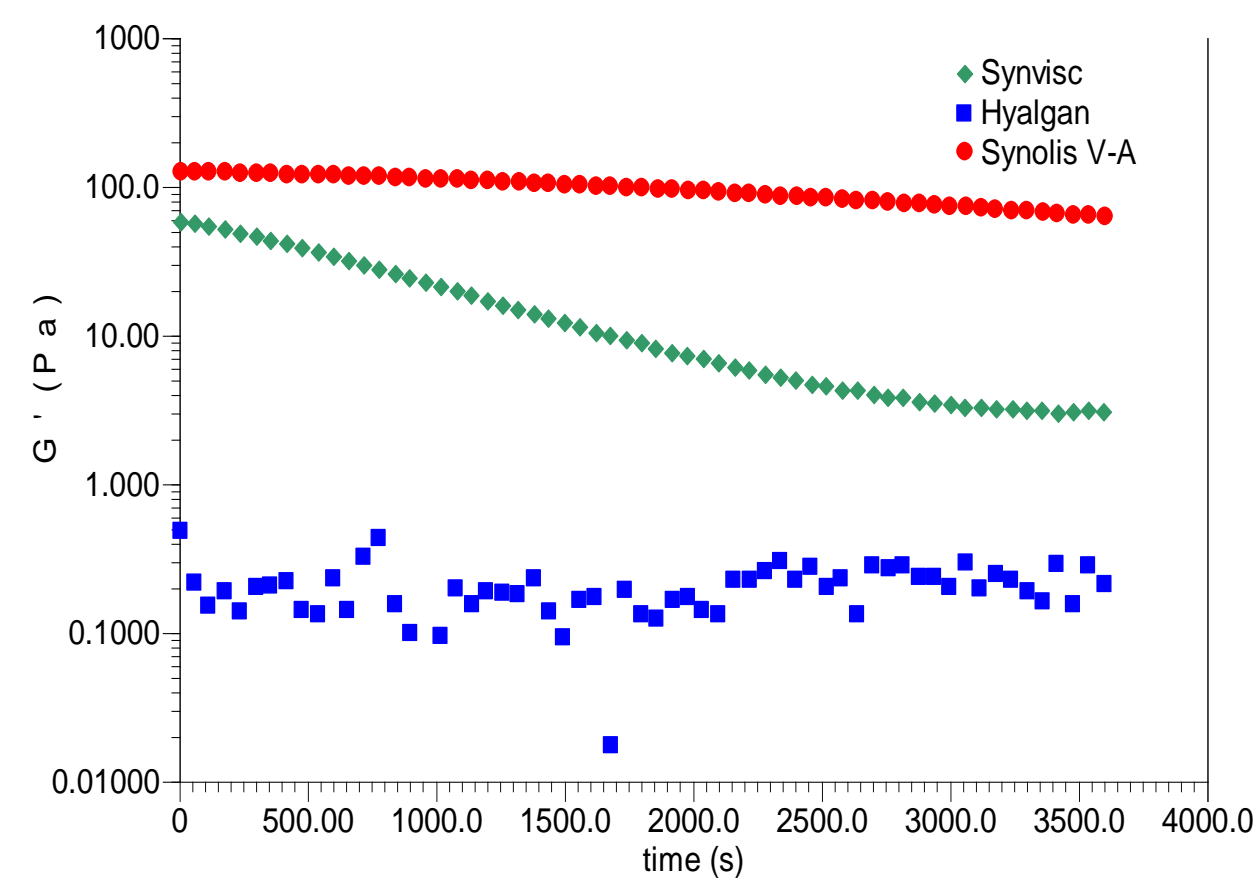


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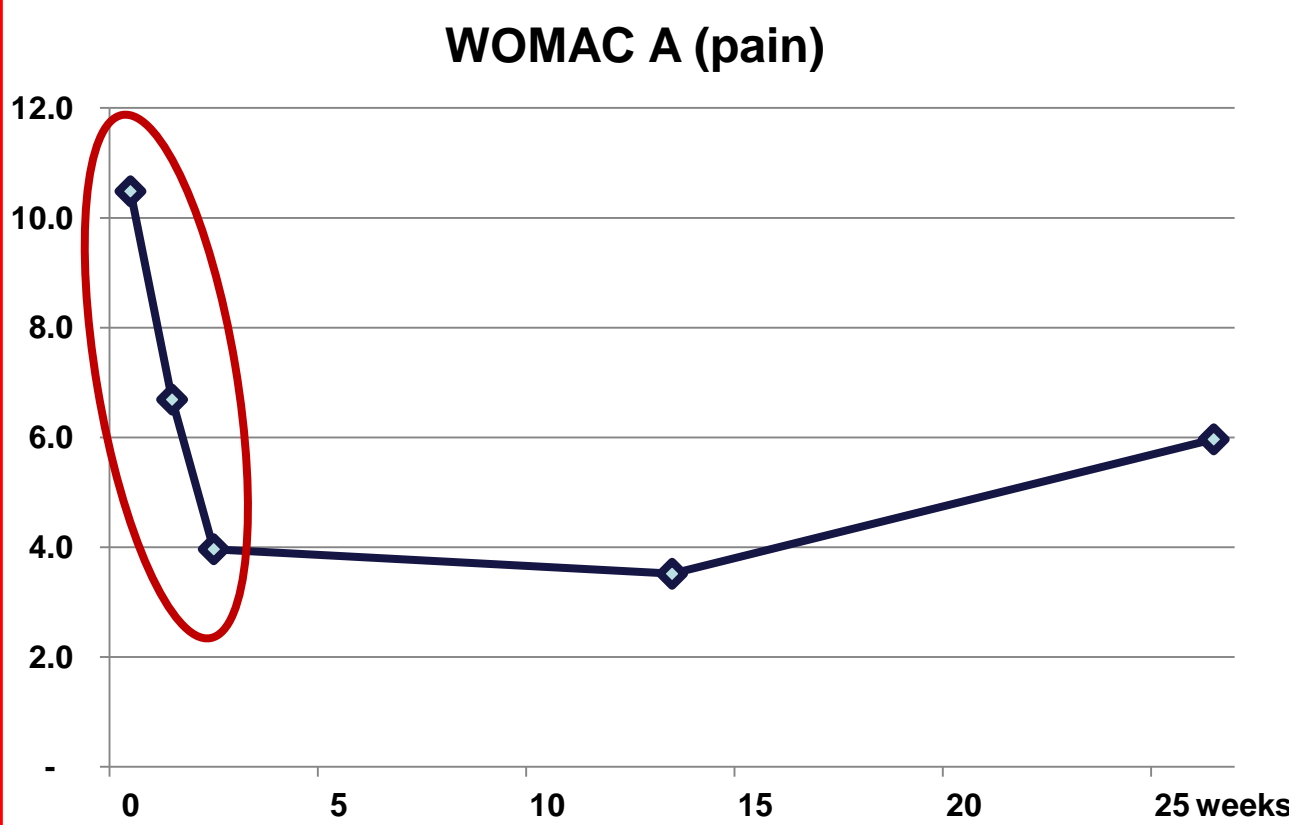


Figure 3

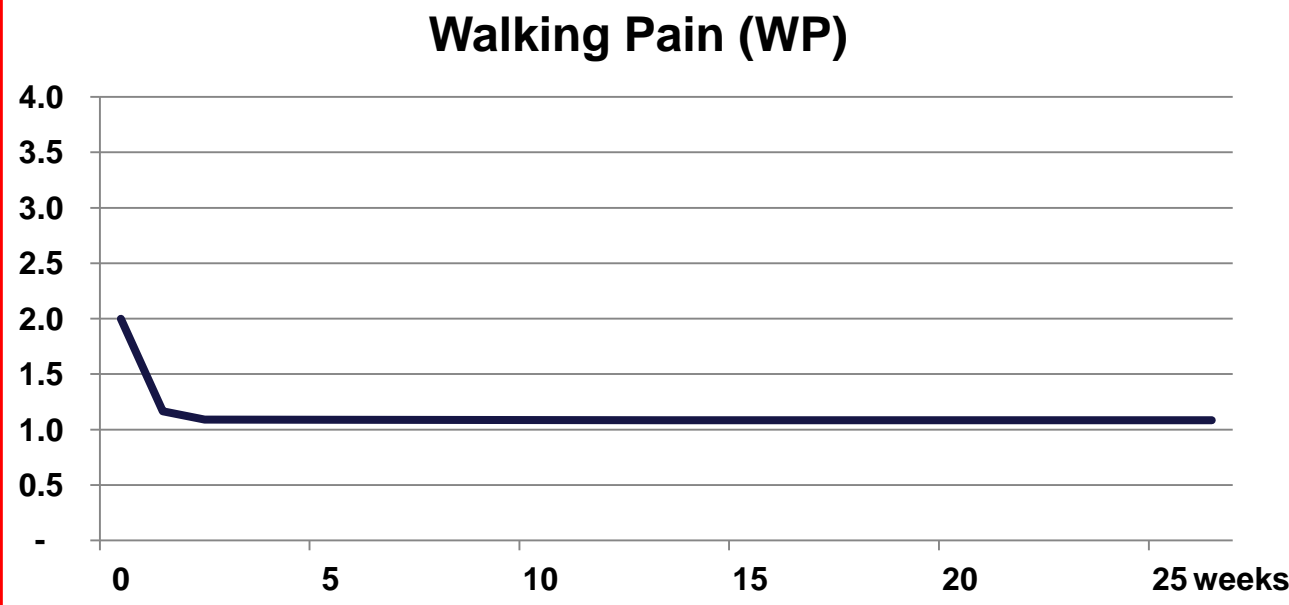


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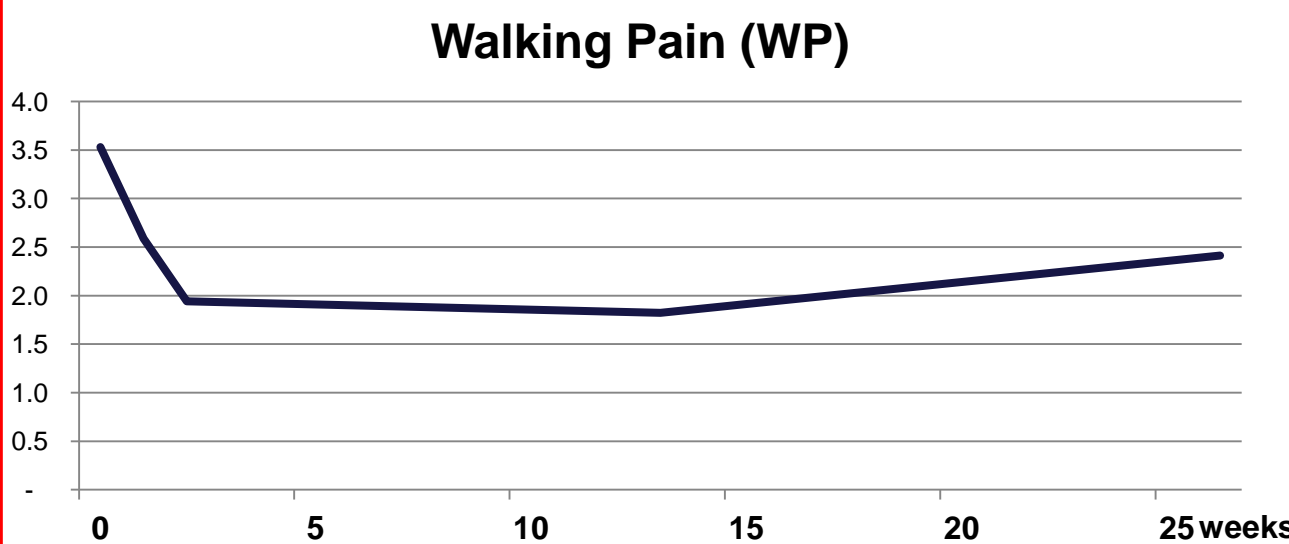


Figure 4b – K-L grades III & IV

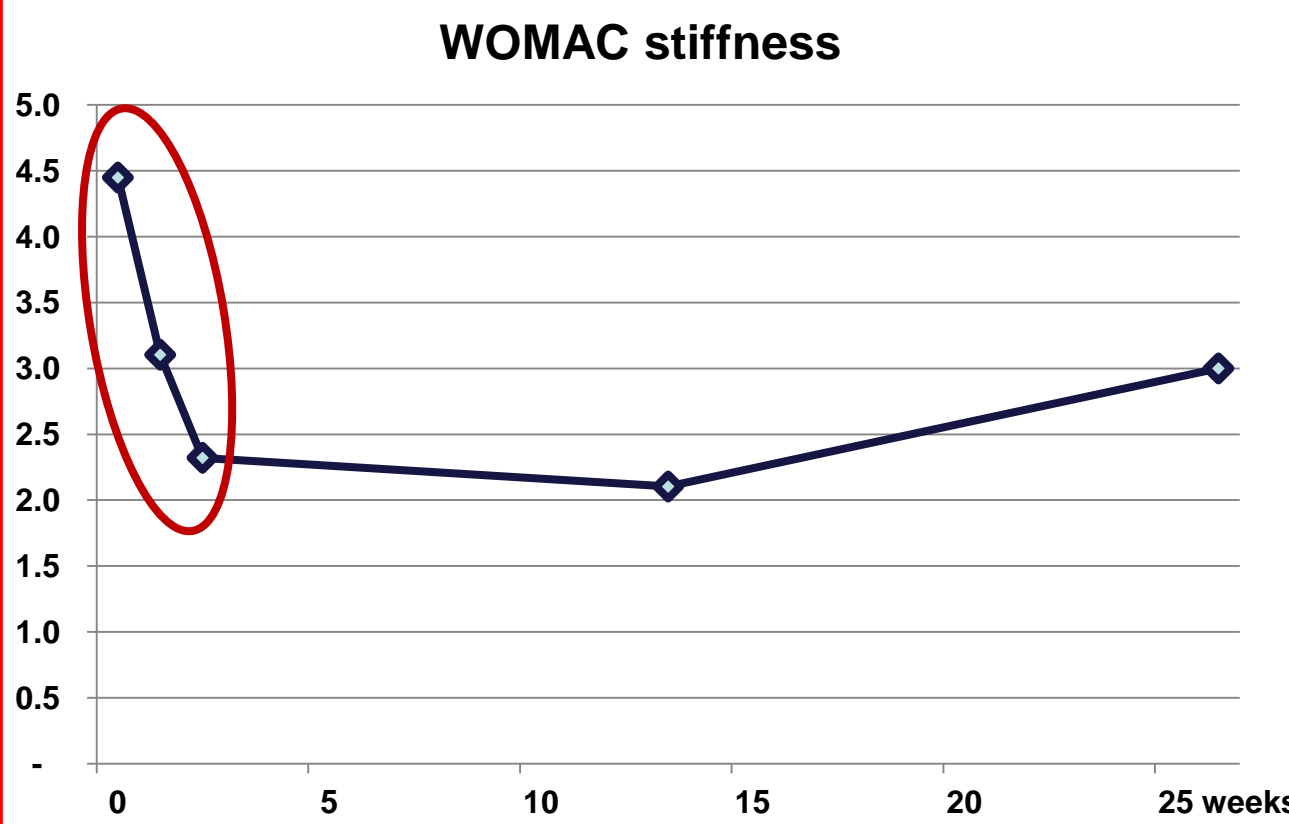


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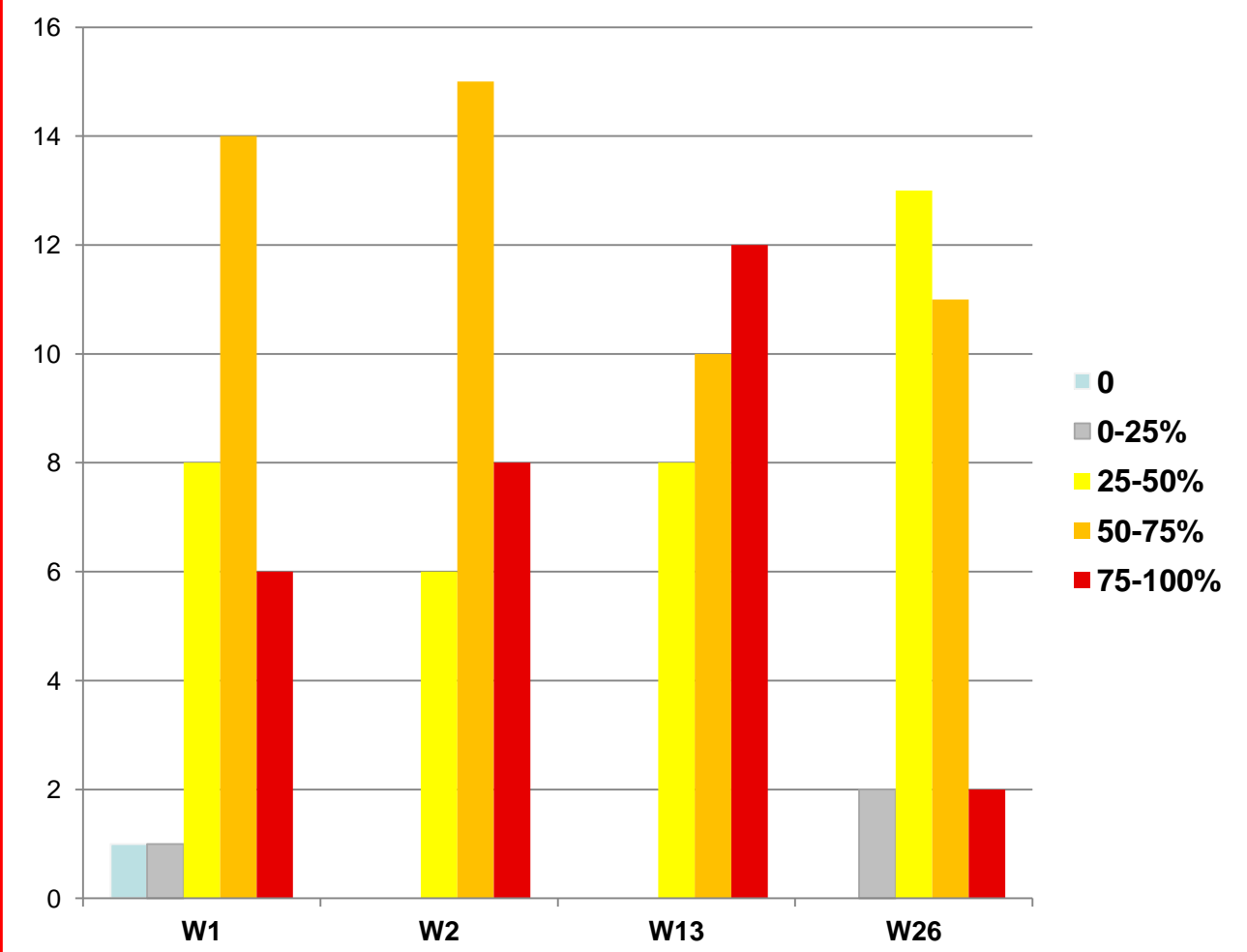


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# PAIN REDUCTION ASSESSMENT IN 1147 PATIENTS USING COMBINED SODIUM HYALURONATE AND SORBITOL VISCOSUPPLEMENTATION

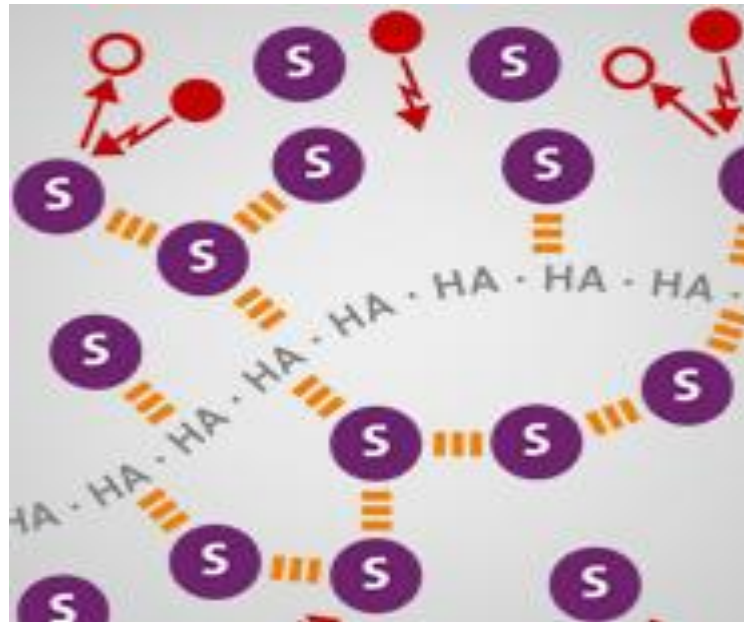
**Dr. C. KIPSHOVEN – Rottapharm / Madaus – Germany**  
**F. RADENNE – Anteis - Switzerland**

## Background

ViscoSupplementation (VS) has been used for more than 20 years and is recommended in the treatment of OA. There are currently more than 20 commercial VS products available worldwide. These products differ in Hyaluronic Acid (HA) origin, concentration, molecular weight, HA chemical modification, rheological properties, dosing regimens, claims for safety and efficacy, and residence time into the joint. The aim of this study was to evaluate the pain reduction performance and to confirm the safety of single or triple injections of 2ml viscosupplement combining sodium hyaluronate and sorbitol.

