Osteoarthritis and Cartilage 19 (2011) 1294–1300

Osteoarthritis and Cartilage

Efficacy evaluation of highly purified intra-articular hyaluronic acid (Sinovial®) vs hylan G-F20 (Synvisc®) in the treatment of symptomatic knee osteoarthritis. A double-blind, controlled, randomized, parallel-group non-inferiority study

K. Pavelka†*, D. Uebelhart‡§

† Institute of Rheumatology, Praha, Czech Republic
‡ Department of Rheumatology, Institute of Physical Medicine, University Hospital of Zurich, Switzerland
§ Valmont Private Rehabilitation Clinic, Glion-sur-Montreux, Switzerland

ARTICLE INFO

Article history:
Received 22 February 2011
Accepted 29 July 2011

Keywords:
Knee osteoarthritis
Hyaluronic acid
Hylan

SUMMARY

Objective: Knee osteoarthritis is a major cause of disability and pain. This phase III, double-blind (patient and observer blinded,) multicenter, randomized, non-inferiority study was conducted to demonstrate the non-inferiority of the highly purified intra-articular injection of hyaluronic acid (Sinovial®) in comparison to Hylan G-F20 (Synvisc®) in the treatment of knee osteoarthritis.
Methods: A total of 381 patients were randomly assigned to receive either the test drug, 16 mg/2 ml (0.8%) highly purified ia hyaluronic acid of biofermentative origin (Sinovial®), or the comparative drug, 16 mg/2 ml of 0.8% hylan G-F20 (Synvisc®). The duration of the treatment was 2 weeks (three injections at 1-week interval), followed by an observation period of 6 months.
The primary efficacy variable was the improvement in mean Western Ontario and McMaster Universities (WOMAC) pain subscore from baseline to the final visit (week 26), compared between the two treatment groups. The acceptable margin for non-inferiority was chosen to be 8 mm.
Results: At week 26, WOMAC pain subscores decreased by a mean of 32.5 for both Sinovial® and Synvisc®. These results met prespecified criteria for non-inferiority for both the Intent-to-Treat and Per-Protocol populations. There were no statistically significant differences between groups at 26 weeks, although Sinovial®-treated patients tended to have a slightly better outcome for select variables, as they did at earlier time-points, some of which reached statistical significance. Both hyaluronic acid preparations were well-tolerated, with no statistically significant differences in tolerability profile between groups.
Conclusion: Sinovial® and Synvisc® treatments were found to be equivalent, both in terms of efficacy and safety.
Clinical Trial Number: NCT00556608 (ClinicalTrials.gov Identifier).

Introduction

Current treatments for knee osteoarthritis include analgesics, non-steroidal anti-inflammatories, exercise, physiotherapy, weight-relieving braces and total knee arthroplasty[1,2]. However, most currently used treatments have limited tolerability[3] and their efficacy is limited to relieving pain. Recently, attention has turned to treatments with the potential to offer disease-modifying activity, such as viscosupplementation, a therapeutic modality first developed in the 1960s[4].

Viscosupplementation is based on restoration of the synovial fluid environment, allowing restoration of normal joint structure and function[5]. Hyaluronic acid is a large glycosaminoglycan that naturally occurs in the synovial fluid[6] and plays an important physiological role in synovial joints[7,8]. In patients with knee osteoarthritis, the average molecular weight and concentration of hyaluronic acid is reduced[4,9]. Viscosupplementation with hyaluronic acid is a well-established[2,5,9] and widely used therapy for osteoarthritis, and is recommended by both the American College of Rheumatology and the European League Against Rheumatism for this indication[10,11]. Intra-articular hyaluronans have been approved by the US Food and Drug Administration (FDA) since 1997 for relief of osteoarthritis knee pain[1], and there are a number of different hyaluronic acid preparations for the treatment of knee osteoarthritis. These include Hylan G-F20 (Synvisc®), a G-F20 preparation that comprises two cross-linked derivatives of hyaluronan

* Address correspondence and reprint requests to: K. Pavelka, Institute of Rheumatology, Na Slupi 4, 128 50 Praha 2, Czech Republic. Tel: 420-234075244; Fax: 420-224914451.
E-mail address: pavelka@revma.cz (K. Pavelka).

1063-4584/$ – see front matter © 2011 Published by Elsevier Ltd on behalf of Osteoarthritis Research Society International.
doi:10.1016/j.joca.2011.07.016

with a molecular weight of 6,000 kDa[12], and Sinovial®, a chemically non-modified sodium hyaluronate, with a molecular weight of 800–1,200 kDa.

The purpose of this non-inferiority study was to evaluate the clinical efficacy and general tolerability of Sinovial® relative to an already marketed producted, Synvisc®, when administered to patients with symptomatic knee osteoarthritis. Synvisc® was chosen as the comparator because it is widely used in several European countries for knee osteoarthritis[13]. The non-inferiority trial design was adopted because of ethical and methodological reasons detailed in the discussion section.

