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# Viscosupplementation for the treatment of osteoarthritis of the knee (Review)

Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G



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[Intervention Review]

# Viscosupplementation for the treatment of osteoarthritis of the knee

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**Editorial group:** Cochrane Musculoskeletal Group.

**Publication status and date:** Unchanged, published in Issue 1, 2006.

**Citation:** Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. *The Cochrane Database of Systematic Reviews* 2005, Issue 2. Art. No.: CD005321. DOI: 10.1002/14651858.CD005321.

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## ABSTRACT

### Background

Osteoarthritis (OA) is the most prevalent chronic joint disorder worldwide and is associated with significant pain and disability.

### Objectives

To assess the effects of viscosupplementation in the treatment of OA of the knee. The products were hyaluronan and hylan derivatives (Adant, Arthrum H, Artz (Artzal, Supartz), BioHy (Arthrease), Durolane, Fermatron, Go-On, Hyalgan, Hylan G-F 20 (Synvisc Hylan G-F 20), NRD-101, Orthovisc, Ostenil, Replasin, SLM-10, Suplasyn, Synject and Zeel compositum).

### Search strategy

MEDLINE, EMBASE, PREMEDLINE, Current Contents up to July 2003, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched. Specialised journals and reference lists of identified randomised controlled trials (RCTs) and pertinent review articles up to April 2004 were handsearched.

### Selection criteria

RCTs of viscosupplementation for the treatment of people with a diagnosis of OA of the knee were eligible. Single and double-blinded studies, placebo-based and comparative studies were eligible. At least one of the four OMERACT III core set outcome measures had to be reported (Bellamy 1997).

### Data collection and analysis

Each trial was assessed independently by two reviewers (NB, JC) for its methodological quality using a validated tool. All data were extracted by one reviewer (JC) and verified by a second reviewer (VR). Continuous outcome measures were analysed as weighted mean differences (WMD) with 95% confidence intervals (CI). Dichotomous outcomes were analyzed by relative risk (RR).

### Main results

Sixty-three trials with a median quality score of 3 (range 1 to 5) were identified. Follow-up periods varied between day of last injection and one year. Thirty-seven trials included comparisons of hyaluronan/hylan and placebo, nine trials included comparisons of intra-articular (IA) corticosteroids, and five trials included comparisons of nonsteroidal anti-inflammatory drugs (NSAIDs). The pooled analyses of the effects of viscosupplements against 'placebo' controls generally supported the efficacy of this class of intervention. In these same analyses, differential efficacy effects were observed for different products on different variables and at different timepoints.

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**Viscosupplementation for the treatment of osteoarthritis of the knee (Review)**

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Of note is the 5 to 13 week post injection period which showed a percent improvement from baseline of 11 to 54% for pain and 9 to 15% for function. In general, comparable efficacy was noted against NSAIDs and longer-term benefits were noted in comparisons against IA corticosteroids. In general, few adverse events were reported in the hyaluronan/hylan trials included in these analyses.

### Authors' conclusions

Based on the aforementioned analyses, viscosupplementation is an effective treatment for OA of the knee with beneficial effects: on pain, function and patient global assessment; and at different post injection periods but especially at the 5 to 13 week post injection period. It is of note that based on non-randomised groups, the magnitude of the clinical effect, as expressed by the WMD and standardised mean difference (SMD) from the RevMan 4.1 output, is different for different products, comparisons, timepoints, variables and trial designs. However, there are few randomised head-to-head comparisons of different viscosupplements and readers should be cautious, therefore, in drawing conclusions regarding the relative value of different products. The clinical effect for some products, against placebo, on some variables at some timepoints is in the moderate to large effect-size range. Readers should refer to relevant tables to review specific detail given the heterogeneity in effects across the product class and some discrepancies observed between the RevMan 4.1 analyses and the original publications. Overall, the analyses performed are positive for the HA class and particularly positive for some products with respect to certain variables and timepoints, such as pain on weight bearing at 5 to 13 weeks postinjection.

In general, sample-size restrictions preclude any definitive comment on the safety of the HA class of products; however, within the constraints of the trial designs employed no major safety issues were detected. In some analyses viscosupplements were comparable in efficacy to systemic forms of active intervention, with more local reactions but fewer systemic adverse events.

In other analyses HA products had more prolonged effects than IA corticosteroids. Overall, the aforementioned analyses support the use of the HA class of products in the treatment of knee OA.

## PLAIN LANGUAGE SUMMARY

Osteoarthritis (OA) is the most common form of chronic arthritis worldwide. Hyaluronan and hylan (HA) products provide opportunity to treat OA in individual knee joints. To evaluate the efficacy, effectiveness and safety of HA products, in knee OA, we have conducted a systematic review using Cochrane methodology. The analyses support the contention that the HA class of products is superior to placebo. There is considerable between-product, between-variable and time-dependent variability in the clinical response. The clinical effect for some products against placebo on some variables at some time points is in the moderate to large effect size range. In general, sample size restrictions preclude any definitive comment on the safety of the HA class of products, however, within the constraints of the trial designs employed, no major safety issues were detected. The analyses suggest that viscosupplements are comparable in efficacy to systemic forms of active intervention, with more local reactions but fewer systemic adverse events, and that HA products have more prolonged effects than IA corticosteroids. Overall, the aforementioned analyses support the use of the HA class of products in the treatment of knee OA.

## BACKGROUND

Of all of the specific joint diseases osteoarthritis (OA) is the most frequent cause of rheumatic complaints. OA of the knee is a major cause of pain and disability. Guidelines for the management of knee OA have been reported in four publications ([ACR Guidelines 2000](#); [Jordan 2003](#); [Pendleton 2000](#); [Walker-Bone 2000](#)).

Viscosupplementation is an intra-articular (IA) therapeutic modality for the treatment of knee OA based on the physiologic importance of hyaluronan in synovial joints. Its therapeutic goal is

to restore the viscoelasticity of synovial hyaluronan, decrease pain, improve mobility and restore the natural protective functions of hyaluronan in the joint. The short-term mode of action of viscosupplementation is believed to be based on the pain-relieving effect of the elastoviscous fluid in the affected joint. In the long term, the restoration of joint mobility due to relief of pain is thought to trigger a sequence of events which restores the trans-synovial flow and subsequently the metabolic and rheological homeostases of the joint.

The principle of viscosupplementation was pioneered by Balazs and coworkers (Balazs 1982; Denlinger 1998; Peyron 1974; Weiss 1999). There are now several different formulations of viscosupplements (hyaluronan and hylan) produced by different manufacturers and of widely different molecular weights. This difference in molecular weight (MW) is thought to be of importance with respect to the volume/amount and number of injections, the residue time in the joint and biologic effects. Aviad and Houpt found no correlation between MW and efficacy (Aviad 1994). Lo et al. reported that at a higher MW HA may have greater effects, but the heterogeneity of the trials used in this meta-analysis limited this conclusion (Lo 2003). Based on results observed in vitro, Maneiro et al. concluded that HA products were different due to differences in biological activity that resulted from the difference in MW (Maneiro 2004).

Viscosupplementation as treatment for knee OA has been the focus of several review publications (Aggarwal 2004; Altman 2003; Altman 2000; Ayrar 2001; Brandt 2000; Collange 1999; Dougados 2000; Espallargues 2003; Haraoui 2002; Hochberg 2000; Kelly 2003; Khanuja 2003; Kirwan 1997; Kirwan 2001; Lussier 1996; Maheu 1994; Maheu 1995; Maheu 2003; Marshall 2000; MSAC 2003; Moreland 2003; Moskowitz 2000; Peyron 1993; Uebelhart 1999; Watterson 2000). Two meta-analyses have been reported (Lo 2003; Wang 2004). A third meta-analysis has been reported only as an abstract (Choi 1999). These publications employ different methodologies and have shown conflicting results. The review by Espallargues and Pons concluded that a hylan (Hylan G-F 20) was a safe and well-tolerated therapy in the short term, but they recommended further work on the effect of multiple courses of hylan (Espallargues 2003). The Medical Services Advisory Committee (Australia) recommended that public funding should not support viscosupplementation for the treatment of knee OA, in March 2003 (MSAC 2003). Choi et al. concluded from their meta-analysis of seven placebo-controlled trials that viscosupplementation significantly reduced pain in patients with knee OA, for a period of 5 to 10 weeks after the last injection (Choi 1999). Lo et al.'s meta-analysis of 18 trials of HA against IA placebo indicated that HA had a small effect when compared to placebo (Lo 2003; Bernstein 2004; Hou 2004).

Given this diversity of opinion there is, therefore, a rational basis for performing a Cochrane review of viscosupplementation in knee OA.

## OBJECTIVES

To assess the effects of viscosupplementation in the treatment of OA of the knee. The products were hyaluronan and hylan derivatives of widely different molecular weights and formulation (Adant, Arthrum H, Artz (Artzal, Supartz), BioHy (Arthrease), Durolane, Fermatron, Go-On, Hyalgan, Hylan G-F 20 (Synvisc

Hylan G-F 20), NRD-101, Orthovisc, Ostenil, Replasin, SLM-10, Suplasyn, Synject and Zeel compositum).

The systematic review of the literature was based on The Cochrane Collaboration methodology and RevMan 4.1. Data were summarised, when possible, using meta-analytic techniques following the Cochrane methodology.

## RESULTS

Results are presented by product. An independent evaluation by product is recommended rather than a by-class meta-analysis since these products differ in their MW, concentration, treatment schedules, and mode of production (Altman 2003; Blue Cross 1998). At the end of the product-by-product evaluation there is a section based on the by-class (pooled) results. Readers are cautioned to note the many differences in study design while reading the results of this analysis. The Discussion section addresses some of these issues.

### Product - Adant

#### Description of studies

One RCT was included: a comparison of Adant and another hyaluronan (Roman 2000).

Roman et al. reported a six-month, parallel-group, blind RCT performed at a single centre comparing five weekly injections of Adant (Treatment: MW 900,000 D biotechnically obtained) to five weekly injections of Hyalgan (Control: MW 800,000 D obtained from rooster crest) in 49 patients with OA of the knee (Roman 2000). The authors concluded that the efficacy of Adant was greater than with Hyalgan at three months after treatment. They reported that maximum improvement was seen at five weeks with response decreasing over time resulting in almost 75% of patients reporting only 'fair' or 'no' clinical response at six months postinjection. Pain at the injection site was almost twice as great with Adant. The Jadad score for this study was 3 out of a maximum of 5; specific details of blinding and randomisation were not reported in the publication. The randomisation allocation was 1.6:1 (e.g. n = 30:19) in favour of the Adant group. Allocation concealment was unclear (i.e. not reported).

In this RCT several design issues were noted: 1) one and a half times as many patients were randomised to the Adant group compared to the Hyalgan group; 2) eighty-four percent of the patients were female; 3) no exclusion criteria were reported in the Materials and Methods section of the publication; 4) details regarding presence or absence of effusion, uni- or bilateral disease, OA diagnosis criteria and disease duration were not published; 5) efficacy was assessed only by the patient subjective assessment, the details of which were not published. However, injection technique was standardised and the effect of concomitant analgesic and/or

anti-inflammatory drugs was considered. Although the authors attributed the 'greater efficacy' with Adant at three months and the higher incidence of pain at the injection site to its greater viscosity and volume, there were no statistically significant differences between the products in either the efficacy or safety profiles.