## Objective

This treatment is a novel patented Visco-Antalgic composed of high molecular weight (> 2 MDa in the final sterilized gel), highly concentrated, non-crosslinked HA (2%) from biofermentation origin combined with a high concentration of sorbitol (4%). Sorbitol is an endogenous molecule that functions as a strong Oxygen Free Radical (OFR) scavenger. We hypothesize that antioxidant effect of sorbitol may play an active role in rapid and strong pain reduction in patients with OA.



## Method

A total of 1147 patients with OsteoArthritis (OA) enrolled in an Non-Interventional Study conducted 398 centres in Germany were mainly been treated with a single 2ml IntraArticular (IA) injection (approximately 55% of patients) or a triple injection (approximately 33% of patients) of sodium hyaluronate (20mg/ml) combined with sorbitol (40mg/ml). Studied population had an average age of 63.3 years, included 499 males, 614 females and 34 patients without reported gender. The majority of patients were treated for knee OA (92.9%) whereas the rest of patients were injected in the shoulder (2.8%), the hip (4.4%) and in other joints (1.6%). No data were reported for 2.1% of patients and 40 patients were treated for multiple joints.

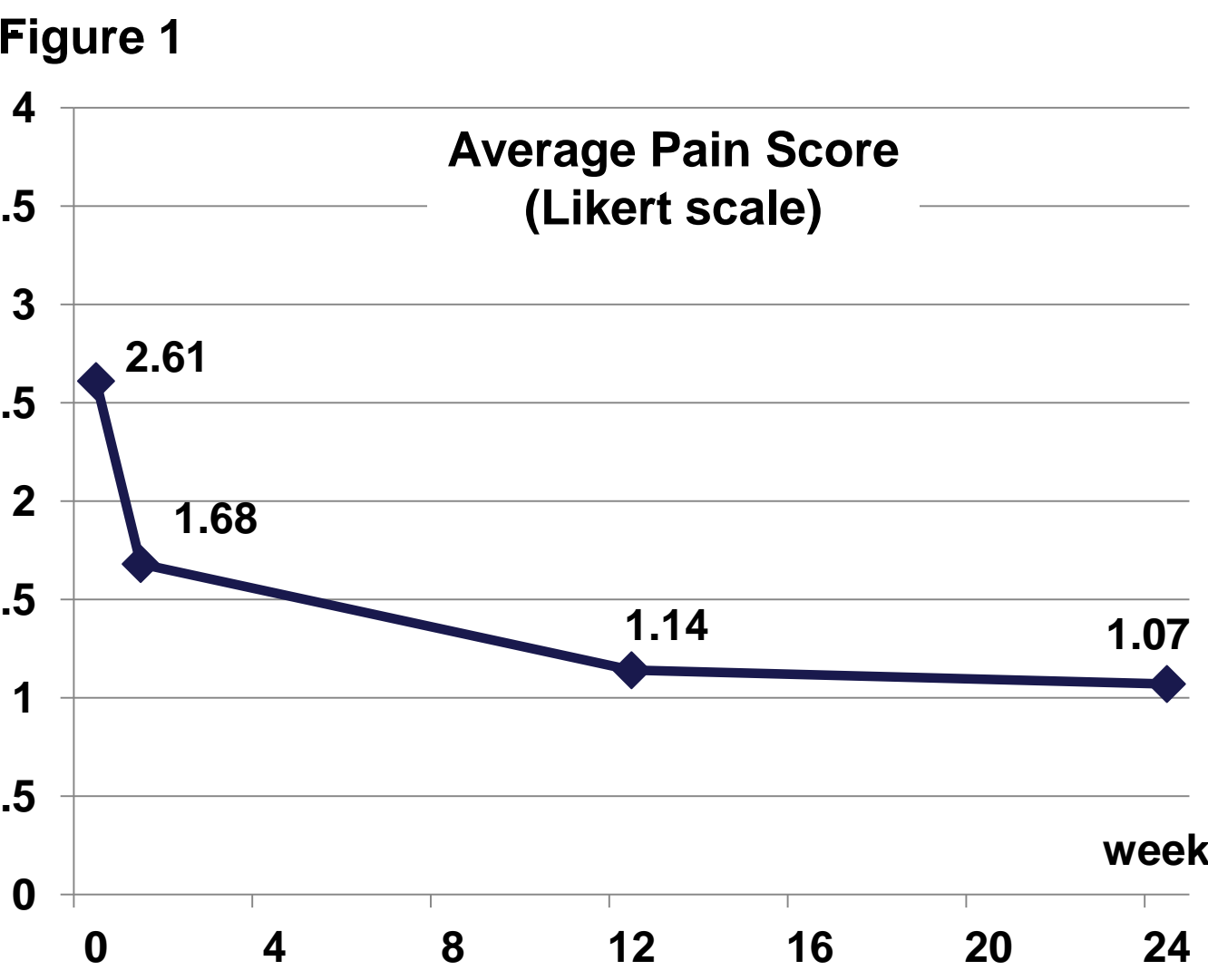
- Patients were distributed into the following grades according to Kellgren-Lawrence (K-L) scale: 6.7% with Grade I, 31.4% with Grade II, 48.0% with Grade III and 13.9% with Grade IV.
- Patients' pain level was assessed using 5 points Likert scale (from "No Pain" scoring 0 to "Very Severe Pain" scoring 4) at 1<sup>st</sup> injection (Visit 1: baseline) and during 5 follow up visits for a treatment period of 24 weeks.

Primary study criteria was the variation of pain score (Likert scale) between baseline and following time points: week1, week 12 and week 24 as well as the variation of the functional impairment score (Likert scale) at baseline, week 12 and week 24.

Secondary study criteria comprised the evaluation of the initial pain level in relation to the reported Kellgren-Lawrence Grade and observation of Adverse Events (AEs) reported during the study.

This post-marketing surveillance was conducted in accordance to "Empfehlungen zur Planung, Durchführung und Auswertung von Anwendungsbeobachtungen" of the BfArM (Federal Institute for Drugs and Medical Devices) and the Paul-Ehrlich-Institute, dated 7 July 2010.

## Results



At week 1, after a single injection, 70.6% (586/830) of patients responded to the treatment, with pain score decreasing by at least 1 point on the Likert scale.

At week 12, 83.8% (896/1069) of patients were responding to treatment. Finally, at week 24, 84.4% (857/1016) of patients were classified as responders.

A total of 1103 patients reported functional impairment score at baseline, 1074 patients at week 12 and 1031 patients at week 24.

-Patients with "No Impairment" evolved from 6.7% at baseline to 26.2% at week 12 and 29% at week 24.

-Patients with "Severe" or "Very Severe impairment" evolved from 30.3% at baseline to 3.8% at week12 and 4.4% at week 24 (figure 2).

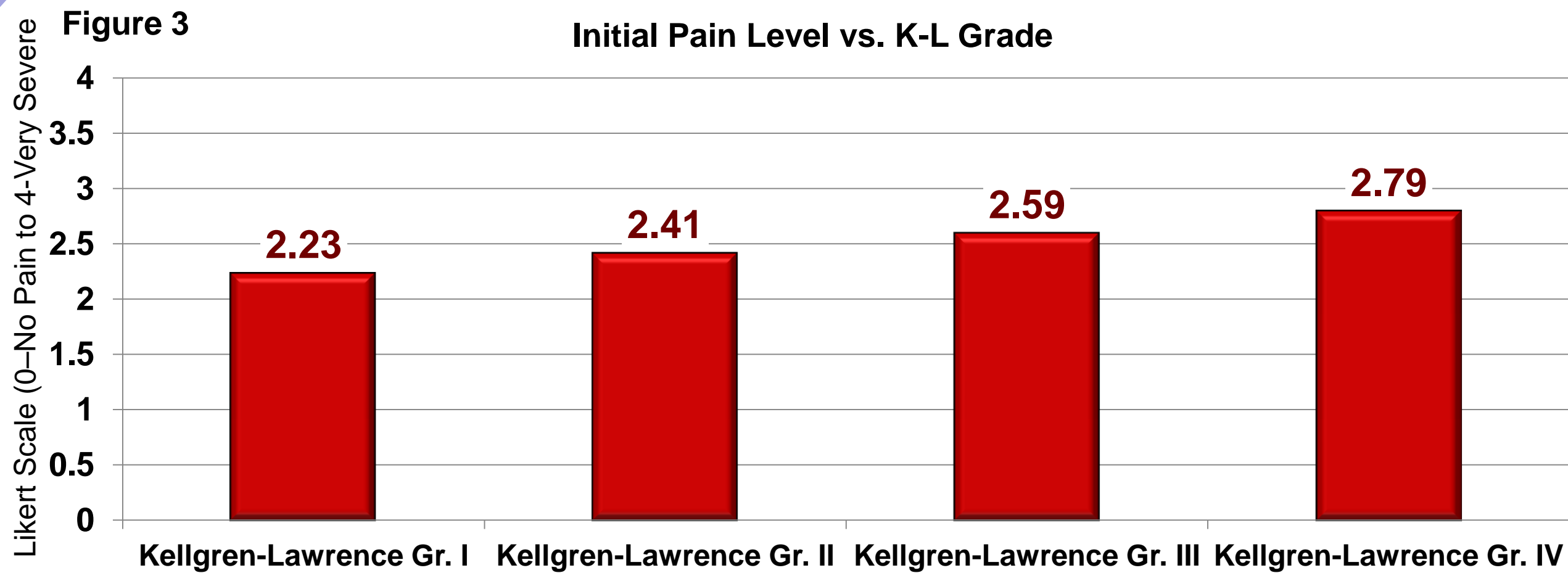
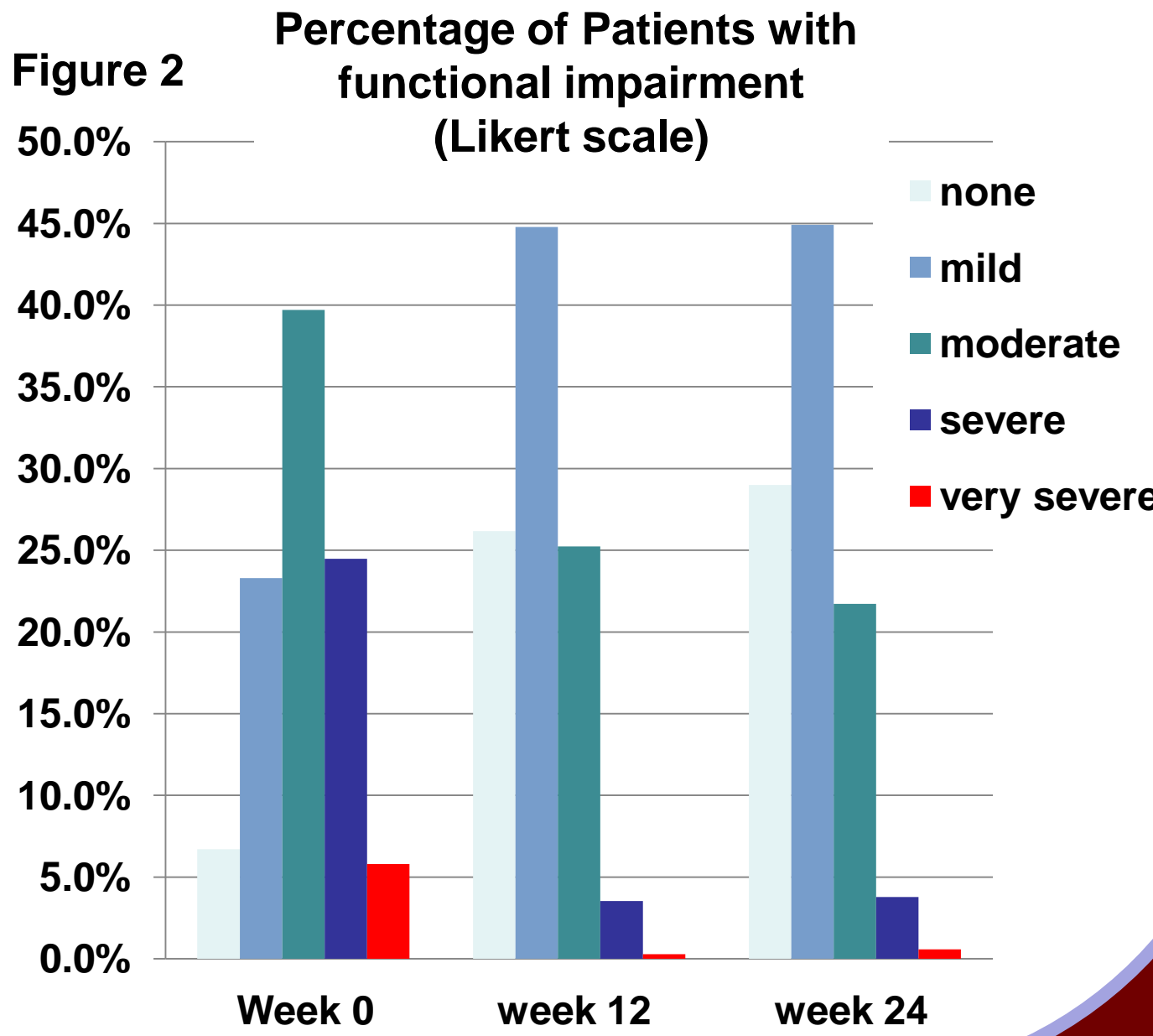


Figure 3 - On the population with Knee OA with both K-L Grade and Initial Pain Level reported (n=509), mean pain level is steadily increasing as a function of Kellgren-Lawrence Grade (K-L Gr.) severity with a mean of 2.23 for K-L Gr. I (n=35), 2.41 for K-L Gr. II (n=160), 2.59 for K-L Gr. III (n=243) and 2.79 for K-L Gr. IV (n=71).

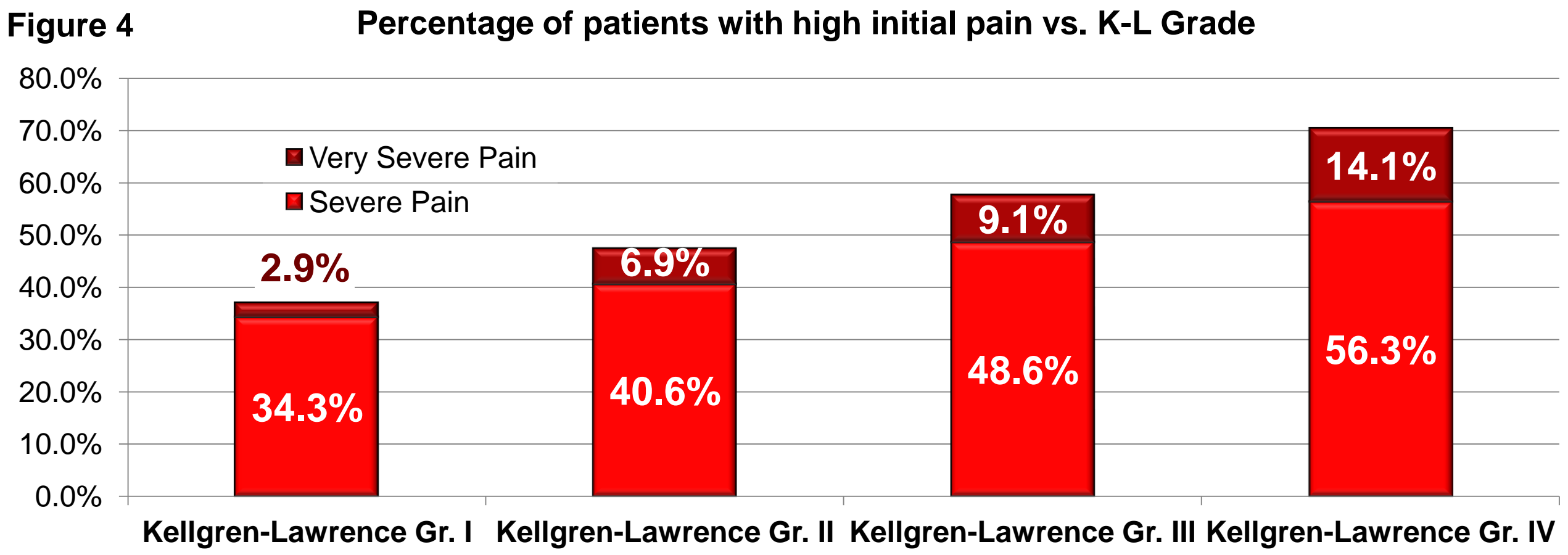


Figure 4 - The percentage of patients with Severe Pain (Likert score 3) and Very Severe Pain (Likert score 4) was correlated to K-L Gr., with 37% of patients with pain level scoring at 3 & 4 in K-L Gr. I, 47% in K-L Gr. II, 56% in K-L Gr. III and 70% in K-L Gr. IV.

Table 1

System Organ Class	Preferred term	n
Musculoskeletal and connective tissue disorders	Injection site joint pain	15
	Joint swelling	4
	Joint warmth	2
	Joint effusion	2
	Joint instability	1
Number of AEs		24

Table 1 - Out of 1147 patients only 24 Adverse Events (AEs) were reported for 22 patients (1.9%), the most common Adverse Event being "Injection site joint pain"

## Discussion

### Efficacy of the treatment

On a large cohort of patients, despite a relatively large number of patients with Kellgren-Lawrence grade IV (13.9%) and despite the majority (about 55%) of patients receiving only a single IA injection of 2ml, the level of pain decrease observed from week 1 to week 24 is extremely high; close to 60% at week 24. It could be hypothesized that this performance is strongly supported by the very high rate of responders (84.4%) observed. The decrease of functional impairment is of the same scale, with a baseline average score of 1.99 decreasing to 1.02 (-48.8%) at week 24.

### Link between Pain Level and Radiographic Severity

Despite several publications questioning the relation between radiographic-determined severity and pain level [1-2], this study conducted on a large scale population demonstrates the existence of a trend linking Kellgren-Lawrence Grades and average pain level (based on Likert scale). The percentage of patients with high pain level (Severe and Very Severe) is increasing in relation to the K-L Grade to reach 70% for K-L Gr. IV.

### Safety

With 1.9% of low severity AEs reported by investigators, this treatment seems to be very safe to perform; especially taking into account that about 30% of injections might miss the intra-articular space [3] potentially generating pain or flare reaction not directly associated with the used viscosupplement.

## Conclusion

**Viscosupplementation using the combination of sodium hyaluronate and sorbitol has been observed to significantly and safely reduce both joints pain and functional impairments for patients with osteoarthritis at all Kellgren-Lawrence grades, on a period of 24 weeks, at least.**

### References:

- 1 - John Bedson, Peter R Croft, The discordance between clinical and radiographic knee osteoarthritis: A systematic search and summary of the literature, BMC Musculoskeletal Disorders 2008, 9:116;
- 2 - Hannan MT, Felson DT, Pincus T, Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee, J Rheumatol. 2000 Jun;27(6):1513-7.
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# Efficacy of Knee OsteoArthritis Viscosupplementation Treatment by Combined Hyaluronic Acid and Sorbitol According to Radiographic Severity or Initial Pain Level

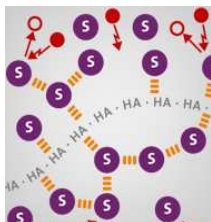
Dr. T. CONROZIER– Belfort Hospital - France

Dr. C. KIPSHOVEN – Rottapharm / Madaus – Germany

F. RADENNE – Anteis - Switzerland

## Background

Synolis V-A is a visco-analgesic formulation indicated for viscosupplementation in OsteoArthritis. Synolis V-A is composed of highly concentrated non-crosslinked hyaluronic acid (2%) from biofermentation origin combined with a high concentration of sorbitol (4%). Sorbitol is an endogenous molecule which functions as an oxygen free radical (OFR) scavenger. Rapid and strong pain reduction in patients with knee OsteoArthritis (OA) has been observed in several previous studies using Synolis V-A.



## Objective

To compare the effectiveness of two dosing regimen (single injection vs. 3 injections one week apart) according to the radiographic and clinical severity.

## Patients and Methods

Among 1147 patients with a majority suffering from knee Osteoarthritis (92.9%) enrolled in a Non-Interventional Study conducted by Rottapharm Madaus in 398 centres in Germany following recommendations from the BfArM (Federal Institute for Drugs and Medical Devices) and the Paul-Ehrlich-Institute, 455 patients met the inclusion criteria (reported Kellgren-Lawrence grade and initial pain level at week 0, week 1 and/or week 24) and received either 1 or 3 injections of Synolis V-A 2ml (GO-ON matrix in Germany) one week apart – figure 1.

The studied population was grouped according to radiographic severity using Kellgren-Lawrence (K-L.) grading system. Two groups were defined: K-L I/II & K-L. III/IV – figure 2.

Four sub-groups according to the K-L. Grading and the number of injection of Synolis V-A 2ml were then analyzed: Low K-L. (Gr. I/II)-1 injection; Low K-L.-3 injections; High K-L. (III/IV)-1 injection and High K-L.-3 injections.

This same population was evaluated for Walking Pain (WP) at baseline, using 5-point Likert scale. Level of pain observed was None (1.1%), Mild (8.6%), Moderate (35.8%), Severe (45.1%), Very Severe (7.5%) and Not Reported (2.0%) – figure 3.