Method

Study design and patients

This was a multicenter, phase III, double-blind, controlled, randomized, parallel-group, non-inferiority study in patients with knee osteoarthritis. The study comprised patients from the Czech Republic, France, Italy, Switzerland, the Slovak Republic and Germany (see the acknowledgments for a list of participating physicians and study centers). After obtaining written informed consent, patients underwent a physical and knee examination and a thorough medical history was obtained. Five to 10 days after screening, patients who required medication washout or X-rays were subjected to baseline evaluation.

Included patients were outpatients aged between 40 and 81 years' with symptomatic primary knee osteoarthritis, with symptoms present in the target knee for at least 3 months. All patients were required to have an American Colleague of Rheumatology (ACR) clinical and radiological-based diagnosis of target-knee osteoarthritis, and Kellgren & Lawrence grade 2–3 osteophytes within 6 months of screening. Included patients were those who had failed to respond sufficiently to analgesics and/or Non-steroidal Antirheumatic Drugs (NSAIDs) taken regularly, or those who responded but who were unable to tolerate such treatment. Mean WOMAC pain subscore at the target knee was required to be $\geq$40 mm and $<$80 mm on a 100 mm visual analog scale (VAS) following NSAIDs/analgesic washout, with mean WOMAC pain subscore $<$30 mm on a 100 mm VAS in the contralateral knee (i.e., non-target knee).

Patients were excluded due to: Body Mass Index (BMI) $\geq$ 32 kg/m^2, secondary target knee osteoarthritis, predominantly femoral-patella knee pain mainly related to femoral patellar syndrome at the target knee, no remaining joint space width at the target knee, symptomatic hip osteoarthritis or other condition that would interfere with study assessments, severe varus/valgus deformity in the target knee, history or current evidence of other joint diseases, such as inflammatory, infective or metabolic joint disease, concomitant rheumatic disease, significant injury to the target knee in the past 6 months, previous joint replacement or arthroplasty on the target knee, arthroscopy, osteotomy or surgery on the target knee in the past year, any surgical procedure scheduled in the next 6 months, venous or lymphatic stasis in the relevant limb, skin infection, disease or trauma at the injection site, systemic or intra-articular (target knee) corticosteroids in the past 3 months, intra-articular corticosteroids (contralateral knee) in the past 4 weeks, viscosupplementation to the target knee in the past year, initiation of target knee physical therapy in the past 3 months, initiation/change in dose of symptomatic slow-acting drugs for osteoarthritis therapy, ongoing anticoagulant therapy, chronic/recurrent use of NSAIDs, analgesics or narcotics other than for osteoarthritis of the target knee, history of allergy or hypersensitivity to hyaluronic acid, paracetamol or avian proteins, participation in a clinical study within the past 3 months, pregnant or lactating women, and women of childbearing potential not willing to use adequate contraception.

The study was approved by the ethics committee of all participating study centers. All patients gave their written informed consent to participate in accordance with the Declaration of Helsinki.

Intervention

Eligible patients were assigned a three-digit randomization number for identification purposes. Patients were given a 1-month supply of rescue medication and instructed not to consume this within the 24 h prior to study visits. Rescue medication use was to be recorded in a patient diary, along with concomitant medication usage, adverse events, lifestyle changes and the weekly global pain assessment. Patients were randomized to receive once weekly for 3 weeks either 16 mg/2 ml (0.8%) of highly purified intra-articular hyaluronic acid of biofermentative origin, a linear unbranched polysaccharide chain with a mean Molecular Weight (MW) of 800–1,200 kDa, Sinovial® (IBSA, Switzerland and Laboratories Genévrier, France) or 16 mg/2 ml (0.8%) of intra-articular hylan G-F20, a cross-linked polysaccharide chain containing hylan A with a mean MW of 6,000 kDa and hylan B a hydrated gel, Synvisc® (Genzyme Biosurgery, Ridgefield, NJ, USA). Control visits were carried out at 4, 12 and 26 weeks.

Prior and concomitant therapy

Ongoing and/or initiation of new concomitant treatment was permitted if essential for patient health, and not specified in the exclusion criteria. Prohibited medications included anti-coagulants, systemic NSAIDs, analgesics other than paracetamol, narcotics, systemic and intra-articular corticosteroids, intra-articular injection of the target knee, topical anti-inflammatories and analgesics at the target knee, articular lavage of the target knee, newly initiated symptomatic slow-acting drugs for osteoarthritis or alteration in dosage (long-term therapy at stable dosage acceptable), newly initiated physical therapy and alternative medicines.

Efficacy outcomes

The primary efficacy variable was change from baseline in Western Ontario and McMaster Universities (WOMAC) Index pain subscore at 26 weeks. The WOMAC Index is a standardized and validated methodology for assessing pain associated with osteoarthritis, and is routinely used as a primary end-point in clinical trials studying the effect of drugs and devices for this particular indication[14].