Three trials were excluded: Couceiro 2003; Guerrero 1999; Guerrero 1999a. One trial is awaiting assessment: Blanco Garcia 2004.

Adant versus placebo: no trials included.

Adant versus corticosteroid: no trials included.

Adant versus NSAID: no trials included.

Adant versus other hyaluronan

#### *Efficacy*

The only efficacy outcome measure extracted from this trial (Roman 2000) was patient global assessment (e.g. number of patients excellent or good). At each of the three timepoints there were no statistically significant differences between the two groups. At 1 to 4 weeks postinjection, 43% of the Adant patients and 37% of the Hyalgan patients were excellent or good (RR 1.18; 95% CI 0.57 to 2.41, P value 0.7). At 5 to 13 weeks post injection, 50% of the Adant patients and 21% of the Hyalgan patients were excellent or good (RR 2.38; 95% CI 0.93 to 6.09, P value 0.07). At 14 to 26 weeks postinjection, 33% of the Adant patients and 16% of the Hyalgan patients were excellent or good (RR 2.11; 95% CI 0.66 to 6.70, P value 0.2).

The RevMan analysis differed from the publication analysis. The publication reported a significant difference in favour of Adant compared to Hyalgan at three months in the number of patients rating the improvement as excellent or good (P value < 0.05).

#### *Safety*

The number of patients reporting painful injections was almost twice as high in the Adant group (6/30, 20%) versus Hyalgan (2/19, 11%). This difference was not statistically significant. The RR of having a painful injection was 1.90 (95% CI 0.43 to 8.46, P value 0.4) at 1 to 4 weeks postinjection.

The RevMan analysis differed from the publication analysis. The publication reported a significant difference in favour of Hyalgan compared to Adant in the number of patients with painful infiltrations (P value < 0.001).

#### **Product - Arthrum H**

##### *Description of studies*

One trial was excluded: Bardin 2004.

#### **Product - Artz (Artzal,Supartz)**

##### *Description of studies*

Nine trials of Artz (Seikagaku Corporation) have been included. Seven included comparisons of Artz against placebo (Day 2004; Karlsson 2002; Lohmander 1996; Puhl 1993; Shichikawa 1983a; Shichikawa 1983b; Wu 1997) and three included comparisons of Artz against three other hyaluronan/hylan products: Hylan G-F 20 (Karlsson 2002), NRD-101 (Tsukamoto 1995 (abstract); Yamamoto 1994) and SLM-10 (Kawabata 1993). Readers are directed to the Hylan G-F 20, NRD-101 and SLM-10 sections for results based on these products. With respect to methodological quality, the average Jadad score was 4.3 out of 5 with three trials scoring 5 (Day 2004; Karlsson 2002; Puhl 1993), three trials scoring 4 (Lohmander 1996; Shichikawa 1983a; Shichikawa 1983b) and one trial scoring 3 (Wu 1997). Allocation concealment was adequate in three trials (Puhl 1993; Shichikawa 1983a; Shichikawa 1983b) and unclear (not reported) in four trials (Day 2004; Karlsson 2002; Lohmander 1996; Wu 1997). Two randomised, double-blind, placebo-controlled, multicentre trials have been completed: one in France (Bourgeois (Artz)) and one in the United Kingdom (Byrd (Artz)) but have only been published as part of the Food and Drug Administration Pre-Market Approval Package (Number P980044, Docket #01M-0342). Fifteen studies, reported between 1982 and 1999, were excluded (Arizono 1997; Dahlberg 1994; Fujii 1994; Hashimoto 1992; Honma 1989; Igarashi 1983; Iseki 1983; Iwasaki 1993; Kawakami 1993; Namiki 1982; Oshima 1983; Shibata 1993; Suzu 1990; Takeuchi 1993; Yoh 1989).

Day et al. reported an 18-week, placebo-controlled, double-blind RCT performed at 17 centres in Australia comparing five weekly injections of Artz to five weekly injections of saline in 240 patients with OA of the knee (Day 2001; Day 2004). A significant difference between the two comparison groups for each outcome measure evaluated was reported. A total of 482 adverse events were reported but only 81 were possibly, probably or definitely related to study medication (Artz n = 50, saline n = 31). Tolerability was reported as being excellent since approximately 95% of patients completed the full treatment schedule. Injection site pain and inflammation, that was mild and of short duration, was the most frequent adverse event and occurred in approximately 10% of patients.

In the Discussion of the Day RCT (Day 2004) the authors suggested that their positive result, in comparison to the Lohmander RCT (Lohmander 1996), may have been due to the inclusion criteria. Specifically, only patients with unilateral, mild-to-moderate disease, with no patellofemoral OA or clinically large effusions, and who were not morbidly obese were entered into the trial. Both lateral and medial approaches were utilised for IA injections in this trial. However, the same approach was used for all injections in one patient.

Karlsson et al. reported a one-year, placebo-controlled, parallel-group, double-blind RCT performed at 19 centres in Sweden comparing three weekly injections of Artzal (Astra Lakemedel) to three

weekly injections of Hylan G-F 20 (Roche) and three weekly injections of placebo (phosphate-buffered saline solution) in 210 patients with OA of the knee (Karlsson 2002). All patients, regardless of treatment, showed clinical improvement during the first 26 weeks of the treatment. Neither hyaluronan/hylan product produced a longer duration of clinical benefit than placebo. However, a significantly longer duration of clinical benefit was achieved when data from the two hyaluronan products were pooled. No serious adverse events due to the treatments were reported. Treatment was discontinued due to adverse events in similar numbers of patients in each of the treatment groups. In this review the Karlsson 2002a reference refers to the Artzal versus placebo comparison (Karlsson 2002a (AvP)), the Karlsson 2002b reference refers to the Hylan G-F 20 versus placebo comparison (Karlsson 2002b (SvP)) and the Karlsson 2002c reference refers to the Artzal versus Hylan G-F 20 comparison (Karlsson 2002c (AvS)).

The Karlsson RCT (Karlsson 2002) inclusion criteria were based on the Lohmander RCT (Lohmander 1996): patients aged 60 years or above, with a baseline Lequesne Index above 10, and radiographically verified OA as Ahlback grade I-II. A Lequesne score of 8 to 10 points represents severe handicap. Surgery is indicated for scores of 10 to 12 points and higher. An Ahlback Stage I is classified as narrowing of the joint space (with or without subchondral sclerosis); joint space narrowing is defined by a space inferior to 3 mm or inferior to the half of the space in the other compartment (or in the homologous compartment of the other knee). An Ahlback Stage II is classified as "obliteration of the joint space" (Karlsson 2003d, Magilavy 2003).

Lohmander et al. reported a 20-week, placebo-controlled, double-blind RCT performed at eight centres in Denmark, Finland, Norway and Sweden comparing five weekly injections of Artzal to five weekly injections of saline in 240 patients with OA of the knee (Lohmander 1996). Prior to code break, patient data were stratified by age (40 to 60 y, 61 to 75 y) and Lequesne algofunctional index score (4 to 10, greater than 10). Although both groups improved from baseline at the end of the study there was no difference between the two groups. However, when the two stratification variables were utilised in the analyses Artzal was found to be more effective than saline in older (greater than 60 y) patients with more severe symptoms (Lequesne greater or equal to 10). Although no serious adverse events were reported seven patients (Artz n = 2, saline n = 5) withdrew from the trial due to adverse events. Severity of injection-site swelling was significantly greater in the Artz group. Dr. S. Lohmander kindly provided unpublished data from the trial for this review.

The well-designed Lohmander RCT (Lohmander 1996) had a pretrial meeting to standardize the injection procedure and assessment procedures. The discussion of this report summarises some of the difficulties in interpreting trials of HA. This is one of the few trials which stratified patients based on baseline age and Lequesne Index scores.

Puhl et al. reported an 18-week, parallel-group, double-blind RCT performed at 25 centres in Germany comparing five weekly injections of Artz to five weekly injections of suspending vehicle (0.25 mg of sodium hyaluronate per 2.5 ml) in 209 patients with OA of the knee (Puhl 1993). A statistically significant difference was reported in the Lequesne Index (the primary outcome measure) in favour of the Artz group from the third injection to the end of the trial. In a subsequent publication (Puhl 1997) a subgroup analysis confirmed the findings of the Lohmander et al. trial (Lohmander 1996) in that patients older than 60 y with a Lequesne score greater than 10 were the most likely to benefit from treatment. Local reactions at the injection site were reported in similar numbers in both groups (Artz n = 4, vehicle n = 5) and all were of short duration and minor severity.

This well-designed trial excluded patients with excessive (greater than 100 ml) joint effusion (Puhl 1993).

Shichikawa et al. reported a five-week, parallel-group, double-blind RCT performed at 38 centres in Japan comparing five weekly injections of Artz (1.0% sodium hyaluronate) plus one placebo tablet (lactose coated) administered three times daily after every meal to five weekly injections of suspending vehicle (0.25 mg, 0.01% sodium hyaluronate) plus one placebo tablet (lactose coated) administered three times daily after every meal in 228 patients with OA of the knee (Shichikawa 1983a). Statistically significant differences in favour of Artz compared to control were reported for final effectiveness and usefulness. No systemic adverse events were reported. Local reactions were reported by four patients in the control group and one patient in the Artz group. One patient in the control group had treatment discontinued due to side effects.

The following design issues were noted: 1) follow-up was limited to one week after final injection; 2) patients with severe joint space narrowing and marked retention of synovial effusion were excluded; 3) patients recorded in symptom diaries at 10:00 daily; 4) authors attributed some of the local pain to injection procedure (Shichikawa 1983a).

Shichikawa et al. reported a five-week, parallel-group, double-blind RCT performed at 16 centres in Japan comparing five weekly injections of Artz (0.5% sodium hyaluronate) plus two placebo tablets (sugar coated lactose) administered three times daily to five weekly injections of suspending vehicle (0.01% sodium hyaluronate solution) plus two placebo tablets (sugar coated lactose) administered three times daily in 107 patients with OA of the knee (Shichikawa 1983b). Statistically significant differences in favour of Artz compared to control were reported for final effectiveness, pain in motion and usefulness. Treatment was discontinued in three patients (Artz n = 1, control n = 2) due to adverse events.

The following design issues were noted: 1) follow-up was limited to one week after final injection; 2) patients with moderate-to-



severe joint space narrowing and synovial effusion were excluded (Shichikawa 1983b).

Wu et al. reported a 26-week, placebo-controlled, double-blind RCT performed at a single centre in China comparing five weekly injections of Artz to five weekly injections of the solvent for Artz in 90 patients with OA of the knee (Wu 1997). Statistically significant efficacy was reported for Artz compared to placebo beginning one week after the fifth injection and lasting up to three months. During the six-month trial no adverse events were reported.

The following design issue was noted: 1) patients with marked joint space narrowing and large amounts of synovial effusion were excluded (Wu 1997).