Four sub-groups according to the Likert score before treatment initiation and the number of injections of Synolis V-A 2ml were then analyzed: Low Pain (mild to moderate)-1 injection; Low Pain-3 injections; High Pain (severe to very severe)-1 injection and High Pain-3 injections

The analysis compared the average response (pain decrease vs. baseline) between sub-groups on the short-term (week 1) and on the mid-term (week 24) following treatment initiation.

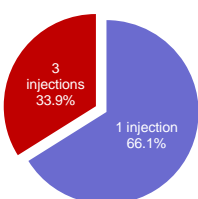


figure 1: Patients repartition by number of injections

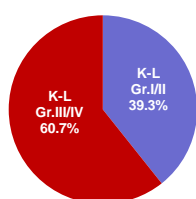


figure 2: Patients repartition based on their Kellgren-Lawrence Grade

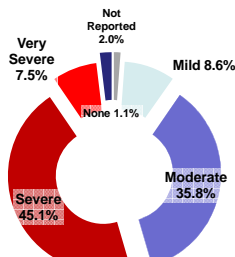
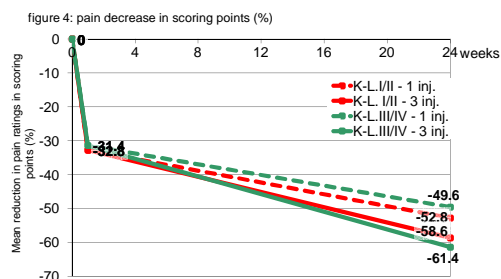


figure 3: Patients repartition based on their Initial Pain level

## Results

At week 1, pain decrease in both Kellgren-Lawrence groups (K-L. I/II & III/IV) was similar, with an average pain decrease of 32.6% and 31.4% respectively ( $p=0.7354$ ) but significant vs. baseline ( $p<0.001$ ).

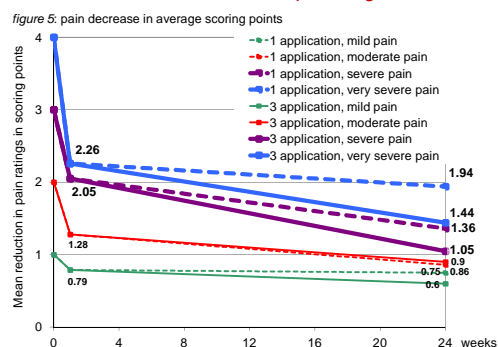
At week 24, 3 injections provided greater pain relief than single injection whatever the patients' sub-groups. Never the less, for the K-L. I/II group, the 3-injection regimen brought 11% additional average pain decrease vs. the 1-injection ( $p=0.0363$ ), whereas for the K-L. III/IV group, the 3-injection regimen brought 24% additional pain decrease vs. the 1-injection ( $p=0.0003$ ) – figure 4.



In WP based groups (Likert scores 1, 2, 3 & 4) at week 1, pain decrease correlated to the pain score observed at baseline: Patients with very severe pain scored an average of 1.74 points below; Patients with severe pain scored 0.95 points below; Patients with moderate pain scored 0.72 points below and patients with mild pain scored 0.21 points below.

At week 24, average pain (for patients with Mild to Very Severe pain receiving 1 or 3 injections) dropped by 56.5% from an average baseline score at 2.52.

More precisely, pain scores reported at week 24 after 3 injections were significantly lower than after 1 injection for Very Severe and Severe initial pain, with respectively 26% and 23% better average score. This difference was not observed for Moderate to Mild initial pain – figure 5



## Conclusion

At week 24, average pain decrease vs. baseline was correlated to both the number of injections and the radiographic severity, with a higher benefit of the 3-injection regimen for K-L Gr. III/IV, despite the absence of observed correlation at week 1.

A fast pain relief proportional to the initial pain level has been observed soon after the first injection of Synolis V-A (week 1). Despite the pain decrease trend preserved until week 24 even with one single injection, patients with Very Severe to Severe pain at baseline particularly benefited from the 3-injection regimen.

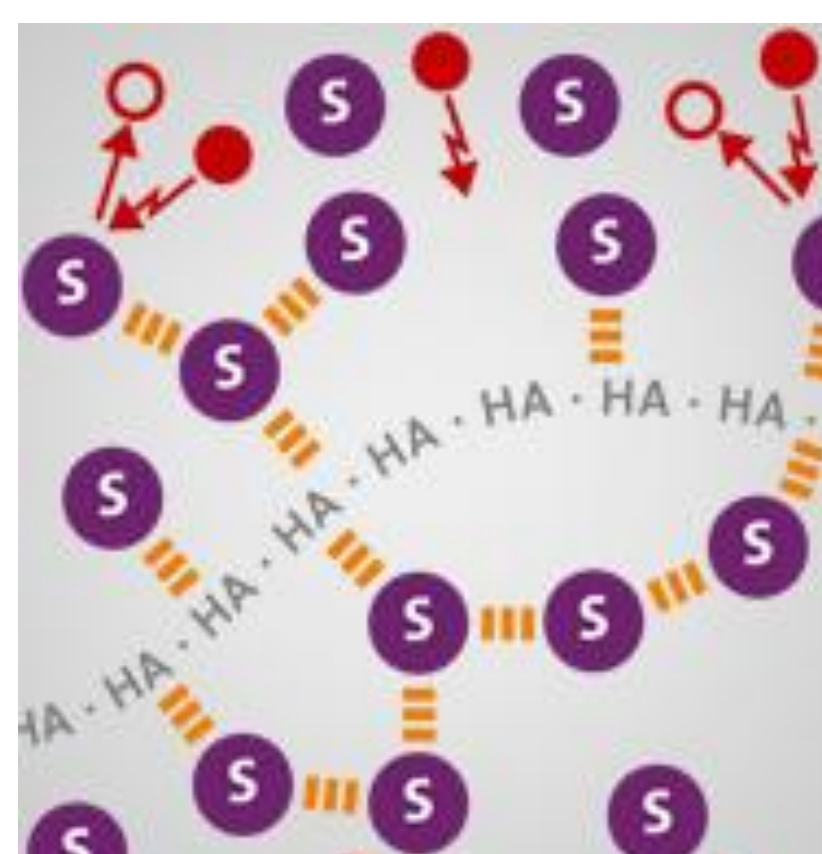


# Knee OsteoArthritis Radiographic Severity and Initial Pain Level Influencing Short and Mid-Term Response Rate After Viscosupplementation Treatment by Combined Hyaluronic Acid and Sorbitol

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F. RADENNE – Anteis - Switzerland

## Background

Synolis V-A is a visco-analgesic formulation indicated for viscosupplementation in OsteoArthritis. Synolis V-A is composed of highly concentrated non-crosslinked hyaluronic acid (2%) from biofermentation origin combined with a high concentration of sorbitol (4%). Sorbitol is an endogenous molecule which functions as an oxygen free radical (OFR) scavenger. Rapid and strong pain reduction in patients with knee OsteoArthritis (OA) has been observed in several previous studies using Synolis V-A.



## Objective

We hypothesize that one of the dimensions of average pain reduction is a variable response rate to treatment. In addition, we hypothesize that this variable response rate could be associated to radiographic severity, initial pain level and intra-articular injection regimen.

## Patients and Methods

Among 1147 patients with a majority suffering from knee Osteoarthritis (92.9%) enrolled in a Non-Interventional Study conducted by Rottapharm Madaus in 398 centres in Germany following recommendations from the BfArM (Federal Institute for Drugs and Medical Devices) and the Paul-Ehrlich-Institute, 455 patients met the inclusion criteria (reported Kellgren-Lawrence grade and initial pain level at baseline, at week 1 and/or at week 24) and received either 1 or 3 injections of Synolis V-A 2ml (GO-ON matrix in Germany) one week apart.

This population was then grouped according to two severity evaluation factors:

- Two groups were created according to Kellgren-Lawrence (K-L) based severity (K-L.) I/II (39.3%) & K-L. III/IV (60.7%) – *figure 1*.
- Two groups were created according to Walking Pain (WP) at baseline (5 points Likert scale): None (1.1%), Mild (8.6%), Moderate (35.8%), Severe (45.1%), Very Severe (7.5%) and Not Reported (2.0%) – *figure 2*. The Low Pain group combined patients with Mild/Moderate pain and the High Pain group combined patients with Severe/Very Severe Pain.

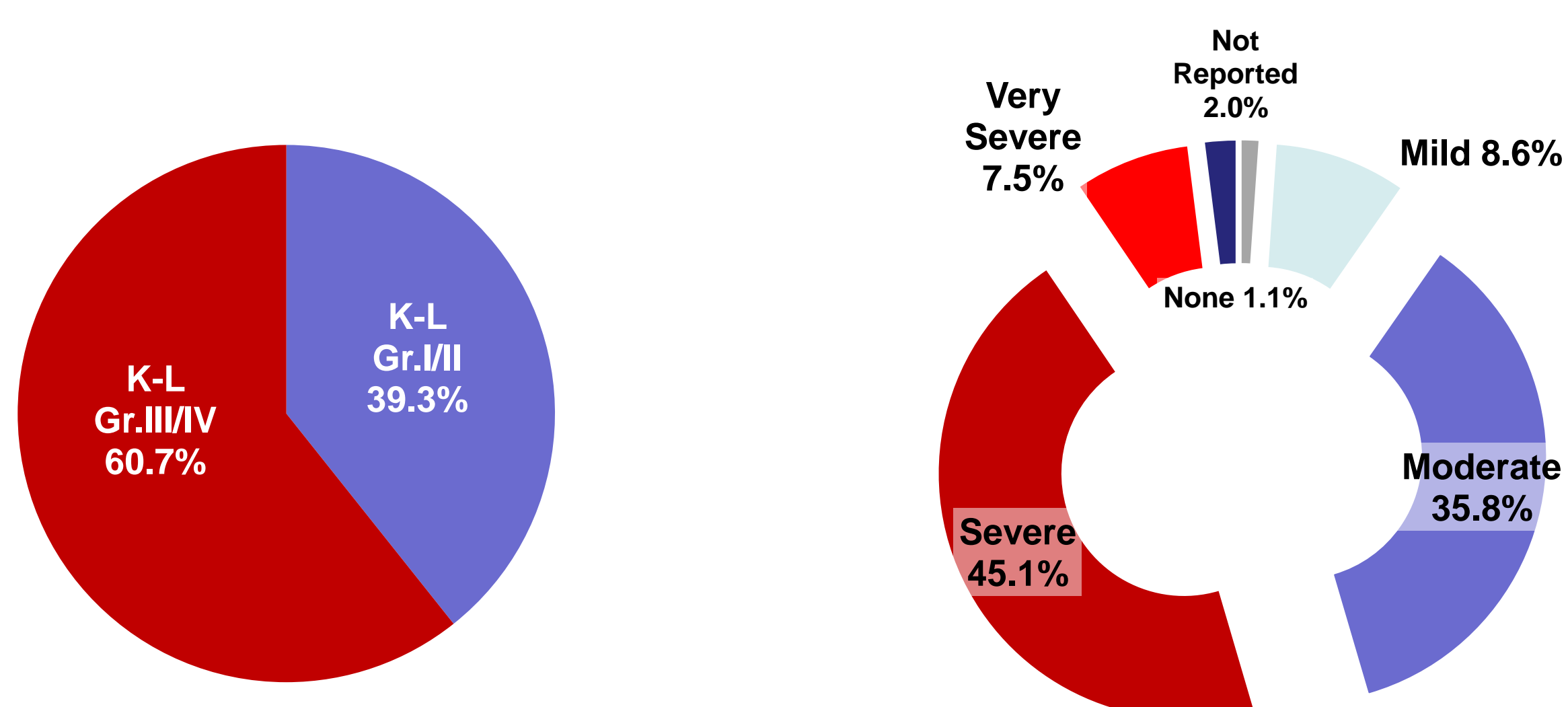


Figure 1: Patients repartition based on their Kellgren-Lawrence Grade

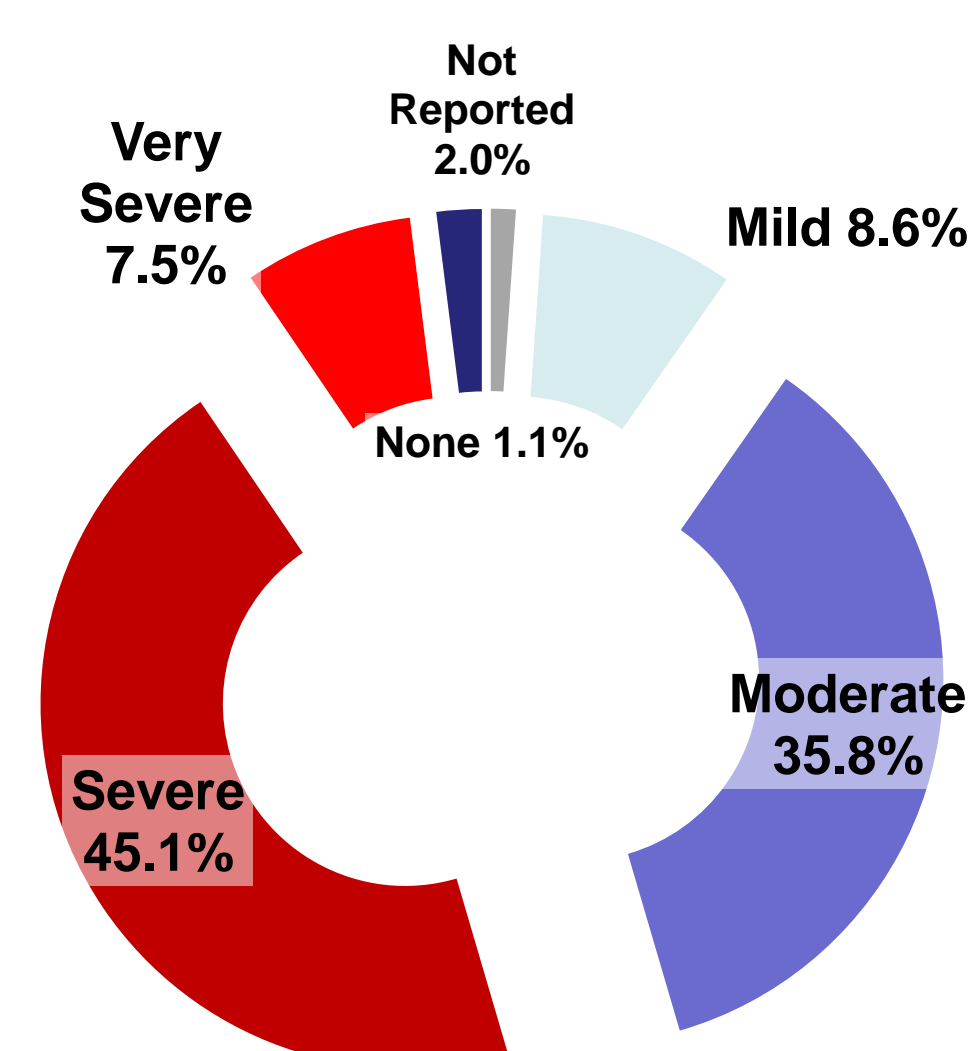


Figure 2: Patients repartition based on their Initial Pain level

Two analyses were conducted comparing at week 1 and week 24 vs. the rate of responders for both 1 and 3 injections regimen vs. baseline, for Low K-L. (I/II) and High K-L. (III/IV) on one hand, and for Low Pain (Mild to Moderate) and High Pain (Severe to Very Severe) on the other hand. Patients defined as responders were patients with pain decrease of at least 1 point on the Likert scale vs. baseline.

## Results

For both Low and High K-L patients groups, the percentage of responders was similar at week 1 with respectively 68.6% and 66.1%.

At week 24 all sub-groups of patients (Low and High K-L groups receiving either 1 or 3 injections) obtained an average response rate above 80%. However, when patients from the Low K-L group receiving 1 or 3 injections and patients from the High K-L group receiving 1 injection had comparable average response rate, comprised between 81.3% and 82.7% of responders; patients from the High K-L group who received 3 injections obtained a much higher responders rate of 93.1% - *figure 3*.

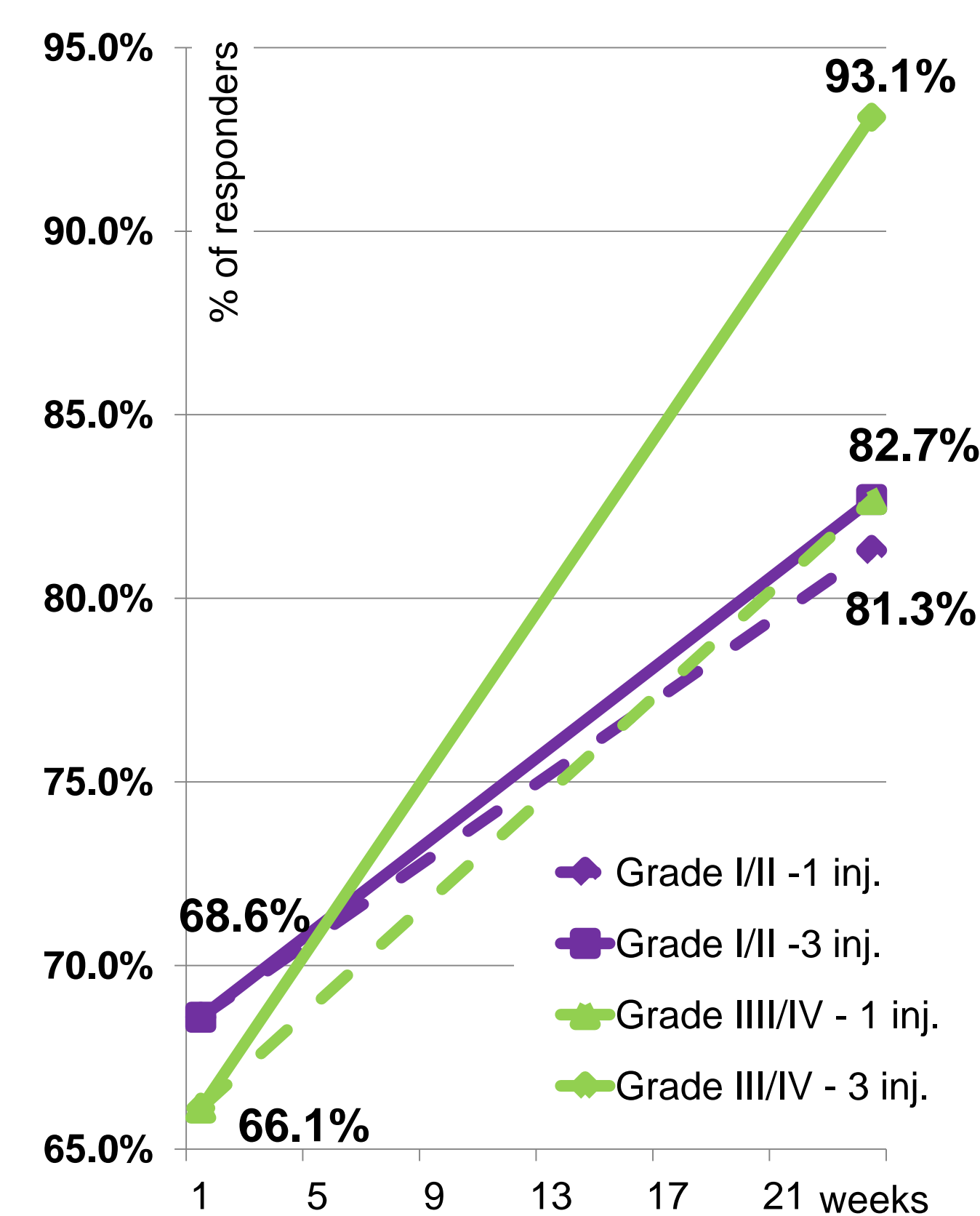


figure 3: rate of responders according to K-L and inj. regimen

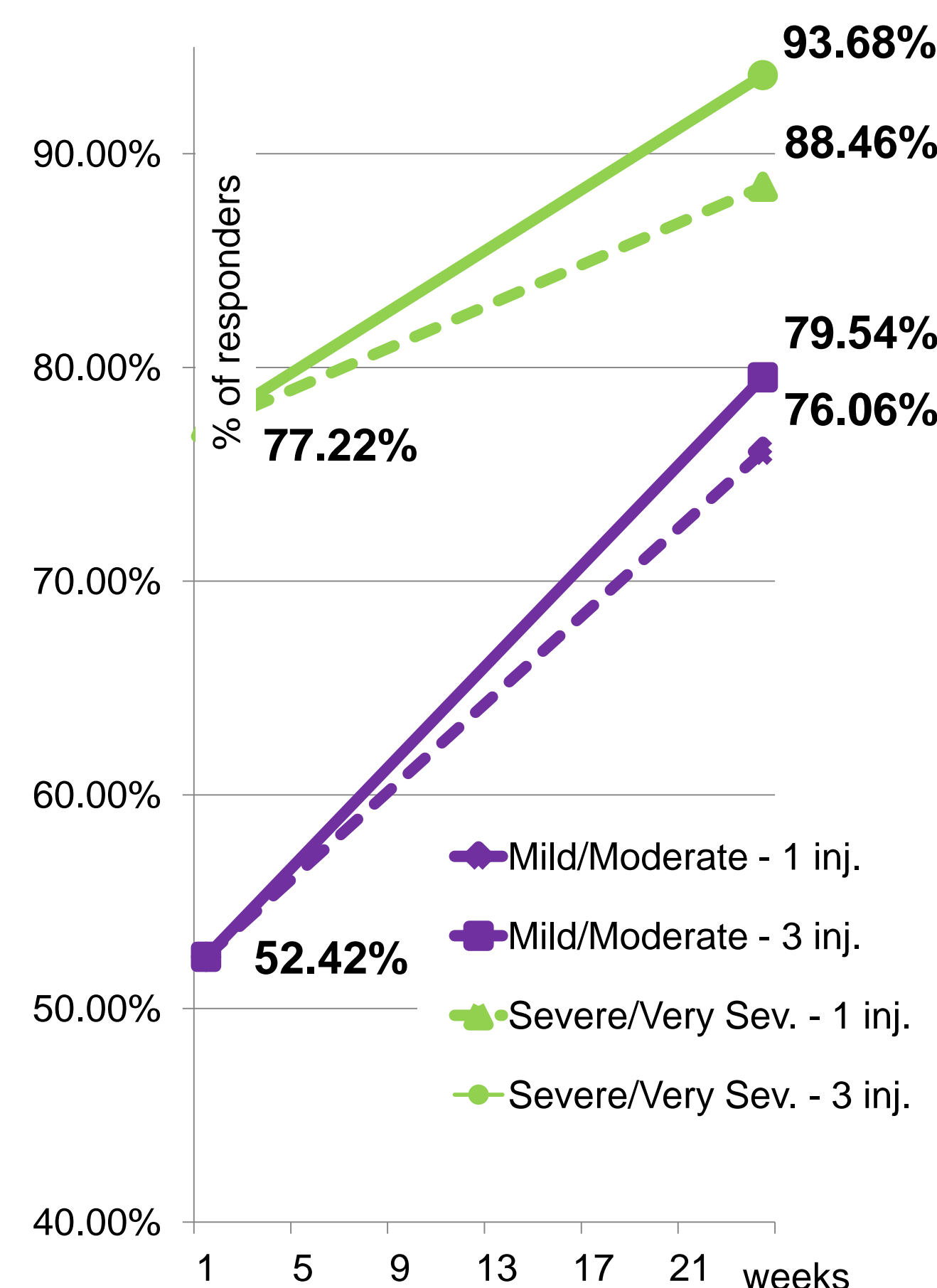


figure 4: rate of responders according to WP Pain and inj. regimen

On the other hand, the percentage of responders between Low Pain and the High Pain groups was different right from week 1 with respectively 52.4% and 77.2%.