Change from baseline in the WOMAC total score, and in the pain, stiffness and function subscores were assessed as secondary efficacy variables. Changes from baseline were also assessed for the Lequesne Algofunctional Index[15], patient assessment of global pain (defined as the amount of pain during the previous 24 h, scored on a 0–100 mm VAS, with 0 representing no pain and 100 unbearable pain)[16] and for patient assessment of global status scored on a 0–100 mm VAS, with 0 representing very poor global status and 100 very good global status[16]. Global status was also assessed by the investigator and scored on a 5-point scale, with 0 being very poor and 4 being very good. Additional efficacy variables were Percentage Sum of the Pain Intensity Differences (SPID%) calculated on the basis of weekly assessment of global pain over the 6-month study period, according to the following formula:

$$\text{SPID\%} = \frac{\text{Sum of Pain Intensity Differences}}{\text{Maximum Scale of Pain Intensity} \times \text{Trial Duration}} \times 100$$

and paracetamol consumption for target knee osteoarthritis. Patient assessment of treatment satisfaction was also evaluated,

using a 4-point scale, with 0 being dissatisfied and 3 being very satisfied. Overall response rate was assessed at 12 and 26 weeks based on the OMERACT-OARSI response criteria[17]. There were no changes to the outcome measurements after the trial commenced.

Safety

Patients were asked at each visit if they had experienced any Adverse Events (AEs) since the last visit and were asked about pain at injection site immediately after the injection, and to rate their perceived pain on a scale of 0 (no pain) to 10 (worst possible pain). Local tolerability was also assessed, by the patient and the investigator, based on a 5-point scale, with 0 being very poor and 4 being very good.

Sample size

For improvement in mean WOMAC Index pain subscore from baseline, the protocol-defined non-inferiority margin for the difference between Sinovial® and Synvisc® was 8 mm on a VAS ranging from 0 to 100 mm. This non-inferiority margin is less than the minimum clinically perceptible difference, usually considered to be 10 mm for the WOMAC pain subscore[18], and lower than the minimum clinically important improvement of 10–20 mm[19–21]. Assuming a standard deviation of 21 mm for both groups[22], with two-sided $\alpha = 0.05$ and $\beta = 0.10$ (90% power), the required sample size was estimated to be 145 patients per group. The protocol proposed a total of 200 patients per group to allow for a protocol violation rate of up to 25%.

The Intent-to-Treat (ITT) population comprised all patients who received at least one dose of Sinovial® or Synvisc®. The Per-Protocol (PP) population was a subgroup of patients with no serious protocol violations selected from the ITT group in a blinded fashion prior to breaking the randomization code. Patients failing to return for the week 26 visit were excluded from the PP population only if their absence could not be attributed to treatment failure.

Randomization and blinding

Patients were randomized according to a Statistical Analysis System (SAS) generated randomization list prepared by IBSA in which patients were assigned to treatment, at a 1:1 allocation ratio, at each site in blocks of four. Randomization numbers were assigned chronologically based upon order of study enrollment. An investigator who was blind to treatment allocation enrolled the study participants, and an unblinded investigator performed the injections.

Because of the evident differences in the marketed packaging between Sinovial® and Synvisc®, it was not possible to use a full double-blind design. However, the study is considered to be a double-blind study in that both the patient and the observer were blinded. More specifically, neither the investigators nor the patients had contact with the study products, which were delivered to the study centers in identical, sealed, unmarked boxes containing three blister-packaged syringes. Separate individuals performed the injection and assessments, and the patient was either blind folded or separated from the physician by an obstructive operative field during the injection process.

Statistical methods

To determine the appropriate statistical test for non-inferiority, the change from baseline improvement in the WOMAC pain score was tested for normality using the Shapiro–Wilk test on the entire patient population. If the distribution was not significantly different ($P < 0.05$) from normality, it was considered appropriate to calculate the 95% confidence interval (CI) using Analysis of Variance (ANOVA) with Least-Squares means (equivalent to Student's t test). If the distribution departed significantly from normality, the nonparametric Hodges–Lehmann method was used. Other continuous variables were analyzed using ordinary hypothesis-testing statistical methods. All variables were analyzed using ANOVA and the nonparametric Wilcoxon rank-sum test. Binary variables were analyzed using the Fisher exact test.

Results

Patients were recruited from November 2007 to January 2009, with the last patient completing the study in July 2009. A total of 381 patients were randomized at the 23 sites, all but one of whom received at least one intra-articular injection of the assigned hyaluronic acid preparation (Fig. 1).

Two populations were analyzed; the ITT population comprising all 380 patients who received at least one injection of Sinovial® or Synvisc®, and the PP population, which excluded 27 patients with serious protocol violations, as follows: a WOMAC score >30 in the contralateral knee at screening/baseline ($n = 9$), a WOMAC score <40 in the target knee at screening/baseline ($n = 6$), patient voluntary study withdrawal ($n = 5$), an adverse event, effusion >15 ml in the target knee, lost to follow-up (two each) and an inclusion error ($n = 1$). All ITT patients received at least one intra-articular injection of either Sinovial® or Synvisc®, with two patients in the Sinovial® group not receiving a second and third injection, compared with three and five Synvisc® patients, respectively. Overall, 99.0% of the Sinovial® group and 97.3% of those assigned to Synvisc® were given all three injections.

Baseline data

The average age of the 380 ITT patients was 65 years (range 41.8–80.9), the majority were female (72.9%) and the predominant prior/ongoing medical condition was hypertension (Table I). Patient-assessed global pain scores at screening and baseline averaged 65.3 and 65.6, respectively, on a 100-point scale, while other indices of disease severity were also suggestive of mild to moderate target knee osteoarthritis. The baseline characteristics of the PP population were virtually identical to their ITT counterparts (Table I).