Artz versus placebo

### *Efficacy*

With respect to the placebo comparisons at 1 to 4 weeks postinjection, there were no statistically significant differences between Artz and placebo for the following outcome measures: pain (0 to 3 scale) (WMD -0.07; 95% CI -0.26 to 0.12, P value 0.5) (Shichikawa 1983b); pain (0 to 100 mm VAS) (WMD 0.22; 95% CI -3.89 to 4.34, P value 0.9) (Karlsson 2002a (AvP); Lohmander 1996; Puhl 1993); Lequesne Index (0 to 24) (WMD 0.19; 95% CI -0.77 to 1.15, P value 0.7) (Puhl 1993); range of motion (degrees) (WMD 3.05; 95% CI -2.49 to 8.59, P value 0.3) (Shichikawa 1983b). There was a statistically significant difference in favour of Artz for patient global assessment (RR 1.17; 95% CI 1.04 to 1.32, P value 0.008) (Lohmander 1996; Shichikawa 1983a; Shichikawa 1983b). With the exception of the Lohmander trial (Lohmander 1996), the NNT for patient global assessment was between 5 and 11 patients.

The RevMan analysis differed from the Puhl et al. publication analysis (Puhl 1993). The publication reported a statistically significant difference in favour of Artz compared to placebo for the Lequesne Index at 1 to 4 weeks postinjection (P value 0.043) compared to the RevMan analysis (P value 0.7).

At 5 to 13 weeks postinjection, there were no statistically significant differences between Artz and placebo for: WOMAC Pain (0 to 20) (WMD -0.77; 95% CI -1.61 to 0.07, P value 0.07) (Day 2004); WOMAC Function (0 to 68) (WMD -2.44; 95% CI -5.33 to 0.45, P value 0.10) (Day 2004); Lequesne Index (WMD -0.36; 95% CI -1.30 to 0.58, P value 0.5) (Puhl 1993); and patient global assessment (RR 1.07; 95% CI 0.95 to 1.21; P value 0.3) (Lohmander 1996; Puhl 1993). However, Artz was significantly better than placebo for pain (100 mm VAS) (WMD -5.00; 95% CI -9.18 to -0.83, P value 0.02) (Karlsson 2002a (AvP); Lohmander 1996; Puhl 1993). Artz was between 5 and 20% more effective than saline in relieving pain at 5 to 13 weeks postinjection.

The RevMan analysis differed from the Day et al. publication analysis (Day 2004). The publication reported statistically significant

between-group differences in WOMAC pain (P value 0.045) and WOMAC stiffness (P value 0.024) in favour of the Artz group compared to the placebo group, whereas the RevMan analysis did not detect a significant difference. The RevMan analysis differed from the Puhl et al. publication analysis (Puhl 1993). The publication reported a statistically significant difference in favour of Artz compared to placebo for the Lequesne Index at 5 to 13 weeks post injection (P value 0.0053) compared to the RevMan analysis (P value 0.5).

At 14 to 26 weeks postinjection, no statistically significant differences were found between Artz and placebo for: the Lequesne Index (WMD 0.51; 95% CI -0.43 to 1.45, P value 0.3) (Karlsson 2002a (AvP); Lohmander 1996); pain (100 mm VAS) (WMD -0.42; 95% CI -6.90 to 6.06, P value 0.9) (Karlsson 2002a (AvP); Lohmander 1996). However, more patients improved in the Artz than placebo group for patient global assessment (RR 1.31; 95% CI 1.00 to 1.72, P value 0.05) (Lohmander 1996). The number of clinical failures was higher in the saline group (11%) versus Artzal (2%) (RR 0.21; 95% CI 0.04 to 0.98; P value 0.0)5 (Karlsson 2002a (AvP)).

At 45 to 52 weeks postinjection there was no statistically significant difference in the number of clinical failures (RR 0.73; 95% CI 0.49 to 1.08; P value 0.12) or in the number of survivors (i.e. patients not requiring additional treatment for study knee) (RR 1.30; 95% CI 0.86 to 1.97, P value 0.2) (Karlsson 2002a (AvP)).

### *Safety*

There was no statistically significant difference in the number of withdrawals, overall, at 1 to 4 weeks postinjection (RR 1.03; 95% CI 0.47 to 2.22, P value 0.9) (Shichikawa 1983a; Shichikawa 1983b); at 5 to 13 weeks postinjection (RR 1.06; 95% CI 0.64 to 1.76, P value 0.8) (Day 2004; Puhl 1993); and at 14 to 26 weeks postinjection (RR 0.60; 95% CI 0.15 to 2.45, P value 0.5) (Lohmander 1996). There was no statistically significant difference in the number of withdrawals due to adverse events at 1 to 4 weeks postinjection (RR 0.26; 95% CI 0.03 to 2.28, P value 0.2) (Shichikawa 1983a; Shichikawa 1983b); at 5 to 13 weeks postinjection (RR 1.06; 95% CI 0.07 to 16.81, P value 1) (Day 2004); at 14 to 26 weeks postinjection (RR 0.40; 95% CI 0.08 to 2.02, P value 0.3) (Lohmander 1996); and at 45 to 52 weeks postinjection (RR 0.73; 95% CI 0.11 to 5.07, P value 0.8) (Karlsson 2002a (AvP)). There were no statistically significant differences in the number of participants withdrawn overall at 5 to 13 weeks postinjection (RR 0.40; 95% CI 0.16 to 0.98, P value 0.05) or at 14 to 26 weeks postinjection (RR 0.93; 95% CI 0.65 to 1.34, P value 0.7). The number of adverse events probably or possibly related to treatment was statistically greater in the Artz group compared to the saline group at 5 to 13 weeks postinjection (RR 1.59; 95% CI 1.12 to 2.26, P value 0.009) (Day 2004; Puhl 1993) but there was no difference at 45 to 52 weeks postinjection (RR 0.53; 95% CI 0.08 to 3.72, P value 0.5) (Karlsson 2002a (AvP)). There was no

statistically significant difference in the number of patients with local adverse events in whom the study treatment was continued at 1 to 4 weeks postinjection (RR 0.25; 95% CI 0.03 to 2.18, P value 0.2) (Shichikawa 1983a). In Karlsson's trial (Karlsson 2002a (AvP)) at 45 to 52 weeks postinjection there was no statistically significant difference in the number of patients reporting adverse events (RR 1.22; 95% CI 0.91 to 1.64; P value 0.18) or in the number of serious adverse events (RR 0.58; 95% CI 0.27 to 1.26, P value 0.17). In Wu's study (Wu 1997) no side effects developed over a six-month period.

Artz versus corticosteroid: No trials included.

Artz versus NSAID: No trials included.

Artz versus other hyaluronan

One RCT included was a comparison of Artzal and Hylan G-F 20 (Karlsson 2002c (AvS)). Readers are directed to the NRD-101 and SLM-10 sections for results based on comparisons of Artz and these products.

### *Efficacy*

With respect to the Artzal comparison against Hylan G-F 20 (Karlsson 2002c (AvS)), there were no statistically significant differences between the two products in pain on weight bearing (0 to 100 mm VAS) at the three assessment times: 1 to 4 weeks postinjection (WMD -1.00; 95% CI -8.41 to 6.41, P value 0.8); 5 to 13 weeks postinjection (WMD 1.00; 95% CI -7.83 to 9.83, P value 0.8); 14 to 26 weeks postinjection (WMD 5.00; 95% CI -4.98 to 14.98, P value 0.3). There was no statistically significant difference between the two products in the Lequesne Index at 14 to 26 weeks postinjection (WMD 1.00; 95% CI -0.37 to 2.37, P value 0.15). There were no statistically significant differences between the two products in the number of clinical failures at both 14 to 26 weeks postinjection (RR 0.32; 95% CI 0.07 to 1.54, P value 0.15) and 45 to 52 weeks postinjection (RR 0.86; 95% CI 0.58 to 1.28, P value 0.5) or in the number of survivors (i.e. patients not requiring additional treatment to study knee) at 45 to 52 weeks postinjection (RR 0.98; 95% CI 0.70 to 1.37, P value 0.9).

### *Safety*

There were no statistically significant differences between Artzal and Hylan G-F 20 at 45 to 52 weeks postinjection in the number of patients withdrawn due to adverse events (RR 1.91; 95% CI 0.18 to 20.70, P value =0.6), the number of adverse events related to treatment (RR 1.23; 95% CI 0.11 to 13.40, P value 0.9), or the number of patients reporting adverse events (RR 1.19; 95% CI 0.92 to 1.56, P value 0.19).

### **Product - Bioby (Arthrease)**

#### *Description of studies*

Two trials of BioHy have been included. One trial included a comparison against placebo (Tamir 2001) and the other trial included a comparison against Hylan G-F 20 (Thompson 2002).

Tamir et al. reported a 20-week, placebo-controlled, single-blind, open-label RCT performed at a single orthopaedic clinic in Turkey comparing three weekly injections of BioHy (Bio-Technology General, manufactured by bacterial fermentation of the non-hemolytic strain of *Streptococcus zooepidemicus*) to three weekly injections of phosphate-buffered saline in 49 patients with OA of the knee (Tamir 2001). The authors reported that this feasibility study was not sufficiently powered to detect between-group differences. However, they found a 'favourable trend' for BioHy in decreasing pain. With respect to safety, they reported that BioHy was well tolerated and no HA-related adverse events were found. With respect to methodological quality, it scored 3 out of 5 on the Jadad scale; specific details of randomisation were not reported in the publication. Allocation concealment was unclear.

In this RCT, several design issues were noted: 1) patients with more than 15 ml of aspirated synovial fluid (SF) were excluded; 2) concurrent and escape medication such as paracetamol and NSAIDs were permitted throughout the trial; 3) although the AAOS MODEMS arthritic module was utilised for assessing pain, stiffness and physical function, all the pain variables were assessed and scored by the investigator and not by the patient; 4) in reporting the results the authors did not provide baseline means, rather they reported change in mean categorical scores without any measure of dispersion excluding this trial from the analysis; 5) the trial was found to be under powered.

The Thompson et al. trial has been published as an abstract (Thompson 2002). Thompson et al. reported a 12-week, parallel-group, double-blind, multicentre RCT performed in Germany comparing three weekly injections of Arthrease to three weekly injections of Hylan G-F 20 in 321 patients with OA of the knee. The authors reported that both groups had a statistically significant reduction in pain compared to baseline but there was no between-group difference. With respect to safety, statistically significantly more cases of joint effusion were reported in the Hylan G-F 20 group (n = 13) compared to the Arthrease group (n = 1). With respect to methodological quality, it scored 2 out of 5 on the Jadad scale; specific details of randomisation and blinding were not reported in the abstract. Allocation concealment was unclear. Biotechnology General (Israel) Ltd. kindly provided the poster of this trial that was presented at the OARSI 2002 Congress as well as an Excel file of the WOMAC pain data.

BioHy versus placebo

### *Efficacy*

No efficacy results have been extracted from this trial (Tamir 2001). Pain and stiffness results were reported as change but neither baseline values nor measures of dispersion were reported.