At week 24 all sub-groups of patients (Low and High Pain groups receiving either 1 or 3 injections) obtained response rate above 75%. Three injections regimen always provided better response rate vs. 1 injection regimen with respectively 79.5% vs. 76.1% for the Low Pain group and 93.7% vs. 88.5% for the High Pain group – *figure 4*.

## Conclusion

This study suggests that the fast average pain relief commonly observed after the first injection of Synolis V-A could partly be explained by the high number of responders reported at week 1 (67.1%).

On the short-term, the initial pain level seemed to be a better predictor of response rate, with a response rate 47.3% higher for High vs. the Low Pain group; which could be explained by the non-linear pain scoring system used.

At week 24, the radiographic severity seemed to be an efficient indicator for adapting the injection regimen, suggesting the use of 3 injections for K-L Gr. III & IV patients since the observed response rate was 12.6% higher than for the single regimen.



# VISCO-SUPPLEMENT COMBINING HIGH MOLECULAR WEIGHT HYALURONIC ACID AND SORBITOL DEMONSTRATES HIGH ANTALGIC ACTIVITY IN OSTEOARTHRITIS PATIENTS

Franck RADENNE      Anteis SA – Geneva - Switzerland



## Background

OsteoArthritis (OA) is a very common joint disorder with increasing prevalence. It is projected that by the year 2030, almost 67 million US adults will have been diagnosed with arthritis [1]. ViscoSupplementation (VS) has been used for more than 20 years and is recommended in the treatment of OA. There are currently more than 20 commercial VS products available worldwide. These products differ in Hyaluronic Acid (HA) origin, concentration, molecular weight, HA chemical modification, rheological properties, dosing regimens, claims for safety and efficacy, and residence time into the joint.

## Objective

Synolis® (Anteis SA) is a novel patented Visco-Antalgic composed of high molecular weight (> 2 MDa in the final sterilized gel), highly concentrated, non-crosslinked HA (2%) from biofermentation origin combined with a high concentration of sorbitol (4%). Sorbitol is an endogenous molecule that functions as a strong Oxygen Free Radical (OFR) scavenger. We hypothesize that antioxidant effect of sorbitol may play an active role in rapid and strong pain reduction in patients with OA.

## Method

1147 OA patients, with a majority suffering from knee OA (92.9%), were enrolled in a Non-Interventional Study conducted in 398 centres in Germany. Studied population had an average age of 63.3 years, included 499 males, 614 females and 34 patients without reported gender. Patients were distributed into the following grades according to Kellgren-Lawrence (K-L) scale: 6.7% with Grade I, 31.4% with Grade II, 48.0% with Grade III and 13.9% with Grade IV. Patients pain level was assessed using 5 points Likert scale (from “No Pain” scoring 0 to “Very Severe Pain” scoring 4) and was distributed into 1.9% patients with missing information, 0.9% with “No Pain”, 5.9% with “Mild Pain”, 35.1% with “Moderate Pain”, 45.3% with “Severe Pain”, 10.9% with “Very Severe Pain”. Statistical analysis was conducted on a subpopulation of 997 patients with knee OA who have received either 1 or 3 IntraArticular (IA) injections of 2ml of Synolis®.

Primary study criterion was the variation of pain score (Likert scale) between baseline and following time points: week1, week 2, week 3, week 12 and week 24.

Secondary study criteria comprised the evaluation of the initial pain level in relation to the reported Kellgren-Lawrence Grade and observation of Adverse Events (AEs) reported during the study.

This post-marketing surveillance was conducted in accordance to “Empfehlungen zur Planung, Durchführung und Auswertung von Anwendungsbeobachtungen” of the BfArM (Federal Institute for Drugs and Medical Devices) and the Paul-Ehrlich-Institute, dated 7 July 2010.

## Results

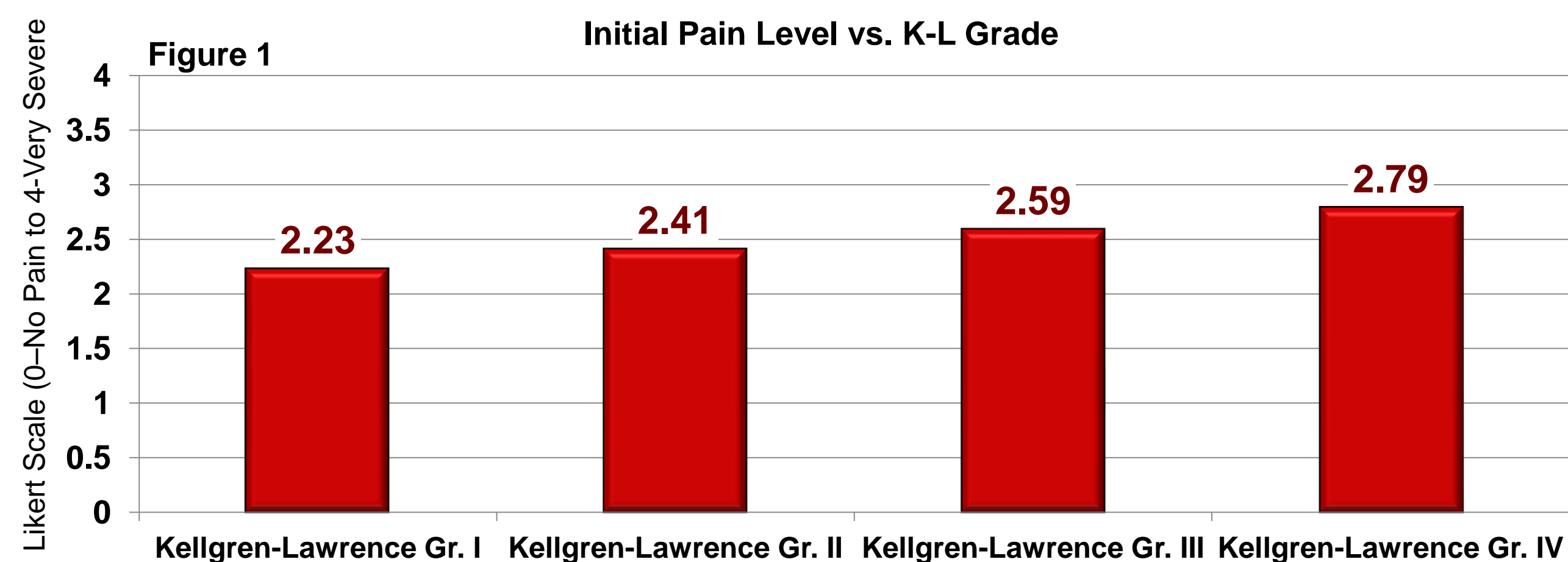


Figure 1 - On the population with Knee OA with both K-L Grade and Initial Pain Level reported (n=509), mean pain level is steadily increasing as a function of Kellgren-Lawrence Grade (K-L Gr.) severity with a mean of 2.23 for K-L Gr. I (n=35), 2.41 for K-L Gr. II (n=160), 2.59 for K-L Gr. III (n=243) and 2.79 for K-L Gr. IV (n=71).

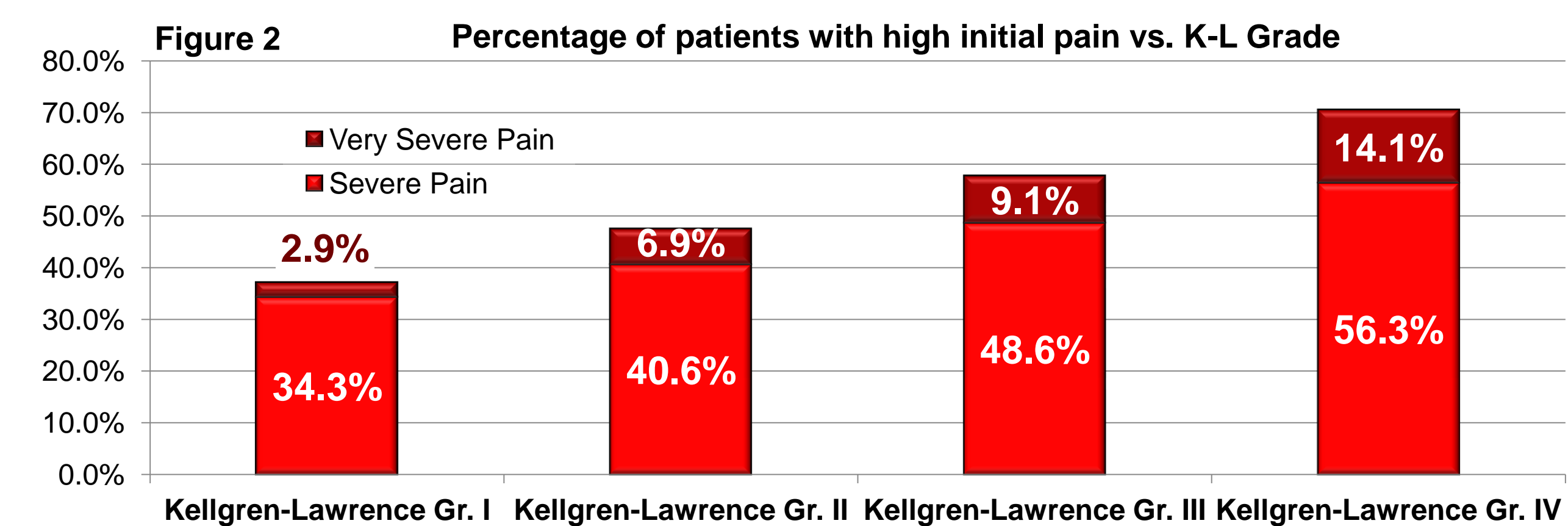


Figure 2 - The percentage of patients with Severe Pain (Likert score 3) and Very Severe Pain (Likert score 4) was correlated to K-L Gr., with 37% of patients with pain level scoring at 3 & 4 in K-L Gr. I, 47% in K-L Gr. II, 56% in K-L Gr. III and 70% in K-L Gr. IV.

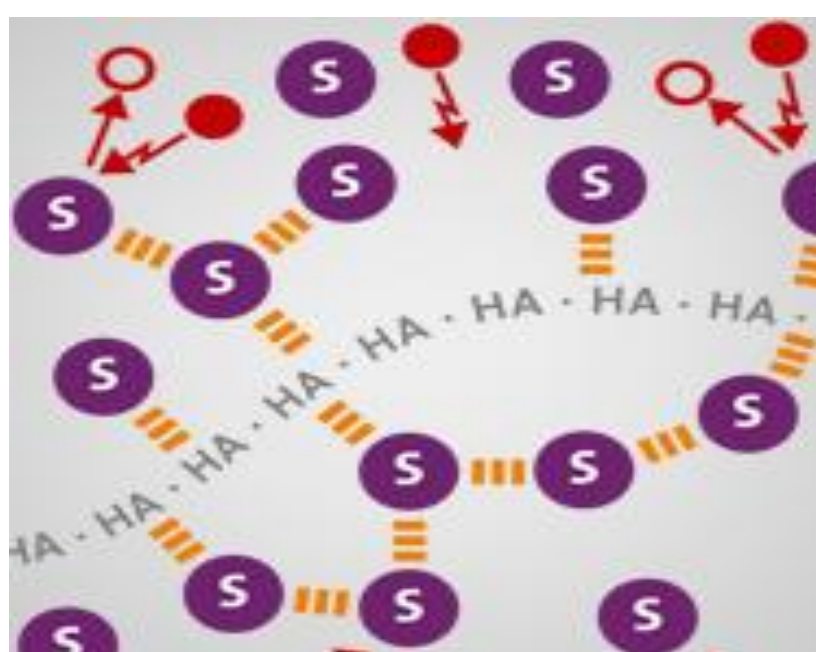
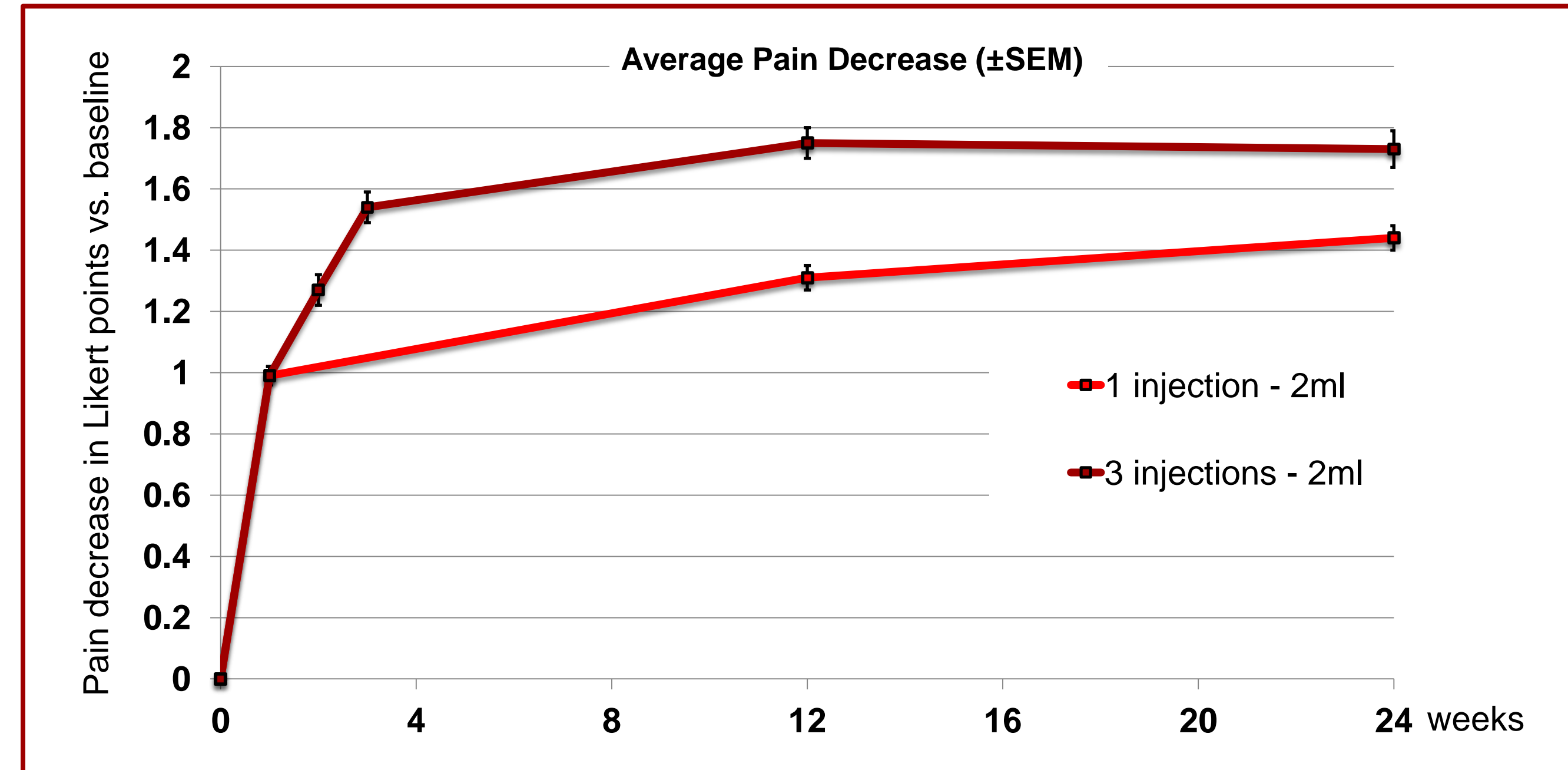


Figure 3



With a treatment regimen of a single injection of 2ml of Synolis®, the average observed pain level (pooled data) was 2.6 at baseline, 1.61 at week 1, 1.29 at week 12 and 1.16 at week 24 (Standard Error of the Mean SEM ≤ 0.04 & n=662). The reported evolution of pain level suggests a prolonged pain relief activity increasing until week 24, and potentially even further.

With a treatment regimen of 3 injections one week apart, the observed average pain level (pooled data) dropped from 2.6 at baseline to 1.61 at week 1, 1.33 at week 2, 1.06 at week 3, 0.85 at week 12 and 0.87 at week 24 (SEM ≤ 0.06 & n=335). The average pain evolution would support the assumption of cumulative effect of the additional injections. Pain relief seems sustained at least until week 24 – Figure 3.

Table 1 - Out of 1147 patients only 24 Adverse Events (AEs) were reported for 22 patients (1.9%), the most common Adverse Event being “Injection site joint pain”

System Organ Class	Preferred term	n
Musculoskeletal and connective tissue disorders	Injection site joint pain	15
	Joint swelling	4
	Joint warmth	2
	Joint effusion	2
	Joint instability	1
Number of AEs		24

## Discussion

### Link between Pain Level and Radiographic Severity

Despite several publications questioning the relation between radiographic-determined severity and pain level [2-3], this study conducted on a large scale population demonstrates the existence of a trend linking Kellgren-Lawrence Grades and average pain level (based on Likert scale). The percentage of patients with high pain level (Severe and Very Severe) is increasing in relation to the K-L Grade to reach 70% for K-L Gr. IV.

### 1 injection regimen vs. 3 injections

One week after the first injection, the observed average pain decrease reached 38% (virtually 1 point drop on the Likert scale). It is hypothesized that unique HA/sorbitol combination of Synolis® confers its high capacity to scavenge free radicals (= antioxidant effect), neutralizing of those key factors of the HA resorption in the joint [4-8] and of inflammation signaling [8]. Following a single injection, evaluated average pain continues to decrease until week 24 (55% pain decrease), suggesting a prolonged, direct or indirect, effect of Synolis® on pain. Whereas, second and third injections seems to bring additional cumulative effect of pain reduction sustained until week 24 (66% pain decrease).

### Safety

With 1.9% of low severity AEs reported by investigators, Synolis® injections seem to be very safe to perform; especially taking into account that about 30% of injections might miss the intra-articular space [9] potentially generating pain or flare reaction not directly associated with the used viscosupplement.

## Conclusion

This study suggests that a strong pain relief occurs immediately after the first injection of Synolis®. Pain relief effect was reinforced by additional injections, reaching a maximum pain decrease of 67% at week 12 after 3 injections, pain decrease was sustained at least until week 24. However, patients who received only a single injection of 2ml of Synolis® also demonstrated a strong and continuous pain decrease, reaching 55% of pain relief at week 24. These results demonstrate efficacy of both 1 and 3 injections regimens of Synolis®. In addition, despite existing literature reporting absence of direct relation between severity of Kellgren-Lawrence Grade and pain level, this study shows existence of a trend linking both criteria. Finally, Synolis® proves to be a safe treatment.