Concomitant medications

Prior to study enrollment and continuing after intra-articular administration of the assigned study medication, 242 (63.7%) of the

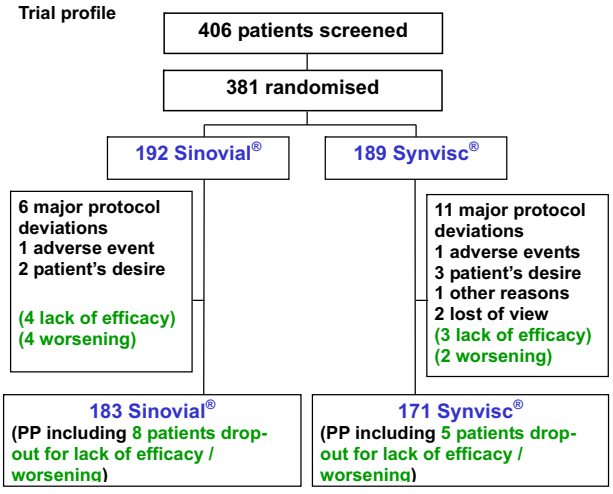

Fig. 1. Flow chart of patient disposition.

Table I
Demographic and baseline clinical characteristics of all patients*

Characteristics	Treatment group	
	Sinovial® ($n = 192$)	Synvisc® ($n = 188$)
Age (years)	65.1 ± 9.1	64.9 ± 8.7
BMI (kg/m^2)	27.1 ± 3.1	27.0 ± 3.1
Women, no. (%)	139 (72.4)	138 (73.4)
Post-menopausal	134/139	134/138
Duration from diagnosis (years)	6.3 ± 5.8	5.6 ± 5.6
Involvement of contralateral knee (%)	66.1	66.0
Location target knee, no. (%)		
Right	102 (53.1)	98 (52.1)
Left	90 (46.9)	90 (47.9)
K/L grade, no. (%)		
2: minimal	85 (44.3)	85 (45.2)
3: moderate	107 (55.7)	103 (54.8)
Medication usage in prior 3 months (%)	63.5	59.6
Prior target knee treatments (%)		
Ambulatory aid	2.10	5.9
Knee surgery	12.5	13.3
Prior medical procedures	24.0	20.7
Therapeutic drug use	90.1	92.0
Non-drug therapy	9.4	8.5
WOMAC score, mm		
Pain	55.2 ± 10.8	55.5 ± 10.9
Stiffness	50.1 ± 19.1	50.1 ± 19.4
Function	53.1 ± 14.6	53.6 ± 13.9
Total	53.3 ± 12.9	53.7 ± 12.5
Lequesne algofunctional index	11.5 ± 3.0	11.6 ± 3.2
Patient global pain, 100-mm (VAS)	64.5 ± 14.2	66.7 ± 14.0

There were no statistically significant differences between groups.
* Except where indicated otherwise, values are the mean ± SD.

ITT patients were taking one or more concomitant medications. Concomitant medications discontinued before the first intra-articular treatment or begun sometime thereafter were generally pain remitting in nature. Significant intergroup differences in concomitant medications consumption were limited to the proportion of patients on a cardiovascular medication, with more Sinovial® patients being treated with a calcium channel blocker over the course of the study, while the converse occurred for angiotensin-converting enzyme inhibitors.

Primary efficacy outcome

At week 26, WOMAC Index pain subscores decreased from a mean of 55.5 in the Synvisc® group to 23.1, a mean difference of 32.5, with corresponding values of 55.2 and 22.7 at baseline and week 26, respectively, for Sinovial®, a mean difference of 32.5 (Fig. 2). These results corresponded to a between-group mean difference in change from baseline at 26 weeks of 0.0 (95% CI −4.7 to 4.8). The WOMAC Index pain subscore results met the prespecified criteria for non-inferiority, irrespective of the patient population analyzed. If actual scores were considered, rather than the change from baseline, results again demonstrated non-inferiority. Taking the WOMAC scores at 4 weeks and at 12 weeks, there were no differences demonstrated between the two treatment groups, with values of 25.4 and 22.7, respectively, for Sinovial®, compared with 27.1 and 24.6, respectively, for Synvisc®, corresponding to between-group mean differences of 1.3 (95%CI −2.6 to 5.3) and 1.6 (−2.8 to 6.0), at 4 and 12 weeks, respectively. The statistical methodology employed (parametric vs nonparametric) again made no impact on the demonstration of non-inferiority of these two hyaluronic acid preparations. The worst-case lower bound CI for the ITT comparisons was −6.2 (ANOVA derived, actual scores at 12 weeks), while a worst-case value of −5.8 was obtained for the PP population (ANOVA derived, change from baseline scores at 26 week).