### *Safety*

There were no statistically significant differences in the safety profile of BioHy and placebo. There were a similar number of withdrawals overall in both groups: BioHy 12% and placebo 17% (RR 0.72; 95% CI 0.18 to 2.89, P value 0.6). The difference in the percentage of patients in the BioHy group (72%) who reported knee pain immediately after the injection, which was related to the injection procedure, was not significantly different from that in the placebo group (46%) (RR 1.57; 95% CI 0.95 to 2.59, P value 0.08). No systemic adverse events were reported in either group.

BioHy versus corticosteroid: no trials included.

BioHy versus NSAID: no trials included.

BioHy versus other hyaluronan

One RCT was included comparing BioHy and Hylan G-F 20 (Thompson 2002).

### *Efficacy*

There were no statistically significant differences in the WOMAC pain subscale either at 1 to 4 weeks postinjection (WMD -3.70; 95% CI -8.13 to 0.73, P value 0.10) or at 5 to 13 weeks postinjection (WMD -3.80; 95% CI -8.10 to 0.50, P value 0.08). There was no statistically significant difference in the number of patients that assessed the treatment as 'very satisfied or satisfied' (Arthrease 80%, Hylan G-F 20 77%) (RR 1.04; 95% CI 0.93 to 1.16, P value 0.5) (Thompson 2002).

The RevMan analysis differed from the publication analysis. The publication reported a statistically significant difference in favour of BioHy compared to Hylan G-F 20 for the number of patients that assessed the treatment as 'very satisfied or satisfied' (P value 0.03) whereas RevMan detected no difference.

### *Safety*

There was no statistically significant difference in the number of patients reporting adverse events (Arthrease 34%, Hylan G-F 20 40%) (RR 0.84; 95% CI 0.63 to 1.11, P value 0.2). There was a statistically significant difference in the number of patients with joint effusion (Arthrease 0.6%, Hylan G-F 20 8%) (RR 0.08; 95% CI 0.01 to 0.58, P value 0.01). The RevMan P value for this last comparison differed from the publication P value of 0.0015.

### **Product - Durolane (NASHA - non-animal stabilized hyaluronic acid)**

#### *Description of studies*

One trial is awaiting assessment: Sinha 2003.

One trial was excluded: Akermark 2004.

### **Product - Fermathron**

#### *Description of studies*

One RCT was included comparing Fermathron to another hyaluronan (McDonald 2000).

McDonald et al. reported a six-month, parallel-group, double-blind RCT performed at 12 centres in Germany comparing five weekly injections of Fermathron (Fermentech Medical Ltd., manufactured by bacterial fermentation) to five weekly injections of Hyalart (Fidia SpA, obtained from rooster combs) in 256 patients with OA of the knee (McDonald 2000). The authors reported that the products were similar in efficacy and that both were well tolerated. With respect to methodological quality, the trial scored 5 out of 5 on the Jadad scale achieving points for both randomisation and blinding details. Allocation concealment was adequate.

This was a well-designed and reported 'non-inferiority' study of two HA products. The importance of escape medication was addressed in the study design. Patients kept a daily diary which was declared as the secondary performance variable. Moreover, the authors investigated the correlation between the route of injection (knee straight or bent, medial or lateral approach) with the local adverse event incident rate. They found that the lowest risk was associated with a lateral approach to a straight knee (Jones 1993). Source of HA (i.e. bacterial fermentation versus rooster combs) did not affect the results.

One trial is awaiting assessment: Sinha 2003.

Fermathron versus placebo: no trials included.

Fermathron versus corticosteroid: no trials included.

Fermathron versus NSAID: no trials included.

Fermathron versus other hyaluronan

### *Efficacy*

The three efficacy outcome measures extracted from this trial were pain (0 to 100 mm VAS), the Lequesne Index (0 to 24), and patient global assessment (very good, good, average, poor, very poor). No statistically significant differences were found between the two products: for pain (WMD 2.30; 95% CI -2.84 to 7.44, P value 0.4) at 1 to 4 weeks postinjection and (WMD 0.80; 95% CI -4.51 to 6.11, P value 0.8) at 5 to 13 weeks postinjection. Results for the Lequesne Index showed a similar pattern (WMD 0.46; 95% CI -0.59 to 1.51, P value 0.4) at 1 to 4 weeks postinjection and (WMD 0.55; 95% CI -0.48 to 1.58, P value 0.3) at 5 to 13 weeks postinjection. No statistically significant difference was found in the number of responders (RR 0.96; 95% CI 0.82 to 1.13, P value 0.6) at 5 to 13 weeks postinjection with 72.4% in the Hyalart group and 69.6% in the Fermathron group that reported feeling better or much better.

### *Safety*

There was no statistically significant difference in the number of related adverse events (Fermathron 21% versus Hyalart 14%) (RR 1.47; 95% CI 0.84 to 2.59, P value 0.18).

These results confirmed the results of the publication indicating that the two products were similar in performance and well tolerated.

### **Product - Go-On**

There were no RCTs of Go-On available (correspondence from Rotta Research Laboratorio July 1, 2004).

### **Product - Hyalgan**

#### *Description of studies*

Twenty-eight randomised controlled trials have been included with **Hyalgan** (marketed also as Hyalart and Polyreumin) (Fidia Pharmaceutical Corporation, Italy, derived from rooster combs): 14 included comparisons against placebo (Altman 1998; Bragantini 1987; Bunyaratavej 2001; Carrabba 1995; Corrado 1995; Creamer 1994; Dougados 1993; Formiguera Sala 1995; Grecomoro 1987; Henderson 1994; Huskisson 1999; Jubb 2003; St. J. Dixon 1988; Tsai 2003), one was a comparison against no treatment (Miltner 2002; Schneider 1997), one was a comparison against arthroscopic washout (Forster 2003), three were comparisons against other hyaluronan products (McDonald 2000; Roman 2000; Brown 2003), five were comparisons against corticosteroids (Frizziero 2002; Leardini 1987; Leardini 1991; Pietrogrande 1991, against methylprednisolone acetate; Jones 1995, against triamcinolone acetate), one was a comparison against NSAID (Altman 1998), one was a comparison against a homeopathic preparation (Zeel Compositum) (Nahler 1998) (readers are directed to the Zeel product section), one was a comparison against mucopolysaccharide polysulfuric acid ester (Graf 1993), one was a comparison against conventional therapy (Listrat 1997) and one was a comparison of treatment regimens (Karras 2001). Except for three trials (Brown 2003; Karras 2001; Tsai 2003) which have been published as abstracts the remaining trials have been published as journal articles. In three trials, **Hyalgan** was the control intervention (McDonald 2000; Nahler 1998; Roman 2000). The frequency of injection varied between studies (3, 4 and 5 weekly injections). Considering only the 25 trials in which **Hyalgan** was designated the experimental intervention (i.e. excluding McDonald 2000; Nahler 1998; Roman 2000), with respect to methodological quality the average Jadad score was 2.7 out of 5 with one trial scoring 5 (Henderson 1994), 7 trials scoring 4 (Altman 1998; Bunyaratavej 2001; Frizziero 2002; Huskisson 1999; Jones 1995; Jubb 2003; St. J. Dixon 1988), 5 trials scoring 3 (Carrabba 1995; Corrado 1995; Formiguera Sala 1995; Forster 2003; Grecomoro 1987), 10 trials scoring 2 (Bragantini 1987; Creamer 1994; Dougados 1993; Graf 1993; Karras 2001; Leardini 1987; Leardini 1991; Listrat 1997; Pietrogrande 1991; Tsai 2003) and 2 trials scoring 1 (Brown 2003; Miltner 2002). Again, considering only the 25 trials in which **Hyalgan** was designated the experimental intervention allocation concealment was adequate in two trials (Forster 2003; Frizziero 2002) and unclear (not reported) in 23 trials.

Twenty studies were excluded (Aglas 1997; Carrabba 1992; D'Agnolo 1988; Dahlberg 1994; Frizziero 1993; Frizziero 1997; Frizziero 1998; Grecomoro 1992; Hamburger 2004; Kotz 1999; Mazzocato 1987; Mensitieri 1995; Milini 1989; Pasquali Ronchetti 2001; Pavelka 2002; Pipino 1990; Punzi 1988; Rao 2001; Scali 1995; Sieliweczyk 1997). Two trials are awaiting assessment (Garcia 2004; Stitik 2004).

Altman et al. reported a 26-week, placebo- and naproxen-controlled, double-blind, double-dummy, stratified, parallel-group RCT performed at 15 centres in the United States comparing five weekly injections of **Hyalgan** plus oral placebo twice daily to five weekly injection of saline plus oral placebo or naproxen 500 mg twice daily in 495 patients with OA of the knee (Altman 1998). Only 67% of the patients completed the trial. **Hyalgan** was more efficacious (pain relief and improved function) than placebo and as effective as naproxen with fewer side effects. Injection site pain was more common in the **Hyalgan** group while gastrointestinal adverse events were more common in the naproxen group.

Several design issues are noted: 1) the placebo group received active treatment in the form of 4 g of acetaminophen and arthrocentesis with synovial fluid aspiration if necessary; 2) the naproxen group did not receive arthrocentesis, they received a subcutaneous injection; 3) a training video was provided to all sites; 4) one criterion of success was defined as an effect size of 0.25 of the standard deviation or 6 mm; 5) the data for all secondary outcome measures was analysed only for those patients who completed the 26 weeks of follow-up since the intent-to-treat analysis detected only a 1.5 mm difference between the **Hyalgan** and placebo groups in the primary outcome measure (pain during the 50-foot walk test); and 6) escape analgesia, as 500 mg acetaminophen up to 4000 mg/day, was permitted. Analyses showed no statistically significant differences between the three arms of the trial.

Bragantini et al. reported a 60-day, placebo-controlled, single-blind, parallel-group RCT performed at a single centre in Italy comparing three weekly injections of **Hyalgan** (both 20 mg and 40 mg) to three weekly injections of saline in 55 patients with OA of the knee (Bragantini 1987). Both dosage levels of **Hyalgan** were significantly superior to placebo. Four patients experienced local pain and burning after injection with **Hyalgan** but these reactions resolved within a short time. In this review, we have only used the **Hyalgan** 20 mg arm for comparison against saline.

Brown and Beinat reported a six-week, parallel-group, RCT performed at a single centre in England comparing five weekly injections of **Hyalgan** to three weekly injections of Hylan G-F 20 in 54 patients with OA of the knee (Brown 2003). This trial was discontinued, with about 50% of enrolment completed, due to a high frequency of acute inflammatory reactions with Hylan G-F 20. The protocol called for a sample size of 100 patients with 50 to be randomised to each group. The trial was designed to last six months. The number of patients that developed an acutely in-

flamed painful knee was 6 out of 29 in the Hylan G-F 20 group compared to 0 of 25 in the [Hyalgan](#) group. Statistically significant improvement in WOMAC pain and function was found for [Hyalgan](#) while a trend of improvement was found for Hylan G-F 20.

Two study design points were noted: 1) this RCT was conducted in a clinical practice setting; 2) randomisation was based on the consultant to whom the patient was referred.