References:  
1 – Altman RD, Pain, osteoarthritis, and intra-articular HA...Today and beyond, OA pain management update, Special report, 2007; 2 – John Bedson, Peter R Croft, The discordance between clinical and radiographic knee osteoarthritis: A systematic search and summary of the literature, BMC Musculoskeletal Disorders 2008, 9:116; 3 – Hannan MT, Felson DT, Pincus T, Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee, J Rheumatol. 2000 Jun;27(6):1513-7. 4 – Henrotin Y, Kurz B, Antioxidant to treat osteoarthritis: dream or reality?, Curr Drug Targets, 2007 Feb;8(2):347-57; 5 – Fermor B, Christensen SE, Youn I, Cernanec JM, Davies CM, Weinberg JB. Oxygen, nitric oxide and articular cartilage, Eur Cell Mater, 2007;13:56-65; 6 – Saari H, Oxygen derived free radicals and synovial fluid hyaluronate, Ann Rheum Dis, 1991 Jun;50(6):389-92.; 7 – Lunec J, Halloran SP, White AG, Dormandy TL, Free-radical oxidation (peroxidation) products in serum and synovial fluid in rheumatoid arthritis, J Rheumatol, 1981 Mar;8(2):233-45; 8 – Ziskoven C, Jäger M, Zilkens C, Bloch W, Brixius K, Krauspe R, Oxidative stress in secondary osteoarthritis: from cartilage destruction to clinical presentation?, Orthopaedic Reviews, 2010, volume 2:e23; 9 – J. Tehranzadeh J, Booya F, Root J, Cartilage metabolism in Osteoarthritis and the influence of viscosupplementation and steroid: a review, Acta Radiol 2005 (3)



# ASSESSING THE EFFICACY OF A VISCOSUPPLEMENT COMBINING HYALURONIC ACID AND SORBITOL (SYNOLIS-VA) IN PATIENTS WITH HIGH GRADES KNEE OSTEOARTHRITIS FOR WHOM CORTICOTHERAPY IS CONTRAINDICATED

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## RATIONALE

Viscosupplementation (VS) by intra-articular (IA) injections of hyaluronic acid (NaHA) reduces pain and improves function in patients with knee osteoarthritis (KOA) but the maximum improvement is delayed and occurs usually 6 to 12 weeks after the injections. Moreover, patients included in most of previous studies only displayed Kellgren-Lawrence (K-L) grades III or below. Only few treatment evaluations have been conducted on patients with Kellgren-Lawrence Grade 4, and especially on patients who have no alternative to corticotherapy and who cannot go under surgery for knee replacement.

Synolis-VA is an innovative viscosupplement made of a high concentration (20 mg/ml) of a 2MDa hyaluronic acid from non animal origin, combined with a high concentration of a free radical scavenger, the sorbitol (40 mg/ml).

The high affinity between NaHA and sorbitol, stabilizes the complex through a very dense network of hydrogen bonds (figure 1).

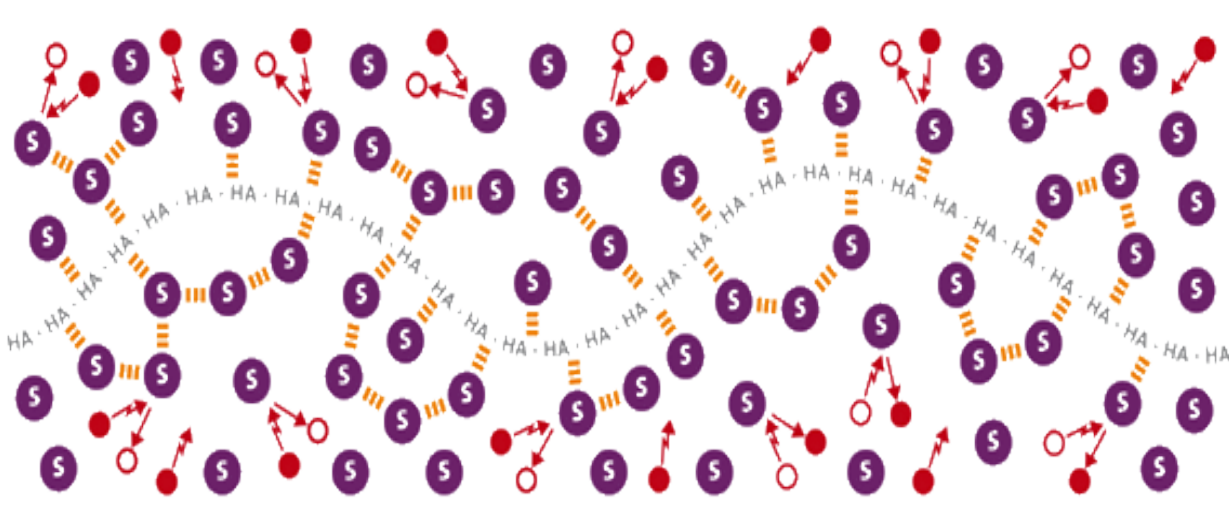


Figure 1

Furthermore the high ability of sorbitol to scavenge and neutralize Oxygen Free Radicals (OFR) has been demonstrated to delay the degradation of the gel, compared to linear and cross-linked NaHA viscosupplements (Figure 2) and are suggested to strongly participate to the neutralizing of Free Radicals contained in the synovial fluid, OFR being one of the vectors of inflammation.

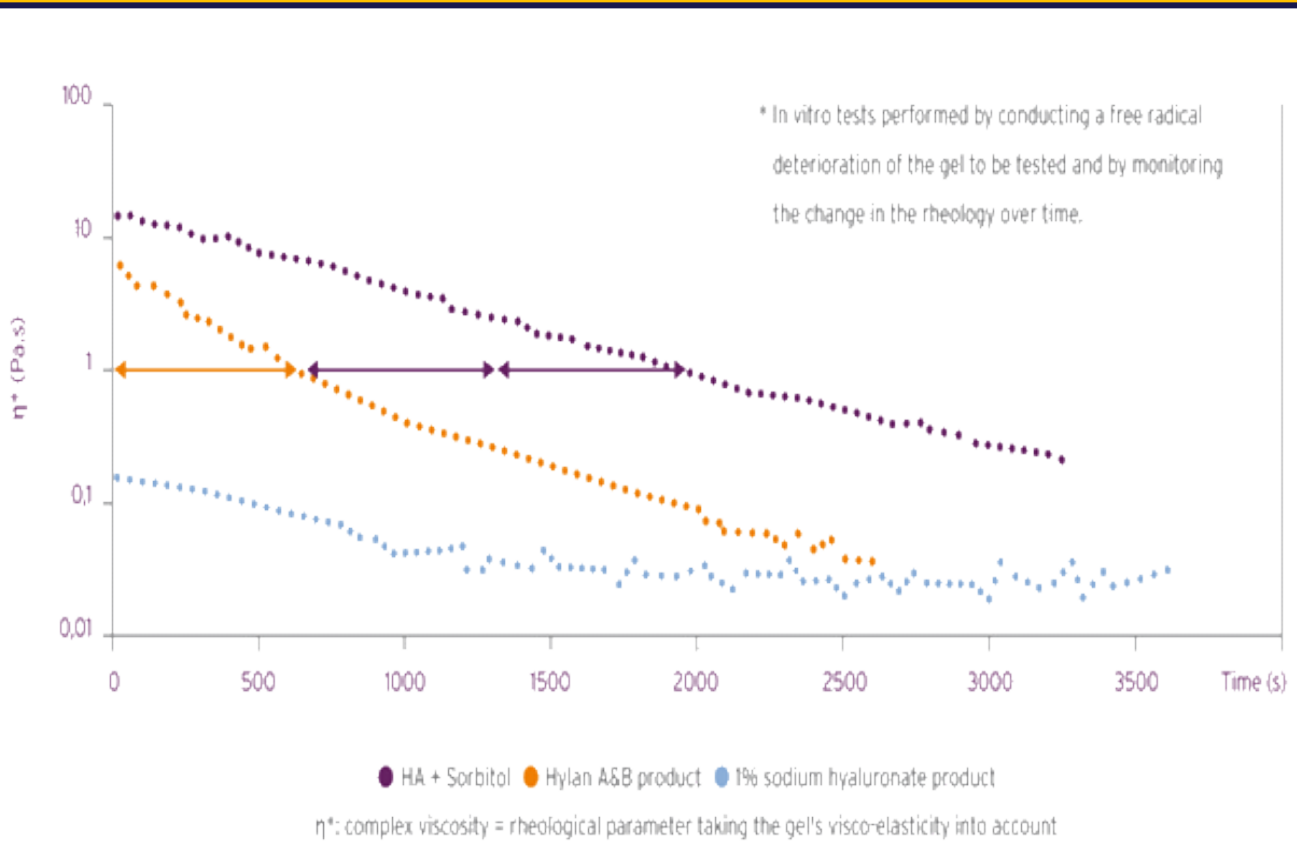


Figure 2

## OBJECTIVES

To evaluate the short and mid term pain-relief effect of Synolis-VA in patients suffering from high KL grades knee osteoarthritis for whom the use of corticotherapy is contraindicated

### Study design

Prospective, open-label 26 weeks study 11 outpatients fulfilling the American College of Rheumatology clinical criteria for the diagnosis KOA.

### Inclusion criteria

- Patients suffering from symptomatic KOA with K-L grades III and IV on standing AP view, Lyon-schuss view, profile and skyline view of the patella and considered by the physician as requiring viscosupplementation
- High surgical risk with cardiovascular disease and/or severe venous insufficiency and/or insulin-dependent diabetes
- Walking Pain and WOMAC Stiffness score equal or higher to 2

### Main exclusion criteria

- VS of any knee within 6 months prior to the initiation of treatment.
- Intra-articular steroid injection of any knee within 3 months prior to the initiation of treatment.
- Know hypersensitivity to sodium hyaluronate and/or sorbitol.

### Treatment procedure

Three 2ml intra-articular injections of SYNOLIS-VA were performed 1 week apart by an experienced rheumatologist.

### Authorized treatments

- Paracetamol  $\leq 4$  g/jour
- NSAIDs if taken before inclusion
- SYSADOAs (*chondroitin sulfate, diacerhein, avocado/soja unsaponifiables, glucosamin, diacerhein*) if taken at stable doses at least 3 months before inclusion and during the whole follow-up period.
- Insulin
- Warfarin sodico
- Cardiovascular treatment

### Evaluation

- At baseline, W1, W2, W13 and W26:
- Walking Pain (WP) - score 0 to 4 (figure 3)
- WOMAC A (pain) - score 0 to 20 (figure 4)
- WOMAC Stiffness - score 0 to 8 (figure 5)
- Number of responders – decrease of at least 1 point vs. baseline on the WP likert scale (figure 6)
- General improvement – rank by step of 25% (figure 7)

Between the third injection and end-point, patients were asked to complete a self evaluation questionnaire for WP, WOMAC A, WOMAC Stiffness.

At baseline, W1, W2, W13 and W26: number of patients responding to treatment (defined as the diminution of at least one point in WP score vs. Baseline) (figure 6)

**Primary criteria :** Variation of WP, WOMAC A and WOMAC Stiffness between baseline and W1, W2, W3, W13 and W26.

**Secondary criteria:** Number of patients responding to treatment (based on WP) between baseline and W1, W2, W13 and W26. Self-evaluated global improvement versus baseline (by step of 25%)