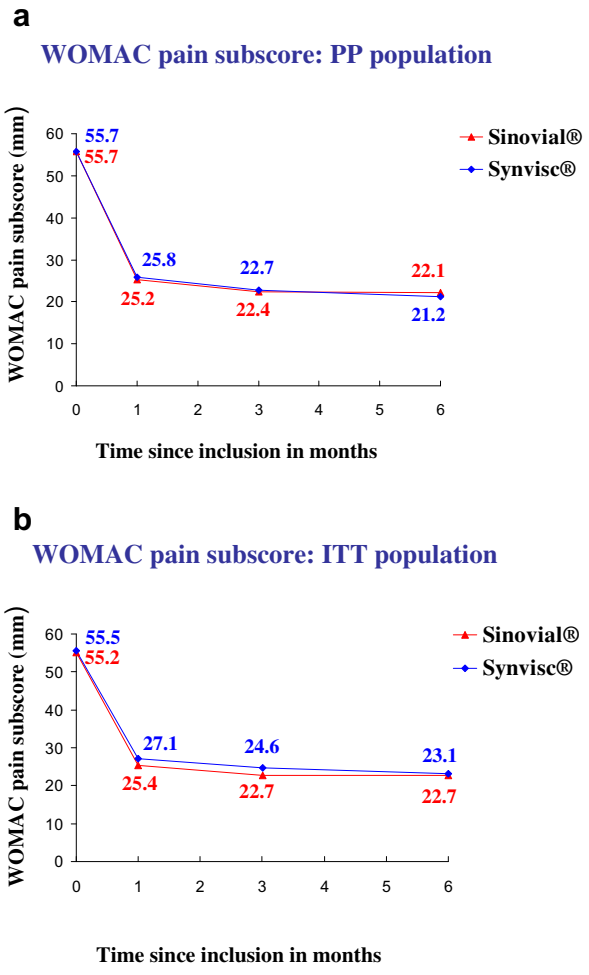

Fig. 2. Change from baseline in WOMAC scores – (a) ITT and (b) PP populations.

Secondary efficacy outcomes

Patient scores for the WOMAC Questionnaire Function and Stiffness components, as well as total score did not differ significantly between treatment groups at any time point, with changes from baseline at 26 weeks for function, stiffness and total score of 28.0, 25.8 and 28.8, respectively, for Sinovial®, and 28.2, 25.7 and 28.8 for Synvisc® in the ITT population. For the PP population, changes from baseline at 26 weeks for function, stiffness and total score were 29.0, 26.6 and 29.7, respectively, for Sinovial®, with corresponding values of 29.7, 26.7 and 30.5 for Synvisc®. Lequesne Questionnaire total score did not differ significantly between treatments at 26 weeks, with a change from baseline of 3.9 for Sinovial® and 3.6 for Synvisc® for the ITT population, and corresponding values of 4.0 and 3.7, respectively, for the PP population. At 12 weeks, the change from baseline in Lequesne total score was significantly higher for Sinovial® than for Synvisc®, at 3.9 vs 3.4 ($P = 0.049$; Fig. 3), although no significant between-group differences were apparent at the 4-week time point: these significant differences were not seen in the PP population.

Decreases in patient-assessed global pain did not differ between groups at any time point, with decreases in the ITT population from 64.5 to 26.9 in the Sinovial® group and 66.7 to 30.5 in the Synvisc® group. Similar results were obtained for the PP population. For patient-assessed global status, measured using a 100-point VAS, with 0 being very poor status and 100 very good status, there were improvements from baseline of a similar magnitude for both

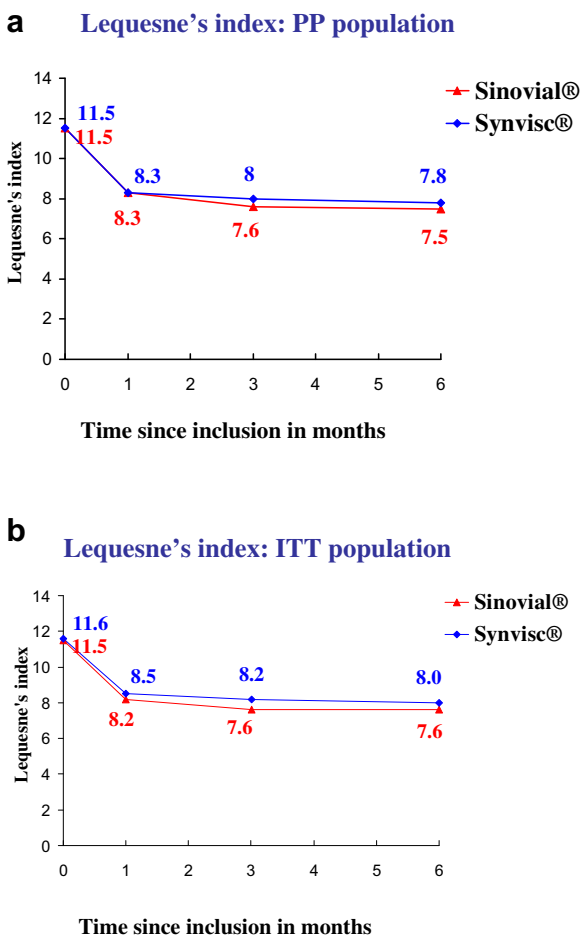

Fig. 3. Lequesne's total score – (a) ITT and (b) PP populations.

groups, with values increasing from 43.8 to 68.7 at 26 weeks for Sinovial® and from 45.0 to 69.4 for Synvisc® in the ITT population, with similar results for the PP population.