Bunyaratavej et al. reported a six-month, placebo-controlled, double-blind RCT performed at three centres in Asia (China, Malaysia, Thailand) comparing four weekly injections of [Hyalgan](#) to four weekly injections of saline in 49 patients with OA of the knee ([Bunyaratavej 2001](#)). Statistically significant differences in favour of [Hyalgan](#) were reported one month after treatment as reflected by decreased pain and increased joint mobility. No local or systemic adverse events related to treatment were observed. No measure of dispersion was reported for the saline group for pain on active movement nor for either treatment group for day pain at baseline. Consequently, this review includes safety but not efficacy data.

This was one of two RCT where a four-injection schedule of [Hyalgan](#) was followed. In addition, acetaminophen (paracetamol) up to 3000 mg daily was permitted.

Carrabba et al. reported a six-month, placebo- and arthrocentesis-controlled, double-blind, parallel-group RCT performed at a single centre in Italy comparing three dose schedules of [Hyalgan](#) (one, three and five weekly injections) to five weekly arthrocentesis or five weekly injections of saline in 100 patients with OA of the knee ([Carrabba 1995](#)). All five groups received arthrocentesis at the baseline visit. A significantly superior effect of five and three injections of [Hyalgan](#) was shown in comparison with placebo, arthrocentesis and one injection of [Hyalgan](#). Four patients reported minor local reactions after injection (one patient each in the arthrocentesis group, the one, three and five injection [Hyalgan](#) groups). This review does not report results based on the one injection [Hyalgan](#) arm. The 1995 reference refers to the five injection [Hyalgan](#) versus saline comparison ([Carrabba 1995](#)); the 1995a reference refers to the three injection [Hyalgan](#) versus saline comparison ([Carrabba 1995a](#)); the 1995b reference refers to the five injection [Hyalgan](#) versus arthrocentesis comparison

([Carrabba 1995b](#)); and the 1995c reference refers to the three injection [Hyalgan](#) versus arthrocentesis comparison ([Carrabba 1995c](#)).

In this RCT paracetamol (acetaminophen) was permitted. However, only 15% of the patients used it at baseline, and there was no change in usage over the duration of the trial.

Corrado et al. reported a two-month, placebo-controlled, double-blind RCT performed at a single centre in Italy comparing five weekly injections of [Hyalgan](#) to five weekly injections of placebo

(water, sodium chloride, sodium phosphate) in 40 patients with OA of the knee ([Corrado 1995](#)). A significant difference in favour of [Hyalgan](#) was reported for pain and range

of motion. Two patients experienced 'accidental trauma' to the knee during treatment.

In order to study the possible anti-inflammatory activity of [Hyalgan](#), Corrado et al. completed a biochemical assessment of synovial fluid and plasma.

Creamer et al. reported a nine-week, placebo-controlled, single-blind, blind-observer RCT performed at a single centre in England comparing five weekly injections of [Hyalgan](#) to five weekly injections of saline in 12 patients with bilateral OA of the knee ([Creamer 1994](#)). This study investigated the mode of action of HA. It was not designed to assess clinical efficacy. No beneficial clinical effect was found for [Hyalgan](#) as compared to placebo. Twelve adverse events were reported by seven patients. Five local reactions (pain and swelling), graded as severe, occurred in three [Hyalgan](#)-treated knees and two placebo-treated knees.

Several design issues were noted: 1) each patient acted as his/her own control; 2) paracetamol up to 4 g daily was permitted; 3) imaging assessments, both MRI and <sup>99m</sup>Tc scintigraphic bone scans, were performed; and 4) four of the treated knees and six of the placebo knees had only patellofemoral disease.

Dougados et al. reported a one-year, placebo-controlled, single-blind RCT performed at a single centre in France comparing four weekly injections of Hyalectin to four weekly injections of the vehicle in 110 patients with OA of the knee ([Dougados 1993](#)). Greater improvement was found in the Hyalectin group compared to the placebo group for pain and function (Lequesne) in the early assessment and for physician's overall assessment of efficacy and the Lequesne Index in the long term. Nine patients did not receive all four injections: four in the Hyalectin group (two due to painful injection, one lack of efficacy, and one improved) and five in the placebo group (one due to painful injection, one lack of efficacy, three due to reasons unrelated to treatment (traumatic hemarthrosis in one, refusal to continue in two)).

Several design issues were noted: 1) this RCT followed a four injection schedule of [Hyalgan](#); 2) one-sided tests were used in the statistical analysis; and 3) the physician that administered the injection also completed the clinical assessment.

Formiguera Sala and Esteve de Miguel reported a 90-day, placebo-controlled, double-blind RCT performed at a single centre in Spain comparing five weekly injections of [Hyalgan](#) to five weekly injections of saline in 36 patients with OA of the knee ([Formiguera Sala 1995](#)). There were no significant differences between the groups at day 35. However, at day 90, statistically significant differences in favour of [Hyalgan](#) were reported for pain outcome measures. Three patients in each group reported pain that "could

be attributed to the route of administration and the individual idiosyncrasies of the patients”.

Several design issues were noted: 1) the supero-external approach with the patient in a supine position was followed for injections; 2) study population consisted of 36 patients, but 40 joints; 3) four patients were recruited twice: two receiving placebo in one knee and Hyalgan in the other, one patient receiving Hyalgan in separate knees at both times, one patient receiving placebo in the same knee on two occasions; and 4) the treatment in the second knee took place some time after the first knee was treated.

Forster and Straw reported a one-year, parallel-group RCT performed at a single centre in England comparing five weekly injections of Hyalgan to arthroscopic washout (two litres 0.9% saline at least) with either general or spinal anaesthesia in 38 patients with OA of the knee (Forster 2003; Forster 2003a). No significant differences between the two groups were found in any of the clinical outcome measures at any assessment point. Two patients in the Hyalgan group reported pain at the injection site following one injection.

Dr. Forster kindly provided an Excel data file from which we calculated means and standard deviations.

Frizziero and Pasquali Ronchetti reported a six-month, parallel-group, single-blind RCT performed at a single centre in Italy comparing five weekly injections of Hyalgan to three weekly injections of methylprednisolone acetate in 99 patients with primary or secondary OA of the knee (Frizziero 2002). The authors found an initial statistically significant difference in favour of methylprednisolone acetate at day 35 but not at day 180. The clinical effect with Hyalgan appeared more gradually but lasted longer than that of methylprednisolone acetate. Arthroscopic evaluations showed that Hyalgan was superior to methylprednisolone acetate in reducing the extent and grade of cartilage damage. No adverse events were reported in the Hyalgan group compared to two patients in the methylprednisolone acetate group, one resulting in withdrawal from the trial.

This RCT was one of the trials which examined the structural effects of Hyalgan using both arthroscopic and microarthroscopic examinations.

Graf et al. reported a six-month, verum-controlled, single-blind RCT performed at a single centre in Germany comparing Hyalgan once per week (seven injections) to mucopolysaccharide polysulfuric acid (MPA) ester twice per week (13 injections) in 60 patients with OA of the knee (Graf 1993). At the end of the treatment phase the improvement in the modified total Larson rating score was significantly better in the Hyalgan group. The authors reported a more rapid onset of pain relief with Hyalgan. At the end of the trial significantly more patients in the Hyalgan group were symptom free or markedly improved. There was a causal relationship with study medication for six adverse events in the

Hyalgan group and for two adverse events in the MPA group.

This RCT was the only trial where a seven injection schedule of Hyalgan was followed.

Grecomoro et al. reported a 60-day, placebo-controlled, double-blind RCT performed at a single centre in Italy comparing three weekly injections of Hyalgan to three weekly injections of phosphate buffer in 34 patients with OA of the knee (Grecomoro 1987). A significant difference between treatments was reported for all the clinical variables assessed. In the Hyalgan group, pain relief was both rapid and long lasting. No 'untoward signs or symptoms' were reported. Two patients withdrew early in the placebo group for reasons unrelated to treatment.

In this RCT results were based on 40 joints of 34 patients.

Henderson et al. reported a five-month, placebo-controlled, double-blind RCT performed at a single centre in England comparing five weekly injections of Hyalgan to five weekly injections of vehicle in 91 patients with OA of the knee (Henderson 1994). Patients were stratified into two groups based on radiological severity. In this review, the reference to Henderson 1994 refers to the milder severity group; while Henderson 1994a refers to the more severe group. No significant differences were found between the two groups. The rate of return to previously prescribed or other NSAIDs or analgesia was significantly slower in the Hyalgan treated group in the subgroup of patients with mild disease. Local reactions (pain and swelling) were observed in 47% of the patients in the Hyalgan group compared to 22% in the placebo group.

Several design issues were noted: 1) all but one patient had bilateral disease; 2) a clinical metrologist was used; 3) injections were into the patello-femoral space with a medial approach; and 4) there was a high percentage of withdrawals (38%).

Huskisson and Donnelly reported a six-month, placebo-controlled, blind-observer, parallel-group RCT performed at a single centre in England comparing five weekly injections of Hyalgan to five weekly injections of saline in 100 patients with OA of the knee (Huskisson 1999). Superiority of Hyalgan over placebo was demonstrated. Local reactions occurred in similar numbers in each group: seven patients in each group reported flare at the joint while effusion was present in three patients in the placebo group and one patient in the Hyalgan group.

This trial was conducted in England to readdress the efficacy of Hyalgan over placebo (see: Henderson 1994).

Jones et al. reported a six-month, double-blind, parallel-group RCT performed at a single centre in England comparing five weekly injections of Hyalgan to one injection of triamcinolone hexacetonide followed by four injections of saline in 63 patients with bilateral OA of the knee (Jones 1995). Active treatment, which was randomised, was always given to the worst knee. The placebo therapy was not randomised, and, therefore, no data were

extracted for comparisons between [Hyalgan](#) and saline. No statistically significant differences were found between the groups in the intention-to-treat analysis. However, in the completer analysis significantly less pain was seen in the [Hyalgan](#) group with other parameters showing a similar trend in favour of [Hyalgan](#). Sixty-eight percent of the patients dropped out of the study, the majority due to lack of efficacy. By week 29 only 26% of the triamcinolone hexacetonide patients and 38% of the [Hyalgan](#) patients remained in the trial.

Jubb et al. reported a one-year, placebo-controlled, double-blind RCT performed at 17 centres in the United Kingdom comparing three weekly injections of [Hyalgan](#) to three weekly injections of saline (vehicle placebo) in 408 patients with OA of the knee ([Jubb 2001a](#); [Jubb 2001b](#); [Jubb 2001c](#); [Jubb 2001d](#); [Jubb 2003](#)). The treatment schedule was repeated twice more at four-monthly intervals. The aim of the study was to investigate structural changes as measured by joint space narrowing (the primary outcome). Statistically significant differences in favour of [Hyalgan](#) were found for the pain outcome measures. Since the primary analysis did not show any differences between the two groups with respect to joint space narrowing, the authors performed a subgroup analysis based on baseline joint space width. Those patients with radiologically milder disease (less than 4.6 mm) had less progression of joint space narrowing when treated with [Hyalgan](#). A total of 7.2% of the [Hyalgan](#) patients and 3% of the saline patients withdrew prematurely due to adverse events; 2.4% and 1.5%, respectively, due to local adverse events. Local effects were reported by 36.1% of the [Hyalgan](#) patients and 27.5% of the saline patients. Serious adverse events, all due to concomitant disease, were reported by 13% of the [Hyalgan](#) patients and 7% of the saline patients.