## RESULTS

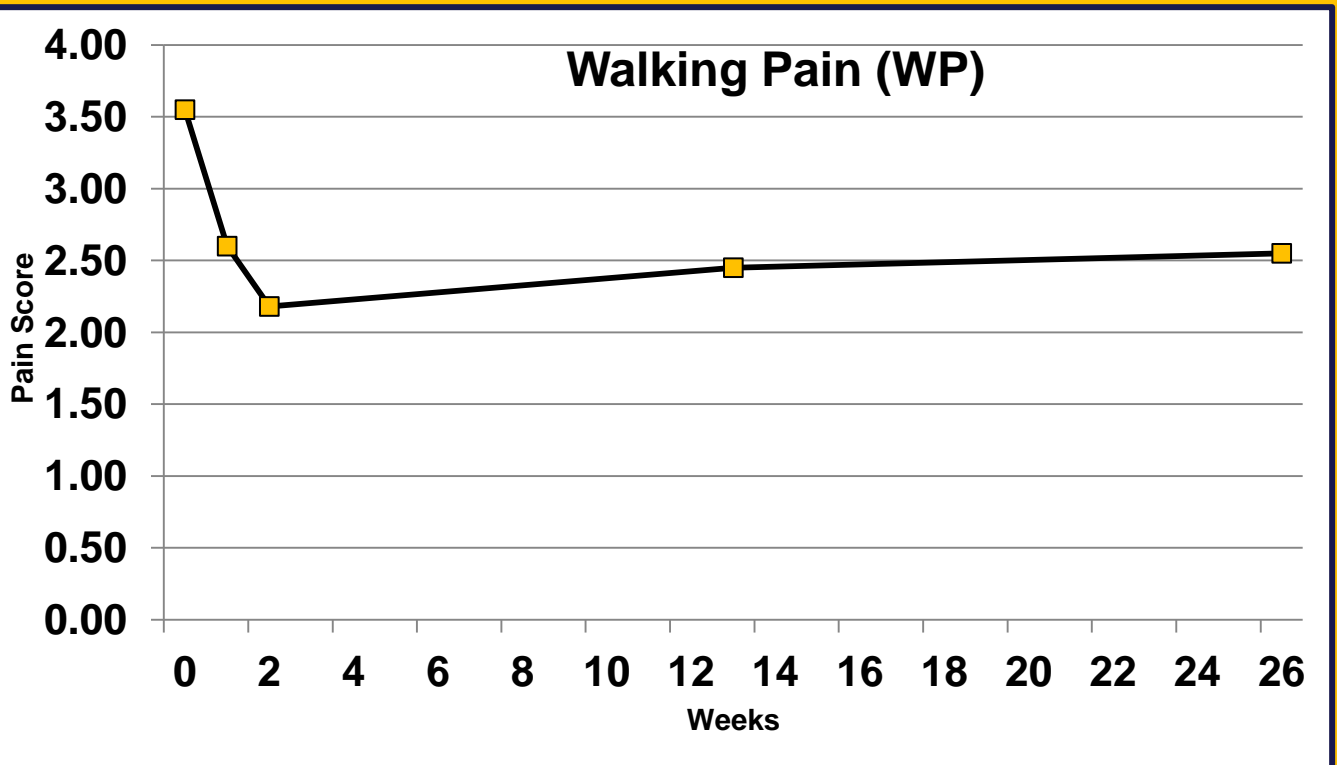


Figure 3

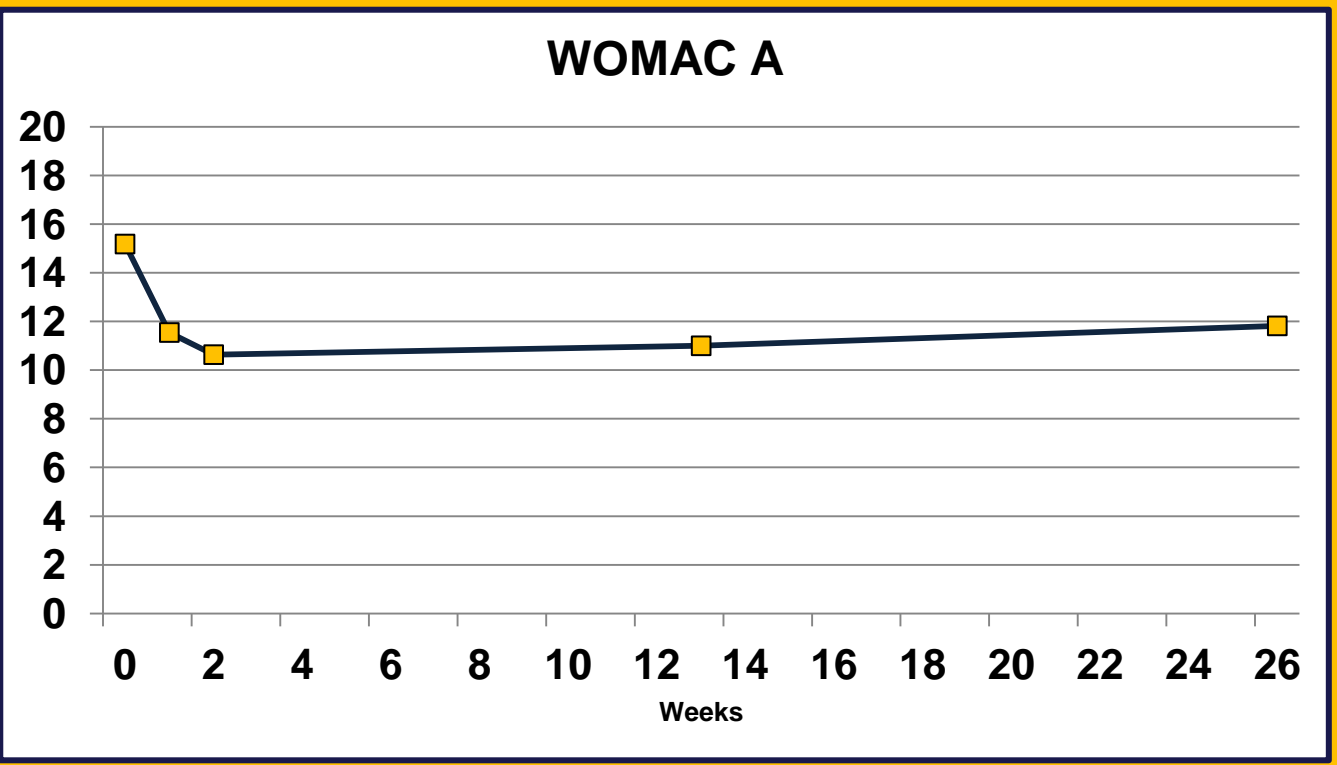


Figure 4

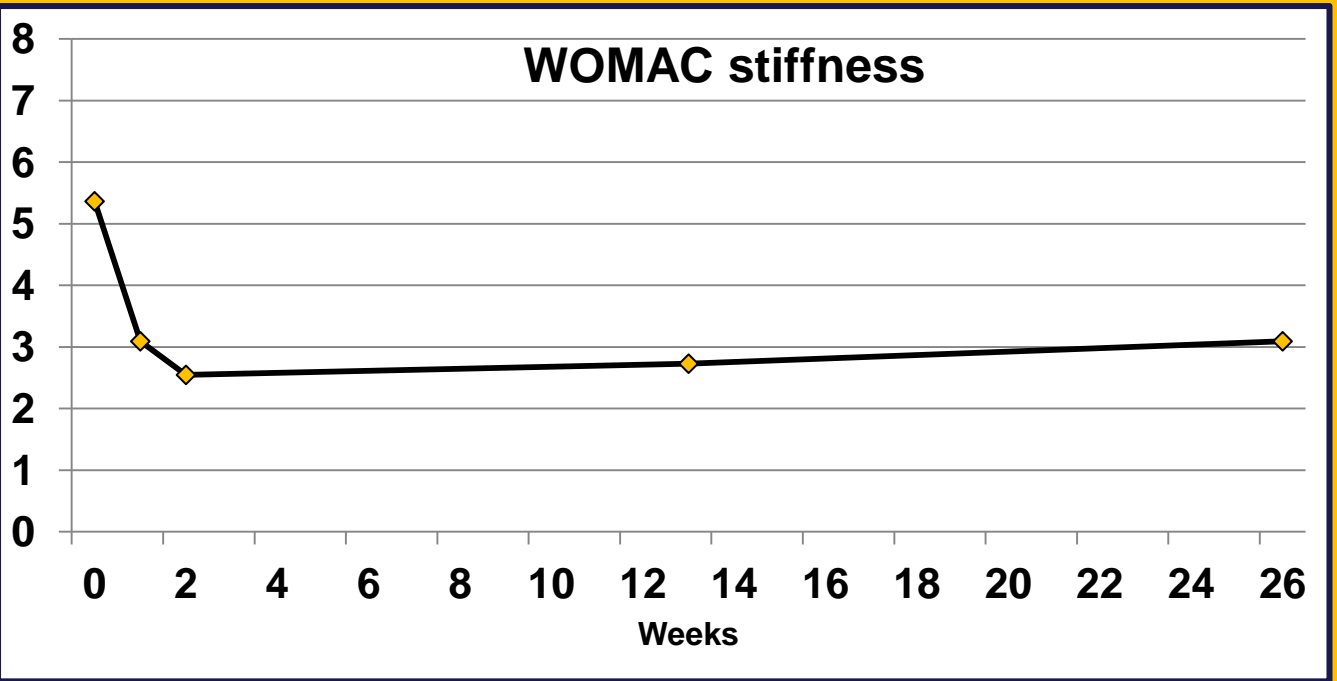


Figure 5

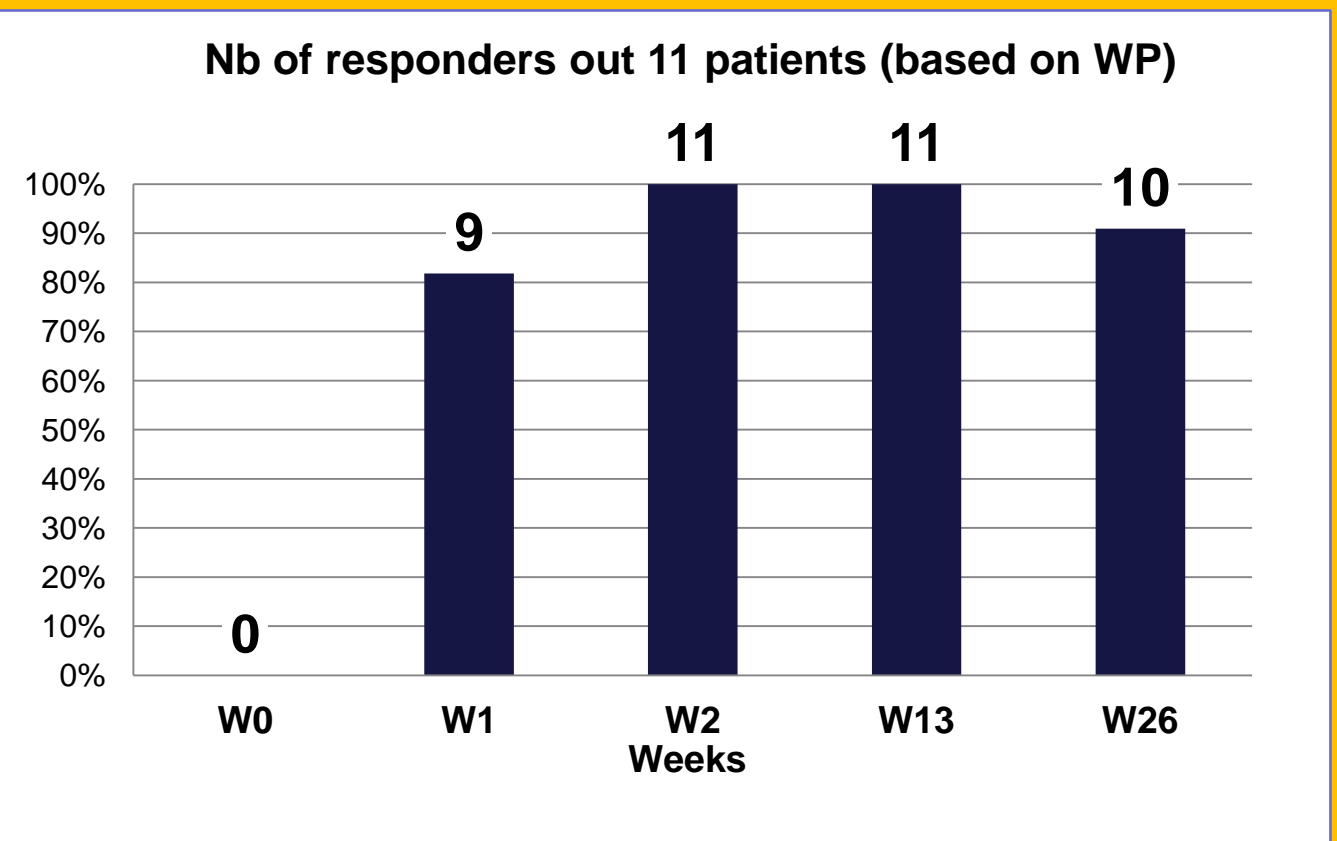


Figure 6

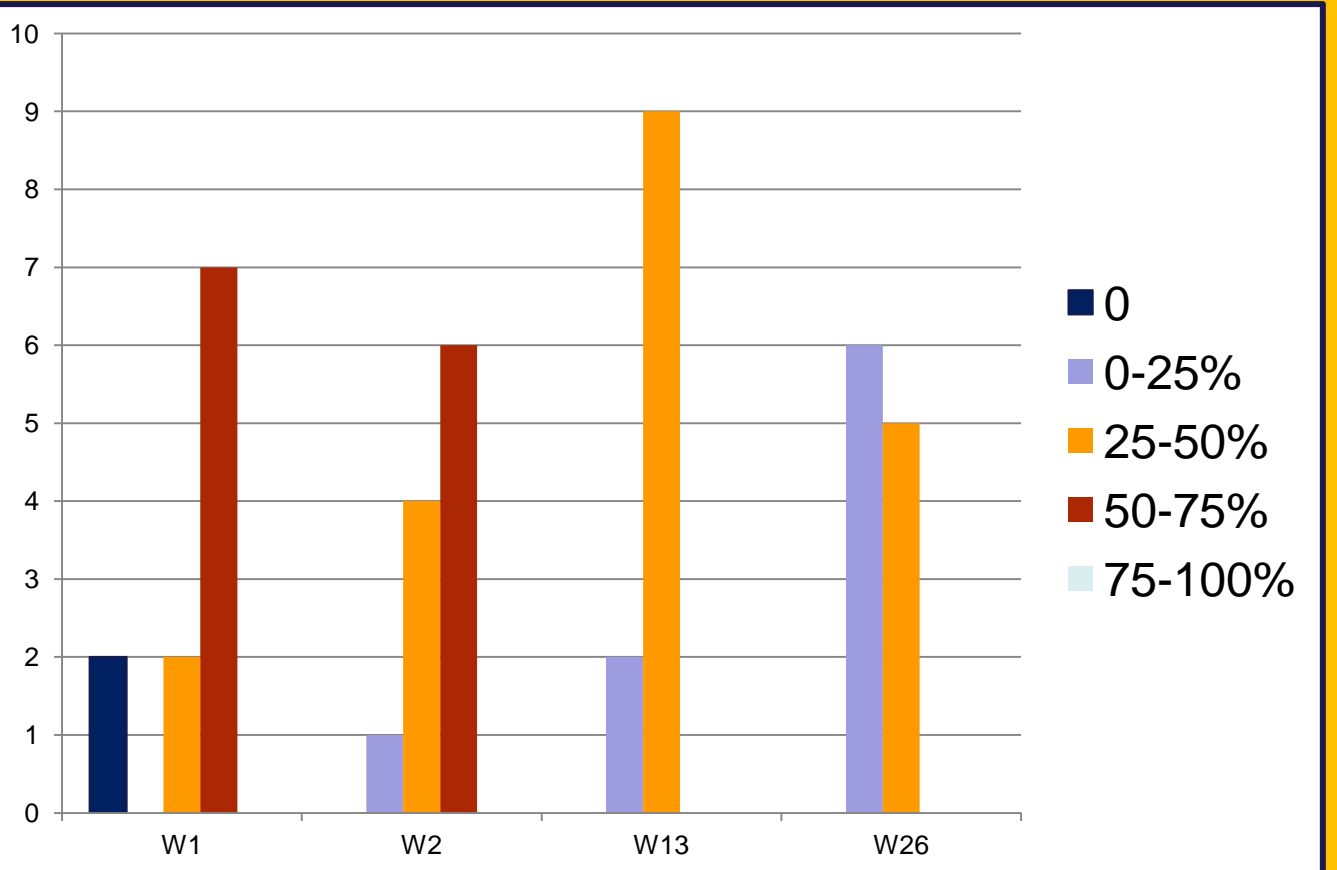


Figure 7

## RESULTS

- Patients:
- 6 female and 5 male
  - 7 monolateral and 4 bilateral OA
  - 1.4 joints diagnosed with OA in average per patient
  - 10 joints with K-L Grade IV for the Tibio-femoral region, 6 joints with KL Grade III and 1 joint with KL Grade IV for the Femoro-patular region

- At baseline:
- Mean WP = 3.5
  - Mean WOMAC pain = 15.2
  - Mean WOMAC stiffness = 5.4

- At week 1:
- Mean WP 2.6 ( $p<0.01$ )
  - Mean WOMAC A = 11.5 ( $p<0.0001$ )
  - Mean WOMAC stiffness = 3.1 ( $p<0.0005$ )

- At week 2:
- Mean WP 2.2 ( $p<0.0001$ )
  - Mean WOMAC A = 10.6 ( $p<0.0001$ )
  - Mean WOMAC stiffness = 2.5 ( $p<0.0001$ )

- At week 13:
- Mean WP 2.5 ( $p<0.0005$ )
  - Mean WOMAC A = 11.0 ( $p<0.0001$ )
  - Mean WOMAC stiffness = 2.7 ( $p<0.0001$ )

- At week 26:
- Mean WP 2.5 ( $p<0.0005$ )
  - Mean WOMAC A = 11.8 ( $p<0.0001$ )
  - Mean WOMAC stiffness = 3.1 ( $p<0.0001$ )

- Variation of WP between baseline and W1, W2, W13 and W26 was respectively -0.9, -1.3, -1.0 and -1.0 (figure 3). Number of responders was still at 10 out of 11 patients at week 26.

- Variation of WOMAC A between baseline and W1, W2, W13 and W26 was respectively -2.1, -2, -2 and -3.9 (figure 4)

- Variation of WOMAC Stiffness between baseline and W1, W2, W13 and W26 was respectively -2.3, -2.9, -2.7 and -2.3 (figure 5)

## CONCLUSION

This exploratory study demonstrates a quick and strong pain relief occurring immediately after the first injection of Synolis-VA followed by an improvement still strongly visible the end of follow-up (W26) despite most of patients diagnosed with Kellgren-Lawrence grade IV (10 out of 11 patients) and despite the absence of corticotherapy.

All patients (n=9) having previously experienced viscosupplementation considered that Synolis-VA acted quicker, probably because of the presence of a high concentration of sorbitol acting through its antioxidant activity.

These data support the need for a large-scale, prospective clinical trial comparing the long term efficacy of Synolis-VA to regular viscosupplement for high Kellgren-Lawrence grades patients



# AN INNOVATIVE HYALURONIC ACID PRODUCT FOR VISCOSUPPLEMENTATION IN PATIENTS WITH OSTEOARTHRITIS

**Samuel GAVARD, Laetitia REYMOND**  
Research Department - Anteïs SA – Genève - Switzerland



## Background

Osteoarthritis (OA) is a very common joint disorder and its prevalence is increasing. It is projected that by the year 2030, almost 67 million US adults will have been diagnosed with arthritis [1]. Viscosupplementation (VS) is used for more than 20 years and is recommended in the treatment of OA. There are currently more than 20 commercial VS products available worldwide. These products differ in hyaluronic acid (HA) origin, HA concentration, HA molecular weight, HA chemical modification, rheological properties, dosing regimens, claims of safety and efficacy and residence time into the joint. Synolis® V-A (Anteïs SA) is an innovative VS launched on the market in 2010. The patented [HA+sorbitol] formulation of this VS is based on a high molecular weight of HA (> 2 MDa in the final sterilized gel) from non animal origin, with a high HA concentration (20 mg/ml), combined with a high concentration of a free radical scavenger, the sorbitol (40 mg/ml).

## Purpose

The aims of this study are to evaluate the rheological properties and the resistance to free radicals degradation of Synolis® V-A



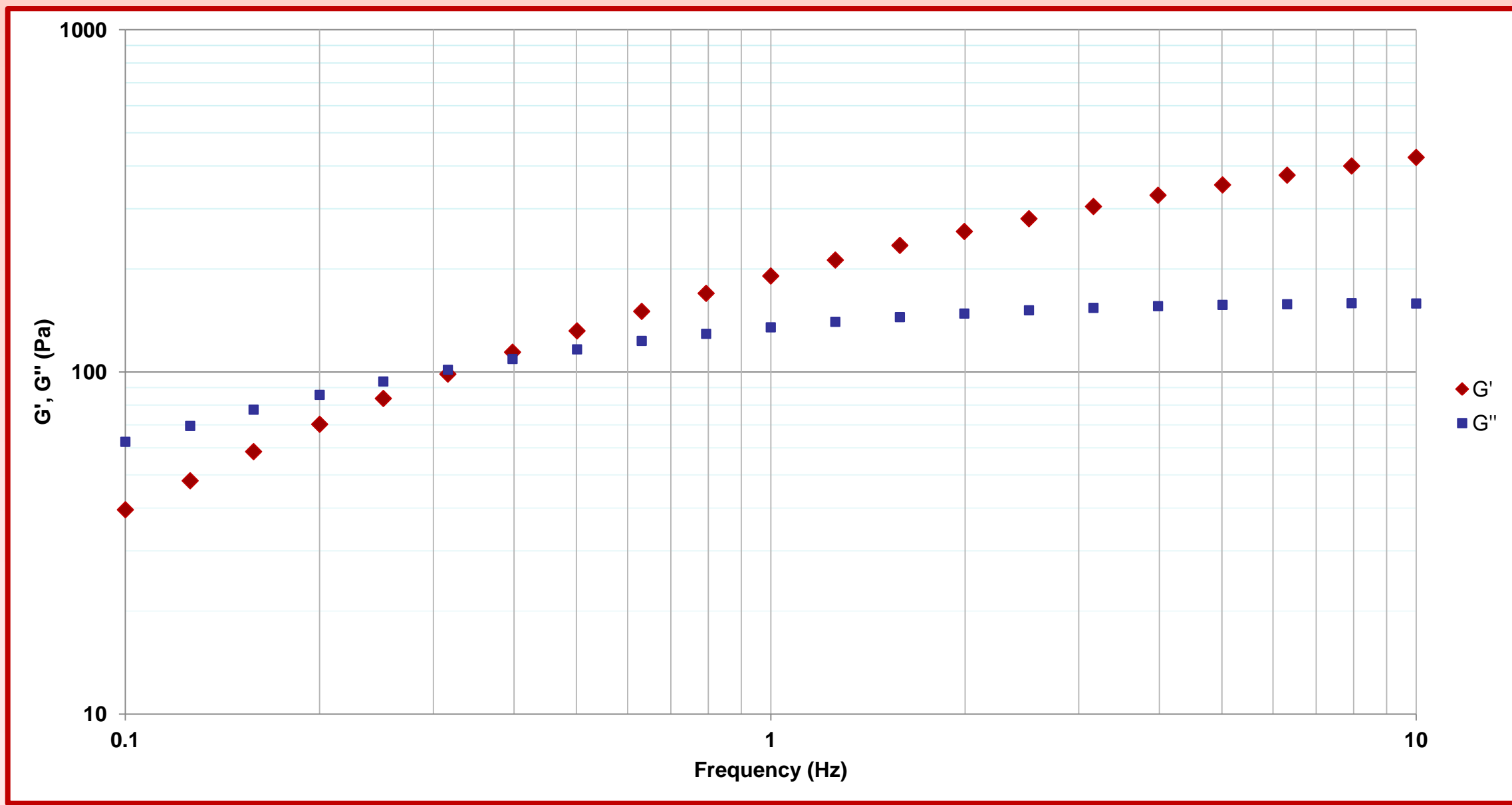
## Method

The rheological properties (elastic and viscous moduli :  $G'$  and  $G''$ ) of Synolis® V-A are measured by frequency sweep experiments at 25°C thanks to an AR2000 rheometer (TA Instruments), using a plate and plate geometry with 1 mm gap.

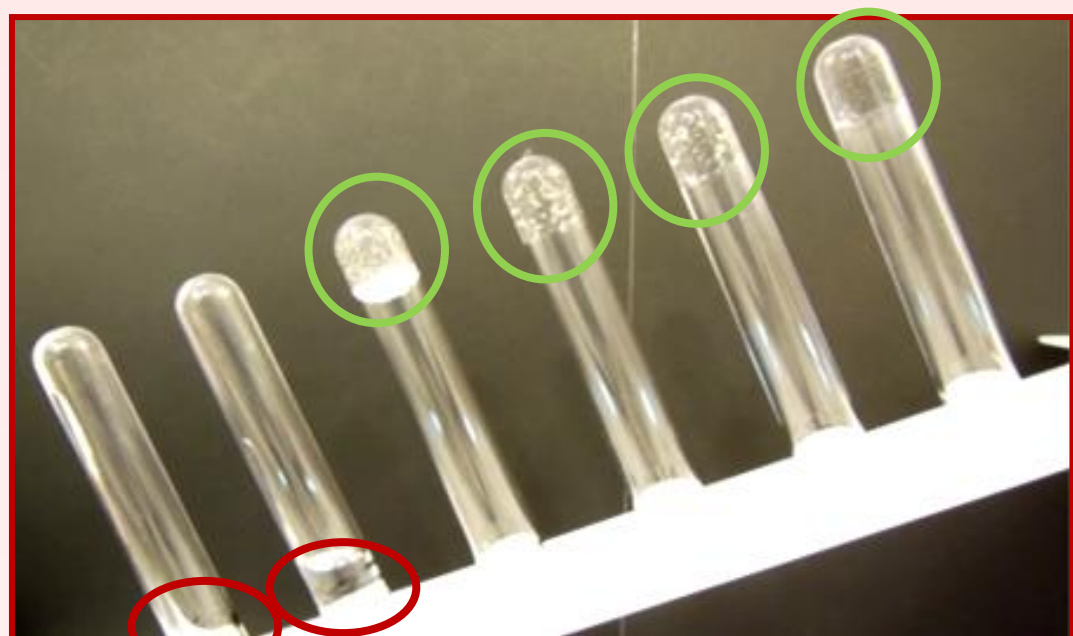
The resistance to free radical degradation of Synolis® V-A is measured with 2 different tests and the results are compared with other VS of the market:  
- Test 1 (visual observation): addition of an oxidant agent ( $H_2O_2$ ) on the tested VS (weight of  $H_2O_2$  = 1/15 x Weight of VS) followed by the heating of the mixture at 60°C in order to accelerate the oxidative reaction. A visual observation of the flow is performed over time.  
-Test 2 (rheological test): addition of an oxidant agent ( $H_2O_2$ ) on the tested VS (weight of  $H_2O_2$  = 1/15 x Weight of VS) and measurement of the rheological properties by time sweep experiments at 37°C thanks to an AR2000 rheometer (TA Instruments), using a plate and plate geometry with 1 mm gap.

## Results

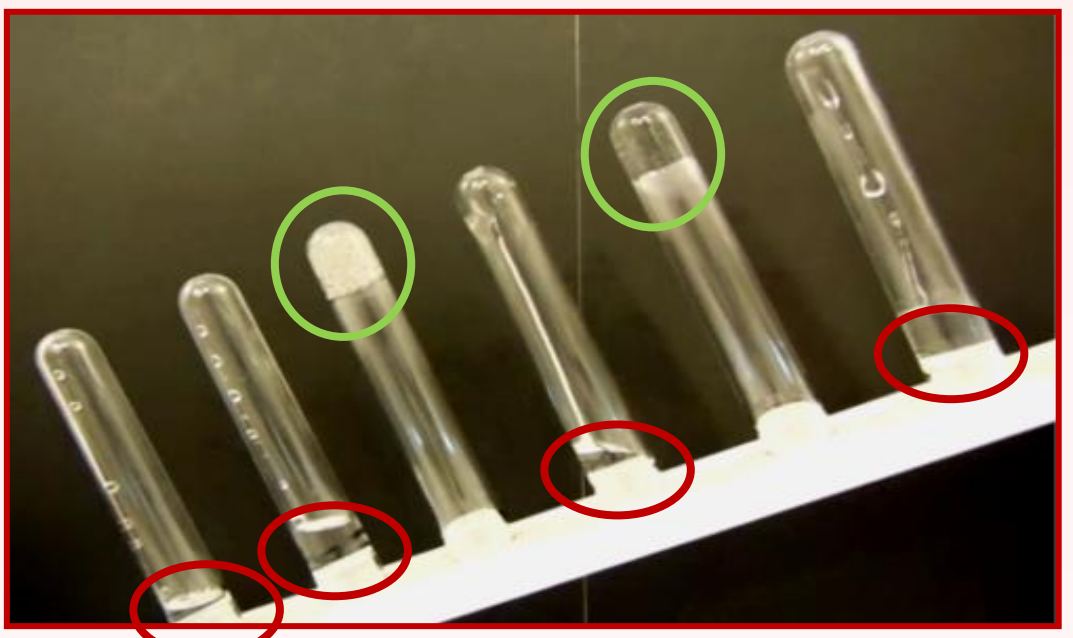
### Rheological properties of Synolis® V-A



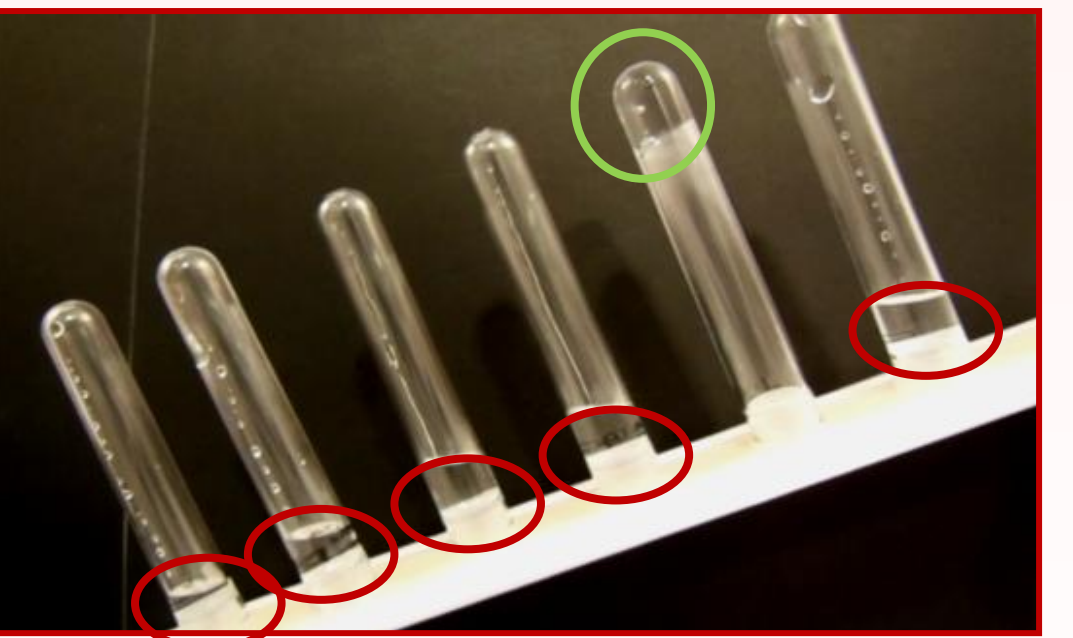
### Resistance to free radical degradation of Synolis® V-A and other products of the market