Investigator assessment of global status was the same for both treatment groups at baseline, 4 weeks and 26 weeks, but at 12 weeks, Sinovial®-treated patients were judged to have had a significantly better overall response, primarily due to a higher percentage being characterized as having a very good outcome, at 37% and 27.2% for Sinovial®, compared with 25% and 26.4% for Synvisc®, for the ITT and PP populations, respectively, (*P*-values 0.014 and 0.044, respectively). Overall, 79.7% and 79.8% of the ITT and PP patients given Sinovial® were judged by the investigator at 26 weeks to have had a good or very good response, compared with 70.7% and 72.0% for Synvisc®.

There were no statistically significant differences between groups for rescue medication usage, overall or specifically for target knee pain (Table II), although total rescue medication usage was higher for Synvisc® than Sinovial® for the period from baseline to 26 weeks, with 76.6% compared with 67.9% ($P = 0.065$) of patients using such medication, respectively, for the ITT population and 68.7% compared with 75.3% ($P = 0.192$) for the PP population. In terms of paracetamol use, both the percentage of patients requiring such treatment for target knee pain and the number of tablets consumed were somewhat reduced for Sinovial® following the first intra-articular injection (tablets for target knee pain ↓ ~30% and 37%, respectively, at 4 and 12 weeks, for both ITT and PP subsets), but these differences were not accompanied by an overall reduction in total consumption of medications.

Table II
Rescue medication usage

	Sinovial® (% of patients)		Synvisc® (% of patients)	
	ITT	PP	ITT	PP
Rescue medication/Target knee				
Screen – baseline	50.6	50.6	48.8	48.7
Baseline – 4 weeks	51.9	52	58.8	58
4–12 weeks	44	44	46.6	46.4
12–26 weeks	41.9	42.2	49.1	48.8
Baseline – 26 weeks	64.2	64.8	69.9	69.4
Total rescue medication usage				
Screen – baseline	34.4	34.4	35.6	33.9
Baseline – 4 weeks	57.4	57.7	64.1	62.9
4–12 weeks	51.1	51.4	57.5	56.8
12–26 weeks	49.7	49.7	55.7	54.8
Baseline – 26 weeks	67.9	68.7	76.6	75.3

There were no statistically significant difference between groups.

At 4 and at 12 weeks the proportion of patients very satisfied with Sinovial® treatment was ~39% and 47%, respectively, while that for Synvisc® was ~30% and 35%. The OMERACT-OARSI overall success rate was the same for both Sinovial® and Synvisc® (ITT, 85.9% vs 82.4%; PP, 87.4% vs 86.0%, respectively).

Subgroups

The relationship between change from baseline in WOMAC pain subscore and select patient baseline variables was explored in individual and multiple regression models. Of the 36 variables evaluated, only six were found in simple regression to be significantly (all positively) correlated with the primary outcome measure, the strongest predictor being the patient's WOMAC pain subscore at baseline, followed by days off-work due to pain in the previous year, the presence of sclerosis, varus knee, flexion, and pain duration. In the final backward regression model ($r^2 = 0.124$), four of the 36 variables provided significant explanatory power for patient response to therapy, but the overall effect on comparisons in outcome for Sinovial® and Synvisc®-treated patients was unaffected by mean adjustments due to the presence of the retained covariates in the model (non-parametric = 37.8 vs 37.2, respectively, in absolute change from baseline, CI = −3.1 to +4.9; parametric = 32.3 vs 32.6, respectively, CI = −4.8 to +4.2).

Additional analyses revealed that patients tended to have a better response to either preparation of intra-articular hyaluronate if they were lighter in weight, visited their doctors more often or took more time-off from work, had more severe disease as indicated by the presence of sclerosis or an excessive number of osteophytes, were bow-legged, or had greater WOMAC pain at baseline, in the absence of significant treatment by subgroup interaction effects for any of these independent variables. Consistent with the results of the intergroup comparison of the primary efficacy variable, the lower bound of the 95% CI for any of the adjusted, treatment group mean comparisons was always greater than the −8 mm delta proposed for this study (i.e., worst-case = −5.4), which was expected given mean score adjustments were relatively unaffected by any of the covariates included in the statistical model.

Safety

Local tolerability was judged as good or very good by 91–93% of patients at the visit following administration, and patient- and investigator-assessed global tolerability at the 4, 12 and 26-week follow-up visits were nearly identical and comparable to local

tolerability scoring, as good/very good scores were obtained from 93% to 97% of the respondents. There were no statistically significant intergroup differences for any of these variables. Pain associated with the initial injection of Sinovial® or Synvisc® in ITT patients averaged 3.0 and 2.9, respectively, on a 10-point scale, declining slightly to 2.9 and 2.7, respectively, and 2.7 and 2.6, respectively, after the second and third injections. Of the adverse events reported in this study, six were considered treatment-related, with five events in four patients in the Synvisc® group [injection site hematoma, injection site pain, arthralgia and joint swelling (two episodes in one patient)] and one case of injection site pain in a patient who received Sinovial®. There were seven severe adverse events reported: six events in six Synvisc®-treated patients, and one in a Sinovial® recipient. Serious adverse events were also relatively rare, with five events among four Synvisc®-treated patients, and with one event in a Sinovial®-treated patient. None of the serious adverse events were thought to be treatment-related.