In the Tables of Comparisons and data [Jubb 2003](#) entries refer to the full journal publication; [Jubb 2001a](#) entries refer to the primary analysis population; [Jubb 2001b](#) entries refer to the subgroup with joint space width equal or greater than 4.6 mm; [Jubb 2001c](#) entries refer to the subgroup with joint space width less than 4.6 mm.

Since reduction of joint space width was the primary efficacy outcome measure in this trial evaluation was based on computerised digital image analysis of anteroposterior weight-bearing radiographs. The trial also addressed the safety of repeated cycles of [Hyalgan](#).

Karras et al. reported a one-year, parallel-group RCT performed at a single centre in Greece comparing five weekly injections every six months of [Hyalgan](#) to three weekly injections every three months of [Hyalgan](#) in 200 patients with OA of the knee ([Karras 2001](#)). The objective was to compare the effectiveness of the two regimens. The authors reported that the three-injection regimen was more effective than the five-injection regimen. Except for three cases of local pain there were no side effects reported.

Leardini et al. reported a one-year, single-blind, parallel-group RCT performed at a single centre in Italy comparing three weekly

injections of [Hyalgan](#) to three weekly injections of methylprednisolone acetate (MPA) in 36 patients with OA of the knee ([Leardini 1987](#)). No statistically significant differences were found between the two groups in the clinical assessments. Local reactions were reported in three patients in the MPA group compared to four patients in the [Hyalgan](#) group.

This trial reported results on 40 joints of 36 patients (four with bilateral disease).

Leardini et al. reported a 60-day, open, parallel-group RCT performed at a single centre in Italy comparing three weekly injections of [Hyalgan](#) to three weekly injections of 6-methylprednisolone acetate (6-MPA) in 40 patients with OA of the knee ([Leardini 1991](#)). Assessments, completed one week after the end of treatment, showed that [Hyalgan](#) was comparable to 6-MPA. In the longer term significant differences were found in favour of [Hyalgan](#) for the pain outcomes. All patients completed the treatment schedule. No local or systemic reactions were reported.

In this trial, all patients were kept 'at rest' for two days after injection.

Listrat et al. reported a one-year, open, parallel-group RCT performed at a single centre in France comparing three weekly injections of [Hyalgan](#) every three months for a total of nine injections to conventional therapy in 39 patients with OA of the knee ([Listrat 1997](#)). All patients underwent knee arthroscopy before randomisation. A statistically significant difference in favour of [Hyalgan](#) was found for the quality of life index. A statistically significant difference for two of three structural parameters was found in favour of [Hyalgan](#). Forty percent of the [Hyalgan](#) patients reported transient local reactions (pain) associated with the injection.

This study evaluated the potential structure-modifying effects of [Hyalgan](#). The arthroscopy was videotaped and assessed by a blinded assessor. The primary efficacy outcomes were the arthroscopic parameters.

Miltner et al. reported a seven-week, right to left comparison RCT performed at a single centre in Germany comparing five weekly injections of Hyalart in the impaired knee to no treatment in the contralateral, untreated knee in 43 patients with OA of the knee ([Miltner 2002](#); [Schneider 1997](#)). The objective of this trial was to assess the effect of Hyalart on total work and isokinetic muscle strength. This pilot study showed that Hyalart was effective with regard to both clinical outcomes (e.g. relieving pain and improving function) as well as to functional outcomes (e.g. peak torque and total work). Schneider et al. published a preliminary evaluation of this trial in German based on 18 patients ([Schneider 1997](#)).

Several design issues were noted: 1) all patients had bilateral disease; 2) the control group received no treatment; and 3) follow-up was limited to one week after the final injection.

Pietrogrande et al. reported a 60-day, open, parallel-group RCT performed at three centres in Italy comparing five weekly injections

of [Hyalgan](#) to three weekly injections of 6-methylprednisolone acetate in 90 patients with OA of the knee ([Pietrogrande 1991](#)). Although both treatments reduced the disease symptoms 6-MPA had a more rapid action that did not last as long as that of [Hyalgan](#). At the final assessment significant differences were found between the treatments for most outcome measures. One patient in the [Hyalgan](#) group had a local reaction which resolved spontaneously but the patient was withdrawn due to lack of efficacy. No systemic adverse reactions were reported in either group.

St. J. Dixon et al. reported a 48-week, placebo-controlled, double-blind, parallel-group RCT performed at three centres in England comparing [Hyalgan](#) (up to eleven injections over 23 weeks) to vehicle (0.2 mg sodium hyaluronate) in 63 patients with OA of the knee ([St. J. Dixon 1988](#)). Knee pain was significantly reduced in the [Hyalgan](#) group compared to the placebo group. No between-group difference was found for function as measured by activities of daily living. Possible treatment-related ([Hyalgan](#)) adverse events occurred in three patients: hemarthrosis developed in one patient, effusion volume increased in one patient, and phlebitis developed in one patient. Ten patients did not complete the trial. Five patients in the placebo group withdrew early because of increased pain; while five patients withdrew early in the [Hyalgan](#) group: one because of a torn meniscus, one because knee was painless, one had increased pain, one defaulted and one had a hemarthrosis. No measure of dispersion was reported for pain on movement, pain at rest, or activities of daily living and, consequently, efficacy data are not included in this review. Only safety data are included in this review.

This is the only RCT where up to 11 injections of [Hyalgan](#) were used.

Tsai et al. reported a 25-week, placebo-controlled, multicentre, double-blind RCT performed in Taiwan comparing five weekly injections of [Hyalgan](#) to five weekly injections of saline in 200 patients with OA of the knee ([Tsai 2003](#)). Statistically significant differences were found in favour of [Hyalgan](#) for pain on 50-foot walk, WOMAC OA Index pain and physical function. No differences between treatments were reported in adverse event occurrence.

Fidia Spa kindly provided an in-house report ([Lin 2004](#)) as only an abstract, based on this trial, had been published in 2003 ([Tsai 2003](#)).

### [Hyalgan](#) versus placebo

#### *Efficacy*

Based on 14 comparisons, there was a statistically significant difference in pain on weight bearing, measured on a 0 to 100 mm VAS, in favour of [Hyalgan](#) compared to placebo at 1 to 4 weeks postinjection (WMD (random-effects model) -6.20; 95% CI -11.02 to -1.38, P value 0.009). [Hyalgan](#) was 2 to 31% more effective than placebo in improving pain. Based on 10 comparisons there was a

statistically significant difference in favour of [Hyalgan](#) compared to placebo at 5 to 13 weeks postinjection (WMD (random-effects model) -9.04; 95% CI -14.10 to -3.98; P value 0.0005). [Hyalgan](#) was 18 to 44% more effective than placebo in improving pain. There was a statistically significant difference in favour of [Hyalgan](#) compared to placebo at 14 to 26 weeks postinjection (WMD -4.12; 95% CI -6.97 to -1.27, P value 0.005) ([Altman 1998](#); [Huskiison 1999](#); [Jubb 2003](#); [Tsai 2003](#)). [Hyalgan](#) was 3 to 26% more effective than placebo in improving pain. There was no statistically significant difference at 45 to 52 weeks postinjection (WMD -2.60; 95% CI -7.40 to 2.19, P value 0.3) ([Dougados 1993](#); [Jubb 2003](#); [St. J. Dixon 1988](#)).

There was a statistically significant difference in spontaneous pain, measured on a 100 mm VAS, in favour of [Hyalgan](#) compared to placebo at 1 to 4 weeks postinjection (WMD -23.88; 95% CI -33.50 to -14.25, P value < 0.00001) and at 5 to 13 weeks postinjection (WMD (random-effects model) -22.28; 95% CI -38.88 to -5.68, P value 0.009) ([Bragantini 1987](#); [Gecomoro 1987](#)). [Hyalgan](#) was 38 to 67% more effective than placebo in improving pain.

There was a statistically significant difference in pain at rest, measured on a 0 to 100 mm VAS, in favour of [Hyalgan](#) compared to placebo at 1 to 4 weeks postinjection (WMD (random-effects model) -6.37; 95% CI -11.57 to -1.18, P value 0.02) ([Carrabba 1995](#); [Carrabba 1995a](#); [Carrabba 1995b](#); [Carrabba 1995c](#); [Corrado 1995](#); [Dougados 1993](#); [Henderson 1994](#); [Henderson 1994a](#); [St. J. Dixon 1988](#)) and at 5 to 13 weeks postinjection (WMD -9.65; 95% CI -14.18 to -5.13, P value 0.00003) ([Carrabba 1995](#); [Carrabba 1995a](#); [Carrabba 1995b](#); [Carrabba 1995c](#); [Corrado 1995](#)). [Hyalgan](#) was 13 to 116% more effective than placebo in improving pain. There was no difference at 45 to 52 weeks postinjection (WMD 1.61; 95% CI -5.28 to 8.51, P value 0.6) ([Dougados 1993](#); [St. J. Dixon 1988](#)).

There was no statistically significant difference in pain at night, measured on a 0 to 100 mm VAS, between [Hyalgan](#) and placebo at 5 to 13 weeks post injection (WMD (random-effects model) -4.55; 95% CI -12.49 to 3.39, P value 0.3) ([Henderson 1994](#); [Henderson 1994a](#)).

There were no statistically significant differences in WOMAC pain, measured on a 0 to 100 mm VAS, between [Hyalgan](#) and placebo at 1 to 4 weeks postinjection (WMD -2.67; 95% CI -6.84 to 1.50, P value 0.2) or at 5 to 13 weeks postinjection (WMD -1.49; 95% CI -5.75 to 2.77, P value 0.5). There was a statistically significant difference in favour of [Hyalgan](#) compared to saline at 14 to 26 weeks postinjection (WMD -5.66; 95% CI -10.06 to -1.26, P value 0.01) ([Lin 2004](#), [Tsai 2003](#)) with [Hyalgan](#) being 14% more effective than saline.

Pain was measured using several dichotomous outcome measures.

There were statistically significant differences in favour of [Hyalgan](#) compared to placebo for the number of joints improved for walk-



ing pain at the end of treatment (RR 1.68; 95% CI 1.02 to 2.78, P value 0.04) (Bragantini 1987); at 1 week postinjection (RR 3.60; 95% CI 1.48 to 8.78, P value 0.005) (Grecomoro 1987); and at 5 to 13 weeks postinjection (RR 2.30; 95% CI 1.26 to 4.19, P value 0.006) (Bragantini 1987). The NNT for walking pain was 2 to 3. Similarly, statistically significant differences in favour of Hyalgan compared to placebo were found for the number of joints improved for pain under load at the end of treatment (RR 0.37; 95% CI 0.19 to 0.73, P value 0.004) (Bragantini 1987); at 1 week postinjection (RR 3.60; 95% CI 1.48 to 8.78, P value 0.005) (Grecomoro 1987); and at 5 to 13 weeks postinjection (RR 0.25; 95% CI 0.10 to 0.60, P value 0.002) (Bragantini 1987). The NNT for pain under load was 2.