**Test 1:**  
Visual observation of the flow for each VS during free radical degradation - after having turned the test tube over:



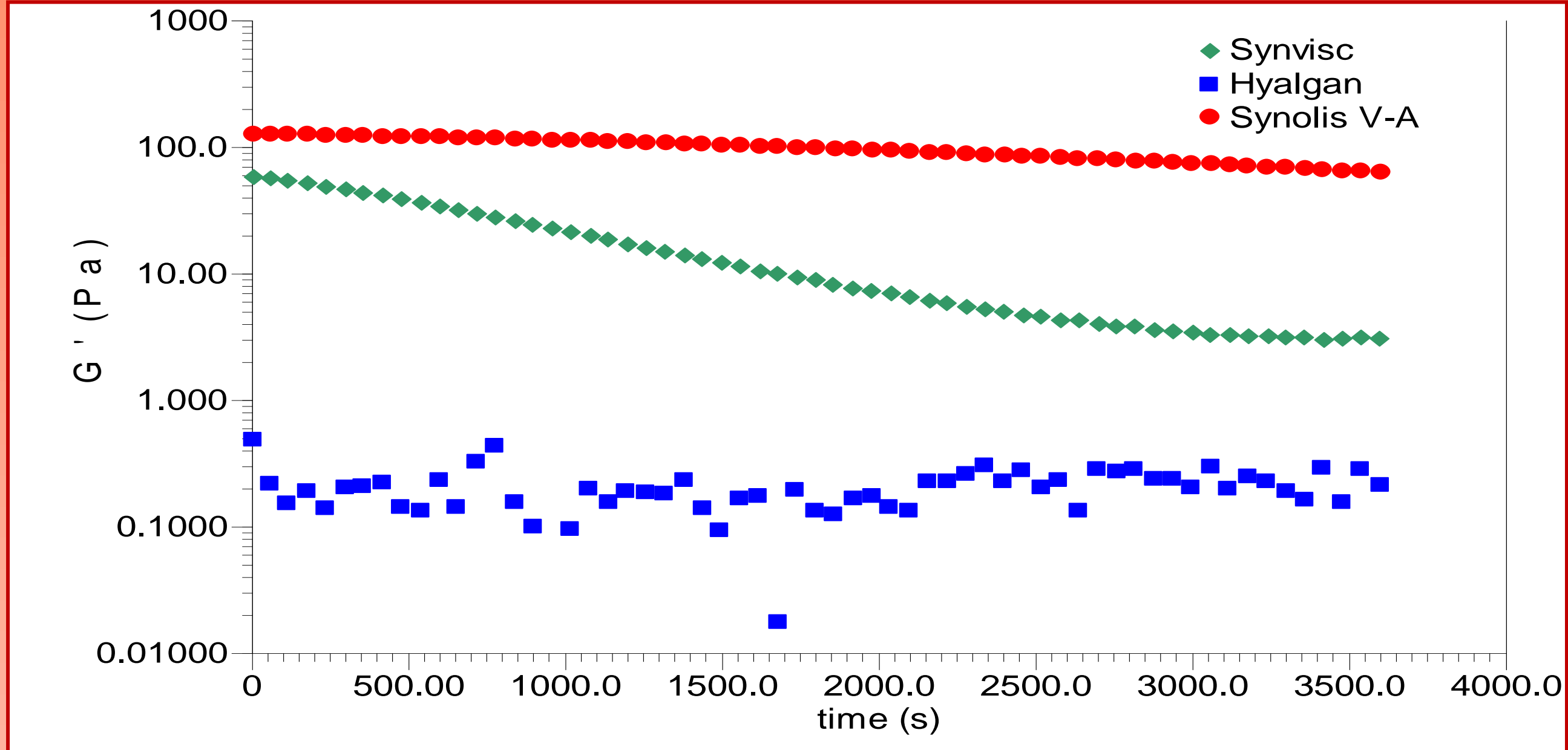
After 1h at 60°C



After 3h at 60°C

- Tubes:
- 1 – Sinovial®
  - 2 – Hyalgan®
  - 3 – Durolane®
  - 4 – Ostenil® Plus
  - 5 – Synolis® V-A
  - 6 - Synvisc®

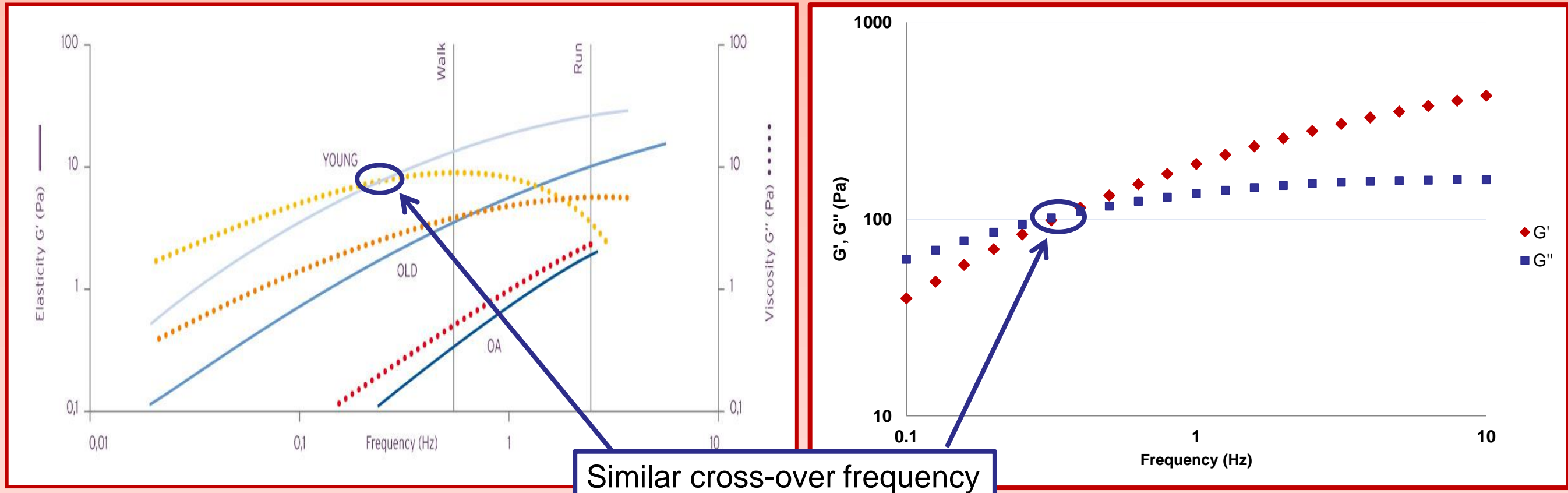
**Test 2:**  
Measurement by rheology of the resistance to free radical degradation



## Discussion

### Rheological properties of Synolis® V-A

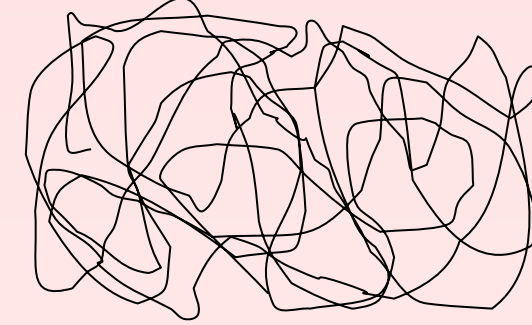
The rheological analysis of Synolis® V-A shows that this VS is characterized by a visco-elastic behavior close to the synovial fluid (viscous and elastic moduli crossing at about 0.4 Hz, as with the healthy synovial fluid) [2-3].



Thanks to this specific frequency crossover, Synolis® V-A mimics the rheological properties of the healthy synovial fluid:

- for a high frequency ( $f > 0.4$  Hz / strong stress exerted in the joint : running, jumping), the elastic modulus of the VS is higher than the viscous modulus: there is a strong protection of the joint by absorption of the produced energy.

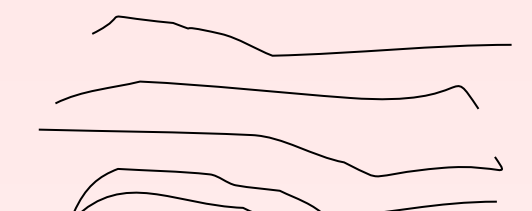
**Synolis V-A response to strong mechanical stress (same as synovial fluid)**



**High elasticity of the VS : Shock absorption in the joint**

- on the contrary, for a low frequency ( $f < 0.4$  Hz / weak stress exerted in the joint: resting), the viscous modulus of the VS is higher than the elastic modulus: there is a good lubrication of the joint.

**Synolis V-A response to weak mechanical stress (same as synovial fluid)**



**High viscosity of the VS : Lubrification of the joint**

Moreover, due to the high affinity between HA and sorbitol, the structure of Synolis® V-A is stabilized through a very dense network of hydrogen bonds. This complex structure of gel presents remarkably high visco-elastic properties, even higher than animal or crosslinked products. It allows Synolis® V-A to have a very high capacity to lubricate and absorb the shock in the joint.

### Resistance to free radical degradation of Synolis® V-A and other products of the market

According to the literature [4-8], the free radical degradation is a key factor of the HA resorption in the joint and is an important factor of the OA. Synolis® V-A was designed to have a high capacity to scavenge and neutralize free radicals (= antioxidant effect) thanks to its unique [HA / sorbitol] combination (high ability of the sorbitol to scavenge the free radicals). As demonstrated by 2 different in vitro tests, Synolis® V-A presents a high capacity to resist to free radicals, better than all the other studied VS. This advantage is key to maintain the Synolis® V-A formulation and its specific rheological properties longer in the joint.

## Conclusion

**Synolis® V-A is an innovative viscosupplement made of a combination of HA and sorbitol. Due to its patented formulation and manufacturing process, Synolis® V-A has outstanding rheological properties and a high resistance against *in vivo* degradation in the joint.**

**As demonstrated by several experiments described in this study, Synolis® V-A is characterized by:**  
▪ a visco-elastic behaviour close to the human synovial fluid and a very high elasticity and viscosity to have a VS with a high capacity to lubricate the joint and to absorb shocks, as with a healthy synovial fluid  
▪ a high capacity to scavenge and neutralize free radicals, which allows to maintain the VS longer in the joint, for better clinical outcomes.

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# Safety and Efficacy Findings from a Non-interventional Study of a New Hyaluronic Acid/Sorbitol Formulation (GO-ON<sup>®</sup> Matrix) for Intra-articular Injection to Relieve Pain and Disability in Osteoarthritis Patients

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## Key words

- viscosupplementation
- ROS scavenger
- rapid onset

## Abstract



This non-interventional study was intended to examine the efficacy and tolerability of intra-articular injections with the GO-ON<sup>®</sup> matrix, a new viscosupplement product made of non-animal sodium hyaluronate combined with the oxygen free radical scavenger sorbitol, when used in routine clinical practice. A total of 1147 patients (43.5% male, 53.5% female, 3% missing) aged on average 63.3 years with osteoarthritis were enrolled in 398 centers and treated with the product. The most commonly treated joint was the knee (92.9%) with a Kellgren-Lawrence classification of Grade I (6.7%), Grade II (31.4%), Grade III (48.0%), and Grade IV (13.9%). Most patients (58–66%, imputing for missing data) received 1 injection, 29–40% received 3 injections.

Using a Likert scale to assess pain, the mean change in pain due to osteoarthritis was a reduction of 56.5% from baseline ( $2.61 \pm 0.80$ ) to 6 months ( $1.07 \pm 0.86$ ). At baseline, 56.2% of patients reported severe/very severe pain versus 5.9% after 6 months. Accordingly, 6.8% of patients reported no pain/mild pain at baseline vs. 67.1% after 6 months. At baseline, 28.9% reported no pain/mild pain vs. 66.4% after 6 months. At baseline, 29.1% of patients reported severe/very severe functional impairment vs. 3.9% 6 months after the first injection. The 3 and 6 month results were comparable.

Adverse reactions were rare and confined to musculoskeletal and connective tissue disorders. No infections were reported in any treated joints. The results confirm that the GO-ON matrix<sup>®</sup> treatment is effective and well tolerated in the treatment of symptoms due to osteoarthritis.

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## Introduction



Osteoarthritis (OA), a primary degenerative joint disease, is the most common joint condition of adults worldwide. The disease currently affects approximately one third of the adult population, with about 25% of 60–65 year-olds and up to 40% of 70–74 year-olds experiencing clinically symptomatic OA of the knee [1,2]. OA leads to pain, physical disability, and reduced quality of life. Perhaps due to its association with obesity and old-age, OA was long believed to result from simple wear-and-tear [3,4]. The role of oxidative stresses in the development of OA, resulting from inflammatory and metabolic disorders, however, is now increasingly well recognized [5,6]. Osteoarthritis involves a substantial reduction in the viscosity of the synovial fluid, reducing its lubricating and shock absorbing capacity, leading to pain and functional impairment of the affected joint [7,8]. Hyaluronic acid (HA) is a key compo-

nent of the synovial fluid, essential for maintaining its physico-mechanical properties [9]. Oxygen free radicals produced within the diseased joint rapidly depolymerize hyaluronate to oligosaccharides, thus changing the viscosity and protective properties of the synovial fluid [10]. Intra-articular injection(s) of sodium hyaluronate preparations may compensate for this loss of intact native hyaluronan, to alleviate pain, restore joint function and mobility, and modify disease progression [11,12].

A new product (GO-ON<sup>®</sup> matrix, Manufacturer: ROTTAPHARM Ltd., Damastown Industrial Park, Mulhuddart-Dublin 15, Ireland) combines sodium hyaluronate of non-animal origin with a high concentration of the oxygen free radical scavenger sorbitol. Sodium hyaluronate and sorbitol develop a complex based on a dense network of hydrogen bonds forming an injectable gel. Sorbitol's capacity as a scavenger and neutralizer of oxygen free radicals has been proven to delay the

degradation of this gel compared to both linear and cross-linked hyaluronic acid viscosupplements [13]. In parallel to the reduction of free radicals, the migration of macrophages in the synovia is decreased [14, 15]. It is hypothesised that the antioxidant effect of sorbitol may also play a role in reducing the time to onset of analgesia [13, 16].

This non-interventional study was intended to extend established knowledge on the safety and efficacy of the GO-ON® matrix product in a setting representative of routine clinical practice.

## Methods

This was a multicenter, non-controlled, non-interventional clinical trial to investigate the efficacy and tolerability of intra-articular injections with the GO-ON® matrix for the treatment of OA in the setting of routine clinical practice. The trial was performed at 398 recruiting centers in Germany between May 2011 and March 2012 in accordance with German regulations on the planning, execution and analysis of observational studies (BfArM and the Paul-Ehrlich-Institute, 7 July 2007). The protocol required provided written informed consent from all patients prior to participation; this was confirmed in writing by the Investigator.

### Patient selection

As a non-interventional study, patient selection was intended to be minimal, resulting in study population that reflected, as nearly as possible, those treated in routine clinical practice. As such, both male and female adult patients were eligible for inclusion if they had radiologically confirmed OA of any joint, and the investigator's independent clinical decision was the use of intra-articular injections of the GO-ON® matrix.

### Treatment and observation

Enrolled patients were interviewed on Day 1 for screening and the collection of the patient's disease diagnosis, medical history (including disease duration), and prior/concomitant medication data, as well as identification of the joint to be treated. The GO-ON® matrix Instructions for Use recommend a treatment series of 3 injections at 1-week intervals per joint, however, the number of treatments actually administered per joint during the trial was at the investigator's discretion. The use of concomitant OA treatments was permitted and documented throughout the trial.

Prior to the first injection on Day 1, the patient assessed their pain and functional impairment due to OA. At both 1 and 2 weeks following the first injection (i.e., Visits 2 & 3), patients attended the clinic for additional treatment visits. Patient's assessment of pain and functional impairment due to OA (prior to injection) as well as independent assessments of global efficacy from the patient and investigator were collected prior to treatment. The GO-ON® matrix injection was then administered at the investigator's discretion. Thereafter, at weeks 4, 12 and 24, patients attended the clinic for assessment of their pain and functional impairment due to OA, as well as independent patient and investigator assessments of global efficacy. Patients were actively questioned regarding possible adverse reactions at all visits.

### Efficacy assessments

Patient subjective assessments of pain and functional impairment due to OA were performed prior to receiving the GO-ON® matrix injection, each using a 5-point Likert scale from none (0), through mild (1), moderate (2), severe (3), to very severe (4).

Global subjective assessments of the OA treatment efficacy were performed independently by both the patient and the investigator using a 5-point scale from much better, through better, no change, worse, to much worse.

A final subjective assessment of therapy success was performed by the investigator rating the GO-ON® matrix as better, equal, or worse than conventional hyaluronic acid.

### Adverse reactions

Adverse events considered by the investigator to be drug-related (adverse reactions, AR) were recorded at all visits and encoded using MedDRA® Version 14.0. The occurrence of pain in the joint, redness, swelling, effusion, infection, and punctuation of the treated joint after the injection were also specifically assessed.

### Statistics

For quantitative variables, the descriptive statistics of mean, median, standard deviation and interquartile range were calculated. Absolute and relative frequencies were calculated for qualitative variables. SAS Version 9.2 was used for all analyses. All analyses were performed on all enrolled set, including all treated patients. Numerical values assigned to the subjective ratings, as described above, were used to allow statistical assessments of the changes in ratings over time.

Additional subgroup analyses of efficacy data were performed, stratifying by the number of GO-ON® matrix treatments administered for all patients, and by the baseline Kellgren-Lawrence grade [17] for patients whose treated joint was the knee. Where the number of treatment applications was missing, best case and worst case imputations were performed; the number of applications was set to the minimum possible for each in the best case scenario, and to the maximum possible for case in the worst case scenario.

## Results

A total of 1147 patients (43.5% males, 53.5% females, 3% no information) were enrolled into the study and treated with at least 1 injection of GO-ON® matrix (see ◻ Table 1, 2). The mean age of treated patients was 63.3 years, and the mean BMI was 27.6. Due to a site error, 1 patient was enrolled under 18 years-of-age (17 years).

Overall, the most commonly selected joint was the knee (92.9%), followed by the hip (4.4%), shoulder (2.8%), or other (1.6%).

**Table 1** Summary of demographics.

Gender	Statistic	
Male	n (%)	499 (43.5)
Female	n (%)	614 (53.5)
Missing	n (%)	34 (3.0)
Age, years, n = 1 140	Mean ± SD (range)	63.3 ± 13.5 (17–93)
Height, cm, n = 1 122	Mean ± SD (range)	170.3 ± 9.3 (146–201)
Weight, kg, n = 1 118	Mean ± SD (range)	79.9 ± 15.0 (48–157)



**Table 2** Summary of baseline disease characteristics.

Parameter	Incidence, n (%)		
Treated joint	Left	Right	Total
Knee	489 (42.6)	577 (50.3)	1066 (92.9)
Shoulder	12 (1.0)	20 (1.7)	32 (2.8)
Hip	20 (1.7)	31 (2.7)	51 (4.4)
Other	8 (0.7)	10 (0.9)	18 (1.6)
Missing	–	–	20 (2.1)
<b>Symptoms</b>			
Swelling of joint in past		874 (76.2)	
Start-up pain		1027 (89.5)	
Retropatellar pain (patellar dislocation pain)		846 (73.8)	
Zohlen sign, positive		723 (63.0)	
Contracture of treated joint		205 (17.9)	
Axis proportion	Normal	527 (45.9)	
	Varus	369 (32.2)	
	Valgus	117 (10.2)	
	NA	35 (3.1)	
<b>Previous medical treatment</b>			
Topical		443 (38.6)	
NSAID		735 (64.1)	
Corticosteroids		385 (33.6)	
Analgesics		421 (36.7)	
Surgery		228 (19.9)	
<b>Previous nonmedical treatment</b>			
Ultrasound		153 (13.3)	
Physiotherapy		497 (43.3)	
Other		220 (19.2)	
Introductory therapy		187 (16.3)	

NA = not applicable; NSAID = non-steroidal anti-inflammatory drug

Of these, 40 patients (3.5%) were treated in 2 joints (37 in both knees, 1 in both hips, 1 in knee and hip, 1 in left “other” and right “other”).

The majority of patients received 1 injection of GO-ON® matrix (best case imputation vs. worst case imputation, 66.1–57.7%), compared with 2 injections (4.7–2.4%) or 3 injections (29.2–39.8%).

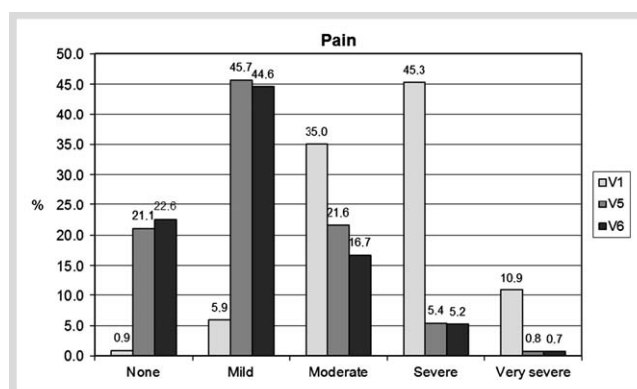
### Efficacy assessments

Due to the large number of patients for whom treatment or efficacy data was not available at Visit 2 (n missing=315/1 147), Visit 3 (712/1 147), and Visit 4 (738/1 147), this report focuses upon comparisons of 3 month and 6 month data vs. baseline.