Discussion

It is evident from the results of this study that both preparations were equally effective in improving clinical performance as assessed through multiple outcome measures. Indeed, the magnitude of the reduction in WOMAC Questionnaire Pain Subscores for patients given three consecutive weekly injections of Sinovial® was shown to be non-inferior to Synvisc® at each of the three post-treatment visits, with the lower bound of the 95% CI generally being well above the relatively conservative −8 mm protocol-defined non-inferiority margin, derived from clinical considerations related to the minimum clinically perceptible difference in WOMAC pain scores. Consistent with the finding of non-inferiority of Sinovial® in comparison to Synvisc® with regard to the primary efficacy variable, there were no statistically significant intergroup differences for any of the 13 secondary outcome variables/time intervals analyzed, except at 12 weeks following the initial hyaluronic acid injection in which a higher percentage of patients in the Sinovial® group were found to be very satisfied with their treatment course, in association with more favorable scoring for Lequesne pain, investigator-assessed global status, and rescue medication consumption for target knee pain.

In any study with pain as the primary outcome measure, a potential source of confounding is concomitant usage of pain-relieving therapies. In addressing this issue, an analysis was performed in which success was defined as a >30% reduction in the WOMAC pain subscore at each of the three follow-up periods. This analysis revealed that a larger proportion of the patients assigned to the Synvisc® group were classified as having failed treatment due to concomitant pain therapy consumption at each of the follow-up intervals, but especially at 4 and 12 weeks where the intergroup differences attained statistical or near-statistical significance. Overall total success rates after adjusting for pain therapy usage were correspondingly higher for the Sinovial®-treated patients at the earlier time-points as well. These data indicate that the non-inferiority of Sinovial® in comparison to Synvisc® was not due to excessive usage of a pain-relieving alternate therapy by Sinovial® patients, and suggest a genuine treatment effect.

The safety data generated in this study are largely unremarkable, with individual injections being generally well-tolerated, and patient/investigator scoring for global tolerability indicating widespread procedural acceptability. There were no statistically significant intergroup differences in the overall incidence of adverse events or in severe, serious or suspected treatment-related AEs. An increased risk of local adverse events associated with hylan over hyaluronic acid has previously been reported[23].

The lack of a placebo arm could be considered a limitation of this trial, but it must be considered that use of an intra-articular placebo in trials such as this presents several problems. First, there are ethical concerns associated with using an invasive procedure, such as an injection, to deliver a placebo in a setting where hyaluronic acid products are routinely used in clinical practice. Second, there are methodological challenges involved in achieving a true placebo when it is necessary to perform arthrocentesis and substitute synovial fluid with saline. For these ethical and methodological reasons, it was considered appropriate to examine the test product in terms of non-inferiority to a marketed product, the effectiveness of which has already been demonstrated by means of randomized placebo-controlled trials. Synvisc® was chosen as a reference product because in recent meta-analyses it displayed the greatest effect size[5,6].

While the use of intra-articular hyaluronan in knee osteoarthritis is a well-established treatment, the generalizability of the findings in this study may be applied to those patients who fail to respond to non-pharmacologic therapy and simple analgesics, or in whom non-selective NSAIDs and cyclooxygenase-2 specific inhibitors are contraindicated or have been associated with lack of efficacy or adverse events.

In conclusion, Sinovial® and Synvisc® treatments were found to be equivalent both in terms of efficacy and safety.

Author contributions

KP and DU have been actively involved in study design, investigation of patient and writing the manuscript.

Role of the funding source

Supported by a research grant from IBSA, Switzerland.

Conflict of interest

The authors received a grant for this clinical study from IBSA.

Acknowledgments

The participating physicians and study centers were as follows:

Czech Republic: K Pavelka (Institute of Rheumatology, Prague); Z Dvořák (Arthromed s.r.o., Pardubice); Z Fojtik (Internal Hemato-Oncological Clinic, Faculty Hospital, Brno – Bohunice); J Vachal (Center of Motoric System Treatment, Prague).

Deutschland: F-U Niethard (Orthopedische Universitätsklinik und Poliklinik der RWTH Aachen Aachen); W Kneer (Orthopedische Praxis, Stockach); T Kühn (Nova Clinic, Biberach an der Riss).

France: P Bertin and C Bonnet, (CHRU de Limoges, Service de Rhumatologie, Limoges Cedex); M Arnaud-Duclos and I Negrier-Chassaing (Limoges); C Bernardeau and D Coyral (Clinique François Chenieux, Service de Rhumatologie, Limoges Cedex); X Le Loet (CHU Bois-Guillaume); L Voisin-Becquet and L Grassin-Delyle (Clinique Mathilde, Rouen Cedex); J Fulpin and A Plantamura (Château d'Argent, Hyères).