There was no statistically significant difference in pain expressed as the number of patients improved at 5 to 13 weeks postinjection (RR 1.19; 95% CI 0.93 to 1.52, P value 0.16). The RevMan analysis differed from the publication analysis where P value was 0.04 (chi square test). A significant difference in favour of Hyalgan compared to placebo was found at 32

weeks postinjection (RR 1.36; 95% CI 1.06 to 1.75, P value 0.02) (Jubb 2003). The NNT for patient global assessment was 9.

There was no statistically significant difference in the number of patients who had moderate to marked pain (RR 0.74; 95% CI 0.53 to 1.04, P value 0.08) or in those who had none to slight to mild pain at 14 to 26 weeks postinjection (RR 1.22; 95% CI 0.98 to 1.52, P value 0.08) (Altman 1998).

There were no statistically significant differences in the number of knee joints without night pain at 1 to 4 weeks postinjection (RR 1.40; 95% CI 0.61 to 3.19, P value 0.4) or at 5 to 13 weeks postinjection (RR 1.40; 95% CI 0.61 to 3.19, P value 0.4) (Creamer 1994). There were no statistically significant differences in the number of participants without rest pain at 1 to 4 weeks postinjection (RR 1.20; 95% CI 0.50 to 2.88, P value 0.7) or at 5 to 13 weeks postinjection (RR 2.50; 95% CI 0.60 to 10.46, P value 0.2) (Creamer 1994).

There was a statistically significant difference in the number of joints with improvement in pain on touch in favour of Hyalgan compared to placebo (RR 2.25; 95% CI 1.12 to 4.53, P

value 0.02) (Grecomoro 1987). The NNT for pain on touch was 2.

There were no statistically significant differences in the WOMAC function, measured on a 0 to 100 mm VAS, between Hyalgan and saline at 1 to 4 weeks postinjection (WMD -1.30; 95% CI -5.52 to 2.92, P value 0.5); 5 to 13 weeks postinjection (WMD -1.06; 95% CI -5.37 to 3.25, P value 0.6); or at 14 to 26 weeks postinjection (WMD -4.05; 95% CI -8.38 to 0.28, P value 0.07) (Lin 2004; Tsai 2003). The RevMan analysis differed from the publication analysis where a statistically significant difference was

found in favour of Hyalgan in WOMAC function from baseline to week 25 (P value 0.0038 (ANOVA)).

Statistically significant differences in the Lequesne Index, measured on a 0 to 24 scale, in favour of Hyalgan compared to placebo were found at 1 to 4 weeks postinjection (WMD -1.50; 95% CI -2.36 to -0.65, P value 0.0006) (Carrabba 1995; Carrabba 1995a; Carrabba 1995b; Carrabba 1995c; Dougados 1993; Huskisson 1999) and at 5 to 13 weeks postinjection (WMD -2.34; 95% CI -3.41 to -1.27, P value 0.00002) (Carrabba 1995; Carrabba 1995a; Carrabba 1995b; Carrabba 1995c; Huskisson 1999). Hyalgan was 11 to 25% more effective than placebo. No difference was found at 14 to 26 weeks postinjection (WMD -1.40; 95% CI -3.40 to 0.60, P value 0.17) (Huskisson 1999) or at 45 to 52 weeks postinjection (WMD -1.11; 95% CI -2.70 to 0.48, P value 0.17) (Dougados 1993). The RevMan analysis differed from the Dougados publication (Dougados 1993) which reported a statistically significant difference (P value 0.046) in the Lequesne Index at week 52.

Although not recommended as core-set outcome measures, data were extracted on range of motion, synovial fluid volume, and joint space width. There was no statistically significant difference in flexion, measured in degrees, between Hyalgan and placebo at 1 to 4 weeks postinjection (WMD 3.50; 95% CI -4.11 to 11.11, P value 0.4) but Hyalgan was significantly better than placebo at 5 to 13 weeks postinjection (WMD 7.60; 95% CI 0.46 to 14.74, P value 0.04) (Corrado 1995). Hyalgan was 6% more effective in improving flexion than placebo. There were no statistically significant differences in synovial fluid volume, measured in ml, between Hyalgan and placebo at 1 to 4 weeks postinjection (WMD -0.76; 95% CI -3.49 to 1.98, P value 0.6) (Corrado 1995; Creamer 1994; Dougados 1993) or at 5 to 13 weeks postinjection (WMD (random-effects model) -3.96; 95% CI -11.10 to 3.19, P value 0.3) (Corrado 1995; Creamer 1994). There was a statistically significant difference in joint space width, measured in mm, in favour of Hyalgan compared to placebo at 45 to 52 weeks postinjection (WMD 0.40; 95% CI 0.03 to 0.77, P value 0.03) (Jubb 2003). However, when the treatment groups were stratified by baseline joint space width there was no difference (WMD (random-effects model) 0.15; 95% CI -0.34 to 0.64, P value 0.6) (Jubb 2003). These RevMan analyses differed from the Jubb publication (Jubb 2003) analysis where no difference was found in the total population but a difference in favour of the subgroup with joint space width equal to or greater than 4.6 mm at baseline was reported.

There was no statistically significant difference between Hyalgan and placebo in patient global assessment, measured as number of patients improved, at 1 to 4 weeks postinjection (RR 1.45; 95% CI 0.97 to 2.15, P value 0.07) (Corrado 1995; Creamer 1994; Formiguera Sala 1995). A statistically significant difference was found in favour of Hyalgan compared to placebo at 5 to 13 weeks postinjection (RR 2.44; 95% CI 1.43 to 4.16, P value 0.0010) (Corrado 1995; Formiguera Sala 1995). The NNT for patient global assessment was 10. A statistically significant difference was

found in favour of *Hyalgan* compared to placebo at 14 to 26 weeks postinjection (RR 1.24; 95% CI 1.03 to 1.50, P value 0.02) (Henderson 1994; Huskisson 1999; Lin 2004). No difference was found at 45 to 52 weeks postinjection in the number of patients rating treatment effective (RR 1.17; 95% CI 0.85 to 1.62, P value 0.3) (Dougados 1993). When patient global assessment was measured by the number of joints that were fairly good to very good, a statistically significant difference in favour of *Hyalgan* compared to placebo was found at 5 to 13 weeks postinjection (RR 2.12; 95% CI 1.22 to 3.70, P value 0.008) (Bragantini 1987; Creamer 1994). The NNT for patient global assessment was 11.

### *Safety*

There were no statistically significant differences in the total number of withdrawals overall at 5 to 13 weeks postinjection (RR 0.60; 95% CI 0.11 to 3.23, P value 0.6) (Carrabba 1995; Corrado 1995); at 14 to 26 weeks postinjection (RR 1.11; 95% CI 0.87 to 1.41, P value 0.4) (Altman 1998; Henderson 1994; Huskisson 1999; Lin 2004); or at 45 to 52 weeks postinjection (RR 1.13; 95% CI 0.81 to 1.56, P value 0.5) (Dougados 1993; Jubb 2003; St. J. Dixon 1988). There were no statistically significant differences in the number of withdrawals due to lack of efficacy during the treatment phase (RR 1.00; 95% CI 0.06 to 15.59, P value 1) (Dougados 1993) or 14 to 26 weeks postinjection (RR 0.80; 95% CI 0.47 to 1.36, P value 0.4) (Altman 1998; Huskisson 1999; Lin 2004). A statistically significant difference in favour of placebo compared to *Hyalgan* was found in the number of patients with local adverse events that caused discontinuation of study drug (RR 3.34; 95% CI 1.31 to 8.56, P value 0.01) (Altman 1998; Dougados 1993; Henderson 1994; Jubb 2003). Similarly, there was a statistically significant difference in favour of placebo compared to *Hyalgan* found in the number of patients with local adverse events but the study drug was continued (RR 1.42; 95% CI 1.10 to 1.84, P value 0.007). There was no difference in the number of patients with serious adverse events at 14 to 26 weeks postinjection (RR 1.67; 95% CI 0.41 to 6.85, P value 0.5) (Huskisson 1999; Lin 2004). There was a trend of more serious adverse events in the *Hyalgan* group compared to the placebo group at 45 to 52 weeks postinjection (RR 1.85; 95% CI 1.00 to 34.3, P value 0.05) (Dougados 1993, Jubb 2003). There was a trend of more patients withdrawing due to adverse events in the *Hyalgan* group compared to the placebo group (RR 2.35; 95% CI 0.99 to 5.56, P value 0.05) (Huskisson 1999, Jubb 2003). There was no difference in the number of knee joints with local adverse events (RR 2.16; 95% CI 0.54 to 8.69, P value 0.3) (Bragantini 1987; Creamer 1994). There was no statistically significant difference in the number of patients with injection site pain (RR 1.39; 95% CI 0.98 to 1.97, P value 0.06) (Altman 1998; Dougados 1993; Formiguera Sala 1995). There was no difference in the number of patients with treatment related adverse events at 5 to 13 weeks postinjection, 0% in both the *Hyalgan* and control groups (Formiguera Sala 1995). There was a statistically significant difference in the num-

ber of patients with treatment-related adverse events at 14 to 26 weeks postinjection (RR 2.19; 95% CI 1.18 to 4.07, P value 0.01) (Bunyaratavej 2001; Henderson 1994; Huskisson 1999) but not at 45 to 52 weeks postinjection (RR 7.68; 95% CI 0.41 to 142.78, P value 0.17). In the Altman trial (Altman 1998) at 14 to 26 week postinjection there was a statistically significant difference in the number of patients with gastrointestinal complaints in favour of placebo compared to *Hyalgan* (RR 1.89; 95% CI 1.24 to 2.90, P value 0.003). There was no difference in the number of patients with local skin rash at 14 to 26 weeks postinjection (RR 0.91; 95% CI 0.54 to 1.52, P value 0.7) (Altman 1998).

### *Hyalgan* versus arthroscopy

One trial was included which was a comparison of *Hyalgan* and arthroscopy (Forster 2003; Forster 2003a).

### *Efficacy*

In the comparison against arthroscopy, there was no statistically significant difference between *Hyalgan* and arthroscopy in pain (0 to 10 cm VAS) at any of the four assessments: 1 to 4 weeks post injection (WMD 1.20; 95% CI -0.88 to 3.28, P value 0.3); 5 to 13 weeks postinjection (WMD 0; 95% CI -2.51 to 2.51, P value 1); 14 to 26 weeks postinjection (WMD -0.90; 95% CI -3.46 to 1.66, P value 0.5); and 45 to 52 weeks postinjection (WMD 0; 95% CI -2.47 to 2.47, P value 1). There was no statistically significant difference between *Hyalgan* and arthroscopy in the Lequesne Index (0-24) at any of the four assessments: 1 to 4 weeks postinjection (WMD 0.60; 95% CI -3.72 to 4.92, P value 0.8); 5 to 13 weeks postinjection (WMD -0.60; 95% CI -5.00 to 3.80, P value 0.8), 14 to 26 weeks postinjection (WMD -3.00; 95% CI -7.58 to 1.58, P value 0.2); and 45 to 52 weeks postinjection (WMD -2.90; 95% CI -8.10 to 2.30, P value 0.3). Although there was a statistically significant difference between groups pre-trial for the Knee Society Function scale score (i.e. *Hyalgan* group better score), except for the 14 to 26 week assessment, there was no statistically significant difference between *Hyalgan* and arthroscopy: at 1 to 4 weeks postinjection (WMD 16.90; 95% CI -6.32 to 40.12, P value 0.15); at 5 to 13 weeks postinjection (WMD 16.20; 95% CI -6.50 to 38.90, P value 0.16); at 14 to 26 weeks postinjection (WMD 23.50; 95% CI 1.68 to 45.32, P value 0.03) (i.e. *Hyalgan* was 2% more effective than arthroscopy); and 45 to 52 weeks postinjection; (WMD 23.90; 95% CI -1.45 to 49.25, P value 0.06). There was no difference between the number of patients requiring further intervention (RR 2.06; 95% CI 0.64 to 6.57, P value 0.2).