### Pain

Using the Likert scale to assess pain, the mean change in pain due to osteoarthritis was a reduction of 56.5% from baseline ( $2.61 \pm 0.80$ ) to 6 months ( $1.07 \pm 0.86$ ). The proportion of patients with severe or very severe pain due to OA reduced substantially from 56.2% at baseline to 6.2% after 3 months and 5.9% six months after the first injection (see ◉ Fig. 1). Similarly, the proportion of patients with no pain, or only mild pain increased from 6.8% at baseline to 66.8% after 3 months, and 67.1% six months after the first injection. The most common outcome for pain due to OA was a 2-point improvement in pain ratings (33.7%, see ◉ Table 3); indeed, only 1.7% of patients reported an overall increase in pain from baseline to 6 months.

Overall, subgroup analyses of the pain profiles based upon the number of injections per joint showed statistically significantly



**Fig. 1** Summary of patients' pain ratings from baseline to V5 (3-month) and V6 (6-month) timepoints.

**Table 3** Categorical summary of changes in patients' pain and functional impairment ratings from baseline to V6 (6 months).

Degree of change	Pain	Functional impairment n (%)
Improvement 4 classes	23 (2.0)	10 (0.9)
Improvement 3 classes	137 (11.9)	74 (6.5)
Improvement 2 classes	383 (33.4)	207 (18.0)
Improvement 1 class	314 (27.4)	354 (30.9)
No change	139 (12.1)	313 (27.3)
Missing	131 (11.4)	149 (13.0)
Deterioration	20 (1.7)	40 (3.5)

greater mean reductions in pain for patients receiving 3 injections (1.65 points) vs. only 1 injection (1.44 points). No statistical differences were apparent based upon Kellgren-Lawrence grading alone although the difference in scoring points between 1 and 3 injections was higher in patients with higher grading (◉ Fig. 2).

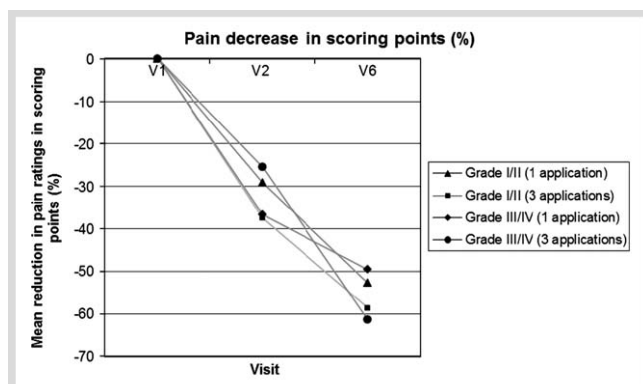
### Functional impairment

After 6 months, the mean improvement in functional impairment was 0.98 points ( $\pm 1.05$ ). The proportion of patients with severe or very severe functional impairment due to OA reduced from 29.1% at baseline to 3.6% after 3 months, and 3.9% six months after the first injection (see ◉ Fig. 3). Likewise, the proportion of patients with mild or no impairment improved from 28.9% at baseline to 66.4% after both 3 months and 6 months after the first injection. After 6 months, the majority of patients reported a 2-class improvement (18.0%), 1-class improvement (30.9%), or no change (27.3%) in functional impairment (see ◉ Table 3). In all, only 3.5% of patients experienced a worsening in functional impairment.

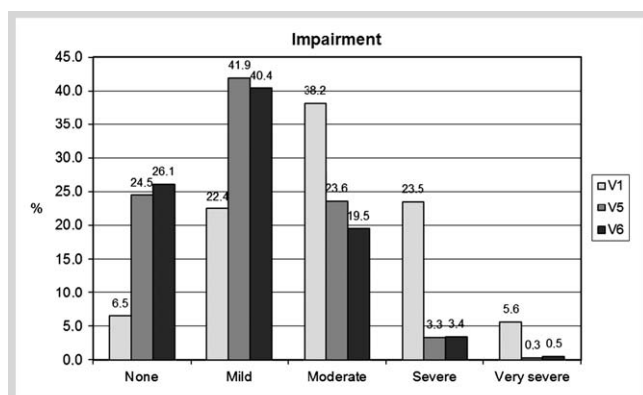
Subgroup analyses revealed statistically greater improvements in functional impairment for patients receiving 2 (1.44 points) or 3 injections (1.13) vs. only 1 injection (0.89). No statistical differences were apparent based upon Kellgren-Lawrence grading.

### Global efficacy and treatment success

At weekly visits, the patient and investigator assessments of global efficacy were very similar. At 1-week after treatment initiation, 61.6% of patients and 51.0% of investigators reported the patient's condition to be better or much better. This improved to 77.7% of patients vs. 78.5% of investigators at 3 months, and



**Fig. 2** Mean reduction in pain ratings in scoring points.



**Fig. 3** Summary of patients' functional impairment ratings from baseline to V5 (3-month) and V6 (6-month) timepoints.

**Table 4** Summary of adverse reaction incidence.

SOC Preferred term (MedDRA®)	n
<b>Total ARs</b>	<b>24</b>
<b>Musculoskeletal and connective tissue disorders</b>	<b>24</b>
Injection site joint pain	15
Joint swelling	4
Joint warmth	2
Joint effusion	2
Joint instability	1

AE = adverse reaction; MedDRA = Medical Dictionary for Regulatory Activities

72.5% of patients vs. 73.0% of investigators at 6 months after treatment initiation.

At the final assessment the investigator rated the treatment success as better than conventional HA therapies for 48.9% of patients and equivalent for 33.9%.

### Concomitant therapies

Most patients (68.0%) did not receive concomitant medications for their OA, of those who did, 27.3% received only 1 concomitant medication. The most common concomitant medications being acetic acid derivatives (37.4%) or propionic acid derivatives (29.1%).

### Adverse reactions

In total, 22 patients reported 24 ARs, all of which were in the SOC musculoskeletal and connective tissue disorders (see **Table 4**). The most commonly reported AR was injection site joint pain (n = 15).

Reactions to the injections were more common following the first injection than subsequent treatments. The most common reaction following each injection with the GO-ON® matrix was pain in joint; this was more common after the first injection (n = 81, 7.1%) than after subsequent injections (2<sup>nd</sup> injection: n = 17, 3.5–4.4% [worst case–best case]; 3<sup>rd</sup> injection: n = 16, 3.5–4.8%). After the first injection only, swelling (n = 14, 1.2%) and effusion (n = 12, 1.0%) also had an incidence ≥ 1.0%. No infections of treated joints were reported during the course of the trial.

### Discussion

Overall, this study shows that intra-articular injections with the GO-ON® matrix, as used in routine clinical practice, is highly effective at reducing both pain and functional impairment as perceived by the patient.

The pain and physical restrictions resulting from OA lead in turn to greater dependence upon health and support systems, further extending the burden upon already stretched regional health systems [1]. With the trend to increasing population age and obesity, this burden is likely to increase, exacerbating the need for more cost-effective, low risk interventions especially for elderly populations. One of the non-surgical treatment options is the intra-articular viscosupplementation with hyaluronic acid, typically as a series of 5 weekly injections. Such treatments are generally efficacious within 4 weeks, reaching peak efficacy after 8 weeks, and their effects may be expected to last at least 24 weeks [18]. Previous results showed that when sorbitol is added to the hyaluronic acid formulation, efficacy was apparent after just 1 week after the first injection [16]. The results of this study demonstrate the improved long-term stability of response using the hyaluronic acid/sorbitol formulations, as efficacy ratings changed little from 3 months to 6 months post treatment initiation. Indeed, nearly 50% of patients were considered by investigators to respond better to GO-ON® matrix than to conventional, non-sorbitol containing formulations.

Using the GO-ON® matrix, 3 weekly injections are recommended for the treatment of OA of the knee. While efficacy was greater for patients receiving 2 or 3 injections, especially for patients with more severe arthritis (Kellgren–Lawrence grades III or IV), more than half the patients were successfully and stably treated with a single injection.

This study was intended to assess efficacy and tolerability under routine conditions in daily practice. Convenience is an important consideration when choosing metrics for use in observational studies. In this case, a Likert scale was considered the most appropriate approach to measure patients outcome since it is easy to administer and comparatively simple to evaluate versus the WOMAC or Lequesne-indices. This approach was intended to maximize assessment compliance, though it also has the disadvantage of essentially precluding comparisons with the results of other clinical studies where these more complex metrics are used.

Overall, it can be concluded that the GO-ON® matrix is effective and well tolerated in the treatment of pain and functional impairment in patients with radiologically confirmed OA, providing fast acting and long-lasting pain relief and joint function.

## Acknowledgements



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## Conflict of Interest



Jürgen Heisel receives fees for lectures and consultancies from different companies as well from Rottapharm|Madaus Madaus GmbH.

Christoph Kipshoven is employed by Rottapharm|Madaus Madaus GmbH.

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# Pain Relief, Functional Recovery and Associated Medical Treatments Reduction in Large-Scale Population with Osteoarthritis Receiving Injections of ViscoSupplement Incorporating High Concentration of Sorbitol

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Poster # 729



## Introduction

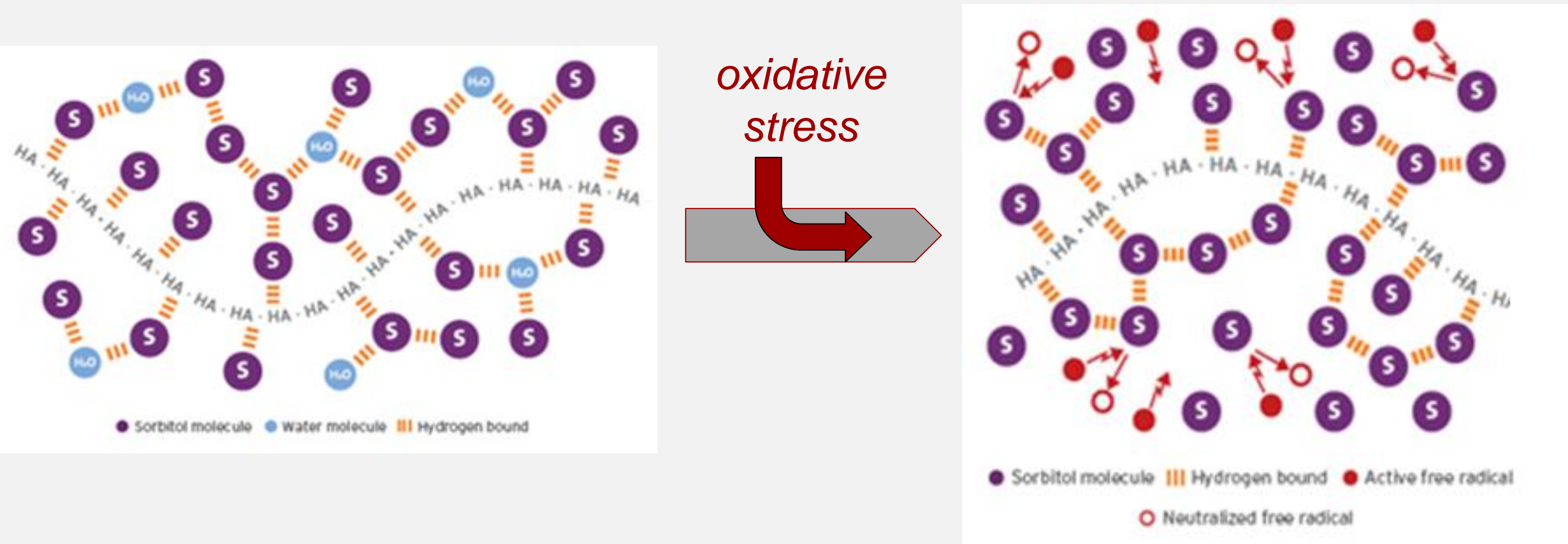
Creamer P. et al.<sup>1</sup> demonstrated that loss of function in knee OsteoArthritis (OA) is determined more by pain and obesity than by structural change. Tallon D. et al.<sup>2</sup> showed that the most commonly prescribed and used treatment for knee OA was oral drugs (analgesics or anti-inflammatories), but they also observed that many patients are suspicious of tablets. The hypothesis is that reducing knee pain and improving functional recovery would result in a reduction of medical treatment (especially oral drugs), therefore answering some of the patients' concerns.

## Background

To compare pain and functional impairment reduction performance in a population of 1147 patients receiving between 1 & 3 injections of 2ml viscosupplement combining Hyaluronic Acid (HA) and sorbitol: ANTI-OX-VS (Synolis V-A).

## Objective

ANTI-OX-VS is a visco-analgesic composed of highly concentrated non-crosslinked hyaluronic acid (2%) from biofermentation origin combined with a high concentration of Sorbitol (4%). Sorbitol is an endogenous molecule which functions as an oxygen free radical (OFR) scavenger. We assume that anti-oxidant effect of sorbitol may play an active role in rapid and strong pain reduction in patients with osteoarthritis by counteracting oxidative stress effects, and therefore influence function recovery and medication intake reduction.



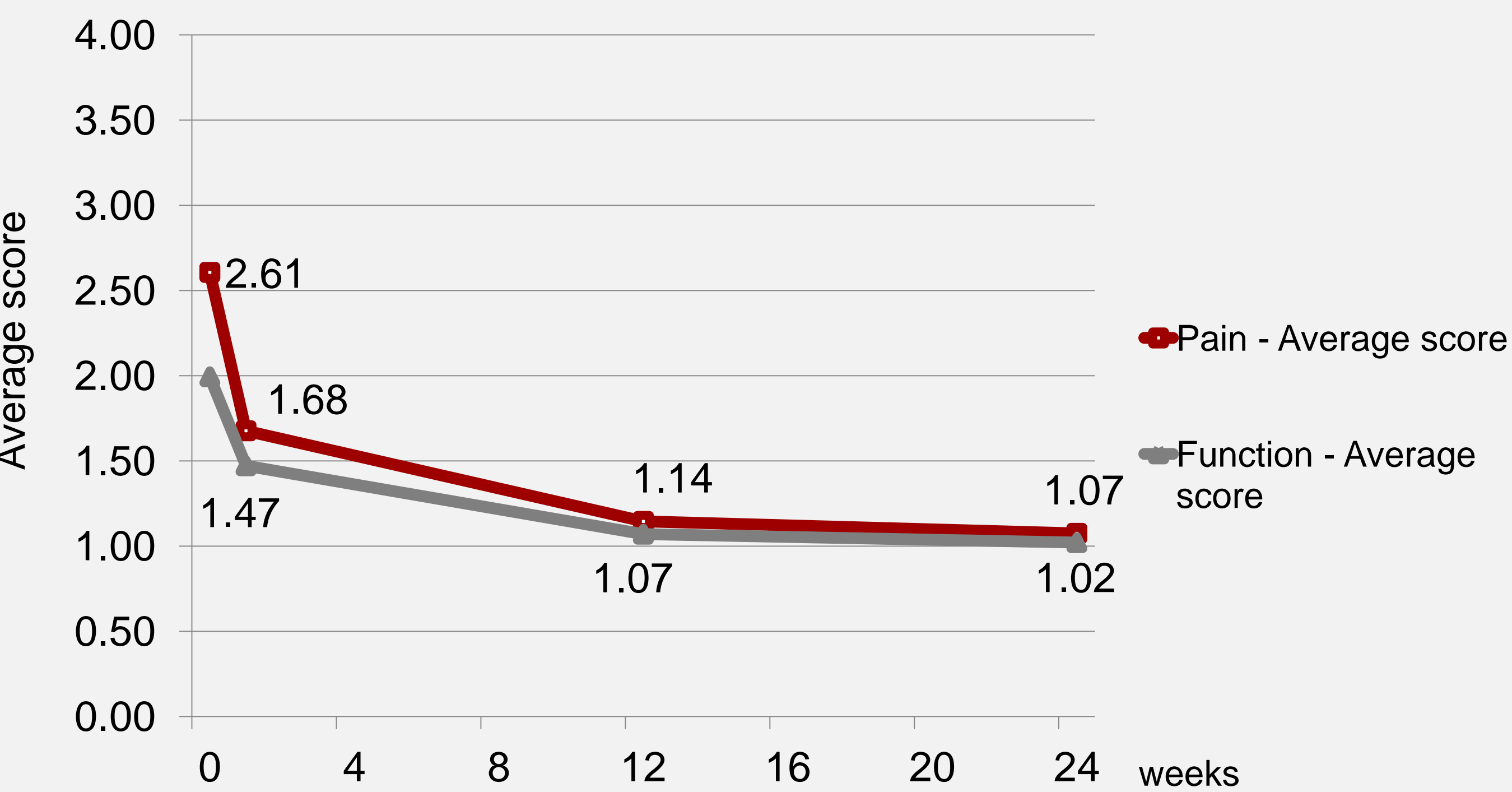
## Material and Methods

1147 patients, with a majority suffering from knee Osteoarthritis (92.9%), were enrolled in a Non-Interventional Study conducted in 398 centres in Germany<sup>3</sup>. Studied population had an average age of 63.3 years, including 499 males and 614 females, and was distributed into the following grades according to Kellgren-Lawrence scale: Grade I - 6.7%, Grade II - 31.4%, Grade III - 48.0% and Grade IV - 13.9%. Patients were assessed for pain level and functional impairment using 5 points Likert scale (scoring from 0=None to 4=Very Severe). Patients received between 1 and 3 intra-articular (IA) injections of 2ml of ANTI-OX-VS (Synolis V-A). Selected primary criteria were variations of pain and function impairment scores, between baseline and the following time points: week 1, week 12 and week 24. Selected secondary criterion was the evaluation of the use of adjunctive medical treatments (topical, NSAIDs, corticosteroids and analgesics) prior to treatment initiation and at week 24.

## Results

Average pain level (pooled data) scored at 2.61 (n=1125) at baseline, 1.68 (n=832) at week 1, 1.14 (n=1085) at week 12 and 1.07 (n=1030) at week 24. Average functional impairment level (pooled data) scored at 1.99 (n=1103) at baseline, 1.47 (n=819) at week 1, 1.07 (n=1074) at week 12 and 1.02 (n=1031) at week 24 (figure 1).

**Figure 1:** Average score (Likert scale) for patients with reported pain and function impairment data



Average number of medical treatments, comprising topical, NSAIDs, corticosteroids, analgesics and surgery decreased from 1.3 given prior viscosupplement treatment initiation to 0.37 over the period of the 24 weeks following the injection(s) of ANTI-OX-VS (table 1).

Patients with no reported medical treatment increased by from 354 patients prior viscosupplement treatment initiation to 780 over the period of the 24 weeks following the injection(s) of ANTI-OX-VS (table 2).

The number of patients taking NSAIDs and analgesics, and who answered the survey, could be reduced by 72.7% with the initiation of viscosupplementation (table 3).

**Table 1:** Number of patients (%) who received medical treatment(s) prior to the initiation of viscosupplementation - multiple citations possible

Previous treatment	n (%)
Topical	443 (38.6)
NSAIDs	735 (64.1)
Corticosteroids	385 (33.6)
Analgesics	421 (36.7)
Surgery	228 (19.9)

**Table 2:** Number of medical treatments (excluding surgery) experienced by patients before and during treatment with ANTI-OX-VS

Number of medical treatments	Number of patients with previous treatment	Number of patients with additional treatment
0	354	780
1	319	313
2	294	51
3	137	3
4	41	0
5	2	0

Specification of previous medical treatment including topical, NSAIDs, corticosteroids and analgesics was given in 793 (69.1%) of all patients

**Table 3:** Number of patients (%) for who NSAIDs / Analgesics could be reduced

NSAIDs / Analgesics could be reduced ?	n	%
Unknown	151	13.2%
Yes	518	45.2%
No	195	17.0%
N/A	283	24.7%

## Discussion

This study suggests that a strong pain relief occurs immediately after the first injection of Synolis V-A, with a relief that amplifies until week 24. Functional improvement has been observed to follow a similar pattern than pain relief. With a baseline score slightly lower, the amplitude of the observed improvement was also slightly inferior to that of pain relief. Never-the-less, both average scores ended up around 1 (Mild) at week 24. The patterns similarities between pain relief and functional improvement suggest a direct link between both factors; link that can be explained by the impact of pain on loss of function.

In parallel to the reduction of pain and functional impairment induced by ANTI-OX-VS, the number of patients using additional pain relief treatment and the number of those treatments have been strongly reduced. This reduction logically results from the decreasing need of addressing pain, but also reinforces the fact that pain reduction observed in the study is mainly the result of the ANTI-OX-VS treatment, and not of adjunctive medical treatments. It can be fairly implied that the reduction of oral medications such as pain killers or anti-inflammatory drugs should help reducing their side effects such as nausea, vomiting and other stomach disturbances. In addition, it should positively impact overall medical costs.

## Conclusion

On a large population, viscosupplementation using ANTI-OX-VS clearly leads to a fast and strong pain relief for at least 6 months, as well as a proportional functional recovery.

This pain relief has been observed to result in an important reduction of adjunctive oral medical treatments, like NSAIDs and analgesics, which would most probably lightening the occurrence of side effects.

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