Italy: M Galeazzi, A Fioravanti, L Cantarini and A Andreou (Rheumatology Unit-Siena University Hospital-Le Scotte Policlinic, Siena); L Frizziero and A Frizziero (Nigrisoli Clinic, Bologna); F Fantini, E Paresce and L Pisoni (Rheumatology Unit-Gaetano Pini Orthopedic Institute, Milano); E Castellacci, T Polieri and E Orsoni (Traumatology and Sports Medicine Unit-AzUSL 2, Lucca); L Sabadini and L Storri (Rheumatology District Unit-AzUSL 8, Arezzo); S Bombardieri, M Doveri and A Consensi (Rheumatology Unit-Santa Chiara Hospital, Pisa).

Slovakia: B Dobrovodský (Rheumatology Clinic, Reumaglobal s.r.o., Trnava); R Jancovic (ROMJAN s.r.o. Policlinic Tehelna,

Bratislava); Z Kmečová (F.D. Roosevelt's University Hospital, Banska Bystrica); D Žlnay (National Institute of Rheumatic Diseases, Piestany).

Switzerland: D Uebelhart, S Blumhardt and D Frey (Universitätsspital Zürich, Rheumaklinik und Institut für Physikalische Medizin und Rehabilitation, Zürich).

References

1. Barron MC, Rubin BR. Managing osteoarthritic knee pain. J Am Osteopath Assoc 2007 Nov;107(10 Suppl 6):ES21–7.
2. Wang CT, Lin J, Chang CJ, Lin YT, Hou SM. Therapeutic effects of hyaluronic acid on osteoarthritis of the knee. A meta-analysis of randomized controlled trials. J Bone Joint Surg 2004 Mar;86-A(3):538–45.
3. Bjordal JM, Ljunggren AE, Klovning A, Slordal L. Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials. BMJ 2004 Dec 4;329(7478):1317.
4. Balazs EA, Watson D, Duff IF, Roseman S. Hyaluronic acid in synovial fluid. I. Molecular parameters of hyaluronic acid in normal and arthritis human fluids. Arthritis Rheum 1967 Aug;10(4):357–76.
5. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database Syst Rev 2006 (2):CD005321.
6. Lo GH, LaValley M, McAlindon T, Felson DT. Intra-articular hyaluronic acid in treatment of knee osteoarthritis: a meta-analysis. JAMA 2003 Dec 17;290(23):3115–21.
7. Bellamy N. Hyaluronic acid and knee osteoarthritis. J Fam Pract 2006 Nov;55(11):967–8.
8. Laurent TC, Fraser JR. Hyaluronan. Faseb J 1992 Apr; 6(7):2397–404.
9. Altman RD. Status of hyaluronan supplementation therapy in osteoarthritis. Curr Rheumatol Rep 2003 Feb;5(1):7–14.
10. American College of Rheumatology. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Arthritis Rheum 2000 Sep;43(9):1905–15.
11. Pendleton A, Arden N, Dougados M, Doherty M, Bannwarth B, Bijlsma JW, *et al.* EULAR recommendations for the management of knee osteoarthritis: report of a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis 2000 Dec;59(12):936–44.
12. Genzyme. Synvisc® Package Insert.
13. Theiler R, Bruhlmann P. Overall tolerability and analgesic activity of intra-articular sodium hyaluronate in the treatment of knee osteoarthritis. Curr Med Res Opin 2005 Nov;21(11):1727–33.
14. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988 Dec;15(12):1833–40.
15. Lequesne M, Samson M, Gerard P, Mery C. [Pain-function indices for the follow-up of osteoarthritis of the hip and the knee]. Rev Rhum Mal Osteoartic 1990 Oct 30;57(9(Pt 2)):32S–6S.
16. Strand V, Kelman A. Outcome measures in osteoarthritis: randomized controlled trials. Curr Rheumatol Rep 2004 Feb;6(1):20–30.
17. Pham T, van der Heijde D, Altman RD, Anderson JJ, Bellamy N, Hochberg M, *et al.* OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. Osteoarthritis Cartilage 2004 May;12(5):389–99.
18. Ehrich EW, Davies GM, Watson DJ, Bolognese JA, Seidenberg BC, Bellamy N. Minimal perceptible clinical improvement with the Western Ontario and McMaster Universities osteoarthritis index questionnaire and global assessments in patients with osteoarthritis. J Rheumatol 2000 Nov;27(11):2635–41.
19. Angst F, Aeschlimann A, Michel BA, Stucki G. Minimal clinically important rehabilitation effects in patients with osteoarthritis of the lower extremities. J Rheumatol 2002 Jan;29(1):131–8.
20. Bijlsma JW. Patient centred outcomes in osteoarthritis. Ann Rheum Dis 2005 Jan;64(1):1–2.
21. Tubach F, Ravaud P, Baron G, Falissard B, Logeart I, Bellamy N, *et al.* Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. Ann Rheum Dis 2005 Jan;64(1):29–33.
22. Kirchner M, Marshall D. A double-blind randomized controlled trial comparing alternate forms of high molecular weight hyaluronan for the treatment of osteoarthritis of the knee. Osteoarthritis Cartilage 2006 Feb;14(2):154–62.
23. Reichenbach S, Blank S, Rutjes AWS, Shang A, King EA, Dieppe PA, *et al.* Hylan versus hyaluronic acid for osteoarthritis of the knee: a systematic review and meta-analysis. Arthritis Rheum 2007 Dec 15;57(8):1410–8.