The RevMan analysis differed from the Forster publication (Forster 2003) analysis. The publication reported no difference in the Knee Society Function scale at six months whereas the RevMan analysis detected a statistically significant difference (P value 0.03) in favour of *Hyalgan* over arthroscopy.

### *Safety*

There was no difference in the number of withdrawals overall: *Hyalgan* 2 out of 19 versus arthroscopy 4 of 19 (RR 0.50; 95% CI 0.10 to 2.41, P value 0.4). There was no difference in the number of patients with pain at the injection site: *Hyalgan* 2 out of 19 versus arthroscopy 0 out of 19 (RR 5.00; 95% CI 0.26 to 97.70, P value 0.3).

#### *Hyalgan* versus corticosteroid

Five RCTs that were included were comparisons of *Hyalgan* and IA corticosteroid.

Four RCT were comparisons of *Hyalgan* and methylprednisolone acetate (Depomedrol, MPA) (Frizziero 2002; Leardini 1987; Leardini 1991; Pietrogrande 1991) and one RCT was a comparison of *Hyalgan* and triamcinolone hexacetonide (Jones 1995).

#### *Efficacy*

There was no statistically significant difference in spontaneous pain intensity (0 to 100 mm VAS) at 1 to 4 weeks postinjection (WMD -4.90; 95% CI -9.91 to 0.10, P value 0.05) (Leardini 1987; Leardini 1991; Pietrogrande 1991). There was a statistically significant difference in favour of *Hyalgan* at 5 to 13 weeks postinjection (WMD -7.73; 95% CI -12.81 to -2.64, P value 0.003) (Leardini 1987; Leardini 1991; Pietrogrande 1991). *Hyalgan* was 11 to 41% more effective than MPA. At 45 to 52 weeks postinjection, there was no difference (WMD 2.50; 95% CI -14.98 to 19.98, P value 0.8) (Leardini 1987). For pain expressed as the number of joints with moderate or severe pain under load (Leardini 1987), there was no statistically significant difference at 1 to 4 weeks postinjection (RR 1.00; 95% CI 0.47 to 2.14, P value 1); at 5 to 13 weeks postinjection (RR 0.86; 95% CI 0.35 to 2.10, P value 0.7); or at 45 to 52 weeks postinjection (RR 0.82; 95% CI 0.46 to 1.49, P value 0.5). For pain expressed as the number of patients with moderate or severe pain under load (Leardini 1991; Pietrogrande 1991), there was no difference at 1 to 4 weeks postinjection (RR (random-effects model) 0.90; 95% CI 0.54 to 1.50, P value 0.7). There was a statistically significant difference in favour of *Hyalgan* at 5 to 13 weeks postinjection (RR 0.61; 95% CI 0.44 to 0.84, P value 0.003). The NNT for moderate to severe pain under load was 10. For the number of joints with moderate or severe walking pain, no statistically significant differences were detected at the three timepoints: at 1 to 4 weeks postinjection (RR 1.22; 95% CI 0.65 to 2.29, P value 0.5), at 5 to 13 weeks postinjection (RR 0.80; 95% CI 0.40 to 1.60, P value 0.5), and at 45 to 52 weeks postinjection (RR 1.04; 95% CI 0.67 to 1.60, P value 0.9) (Leardini 1987). For the number of patients with moderate or greater night pain, there was no statistically significant difference at 1 to 4 weeks postinjection (RR (random-effects model) 1.12 (95% CI 0.06 to 21.12) P value 0.9) or at 5 to 13 weeks postinjection (RR 0.14; 95% CI 0.02 to 1.13, P value 0.07) (Leardini 1991; Pietrogrande 1991). For the number of patients with moderate or greater rest pain, there was no statistically significant difference at 1 to 4 weeks postinjection (RR 0.68; 95% CI

0.38 to 1.24, P value 0.2), but a significant difference in favour of *Hyalgan* at 5 to 13 weeks postinjection (RR 0.39; 95% CI 0.19 to 0.78, P value 0.008) (Leardini 1991; Pietrogrande 1991). The NNT for rest pain was 20.

Statistically significant differences in range of motion (flexion) in favour of *Hyalgan* were found at 1 to 4 weeks postinjection (WMD 5.93; 95% CI 0.71 to 11.14, P value 0.03) and at 5 to 13 weeks post injection (WMD 5.41; 95% CI 0.54 to 10.28, P value 0.03) (Leardini 1987; Pietrogrande 1991) (i.e. *Hyalgan* was 2% more effective than MPA) but no difference was detected at 45 to 52 weeks postinjection (WMD 1.50; 95% CI -12.92 to 15.92, P value 0.8) (Leardini 1987).

The global assessment, expressed by number of patients good or very good, was not significantly different between groups at 1 to 4 weeks postinjection (RR (random-effects model) 0.98; 95% CI 0.47 to 2.06, P value 1) (Frizziero 2002; Leardini 1991; Pietrogrande 1991). There was a statistically significant difference in favour of *Hyalgan* at 5 to 13 weeks postinjection (WMD 1.86; 95% CI 1.26 to 2.75, P value 0.002) (Leardini 1991; Pietrogrande 1991). The NNT for patient global assessment was 7. At 45 to 52 weeks postinjection, there was no difference (WMD 1.05; 95% CI 0.81 to 1.36, P value 0.7) (Frizziero 2002).

One RCT was a comparison of *Hyalgan* and triamcinolone hexacetonide (Jones 1995). Except for pain at night at the latter assessment time, there were no statistically significant differences between treatment detected by the three pain measures (100 mm VAS): pain on nominated activity (WMD -0.20; 95% CI -17.39 to 16.99, P value 1) at end of treatment; and (WMD -10.00; 95% CI -31.83 to 11.83, P value 0.4) at 14 to 26 weeks postinjection; pain at rest (WMD -0.70; 95% CI -18.17 to 16.77, P value 0.9) at end of treatment; and (WMD -20.40; 95% CI -43.92 to 3.12, P value 0.09) at 14 to 26 weeks postinjection; pain at night (WMD -7.10; 95% CI -24.30 to 10.10, P value 0.4) at end of treatment; and (WMD -20.70; 95% CI -37.74 to -3.66, P value 0.02) at 14 to 26 weeks postinjection. That is, *Hyalgan* was 26% more effective than triamcinolone hexacetonide in relieving pain at night at 14 to 26 weeks postinjection. The RevMan analysis differed from the Jones publication (Jones 1995) analysis. The publication reported significant differences in favour of *Hyalgan* in pain on nominated activity and pain at rest at 14 to 26 weeks postinjection.

#### *Safety*

There were no statistically significant differences in any of the extracted safety outcomes. There was no difference in the total number of withdrawals overall at 1 to 4 weeks postinjection (RR 0.54; 95% CI 0.21 to 1.38, P value 0.2) (Frizziero 2002); at 5 to 13 weeks postinjection (RR 3.00; 95% CI 0.13 to 71.74, P value 0.5) (Leardini 1991; Pietrogrande 1991); at 14 to 26 weeks postinjection (RR 1.81; 95% CI 0.67 to 4.91, P value 0.2) (Frizziero 2002); or at 45 to 52 weeks postinjection (RR 1.67; 95% CI 0.46 to 6.06, P value 0.4) (Leardini 1987). There was no difference in

the number of patients withdrawn due to lack of efficacy at 5 to 13 weeks postinjection (RR 3.00; 95% CI 0.13 to 71.74, P value 0.5) (Pietrogrande 1991). There was no difference in the number of joints with local reactions at 1 to 4 weeks postinjection (RR 1.33; 95% CI 0.34 to 5.21, P value 0.7) (Leardini 1987). There was no difference in the number of patients with local or systemic reactions at 5 to 13 weeks postinjection (RR 3.00; 95% CI 0.13 to 71.74, P value 0.5) (Leardini 1991, Pietrogrande 1991). There was no difference in the number of patients withdrawn due to adverse events after the first injection in the Frizziero trial (Frizziero 2002) (RR 0.30; 95% CI 0.01 to 7.24, P value 0.5).

There were no statistically significant differences between Hyalgan and triamcinolone hexacetonide (Jones 1995) in the total number of withdrawals overall at the end of treatment (RR 0.73; 95% CI 0.18 to 2.99, P value 0.7) or at 14 to 26 weeks postinjection (RR 0.80; 95% CI 0.56 to 1.14, P value 0.2). There were no statistically significant differences in the number of withdrawals due to lack of efficacy at the end of treatment (RR 4.85; 95% CI 0.24 to 97.11, P value 0.3) or at 14 to 26 weeks postinjection (RR 0.89; 95% CI 0.49 to 1.65, P value 0.7). There were no statistically significant differences in the number of withdrawals due to adverse events at the end of treatment (RR 0.97; 95% CI 0.06 to 14.82, P value 1) or

at 14 to 26 weeks postinjection (RR 0.78; 95% CI 0.23 to 2.62, P value 0.7).

#### Hyalgan versus other IA therapy

One RCT included was a comparison of Hyalgan and mucopolysaccharide polysulfuric acid ester (Graf 1993).

#### Efficacy

The results were presented as change scores. The six-month data reported in the publication were not used since it was presented as the change from end of treatment not the change from baseline. For the Larson rating scale, a higher score indicated improvement. At the end of treatment (week 6), there was a statistically significant difference in favour of Hyalgan compared to mucopolysaccharide polysulfuric acid ester for pain (0 to 30) (WMD 4.00; 95% CI 0.98 to 7.02, P value 0.009) and for the total Larson rating score (0 to 77) (WMD 5.90; 95% CI 1.31 to 10.49, P value 0.01). This means that Hyalgan was 25% more effective than mucopolysaccharide polysulfuric acid ester in relieving pain and 13% more effective in improving 'overall' function. There was no statistically significant difference for function (0-30) (WMD 0.60; 95% CI -1.95 to 3.15, P value 0.6) or for range of motion (0 to 10) (WMD 0.30; 95% CI -0.06 to 0.66, P value 0.10). The global assessment, expressed by the number of patients symptom free or markedly improved, was significantly better in the Hyalgan group (76%) compared to the mucopolysaccharide polysulfuric acid ester group (46%) (RR 1.65; 95% CI 1.03 to 2.66, P value 0.04) at 14 to 26 weeks postinjection. The NNT for patient global assessment was 3.

#### Safety

There were no statistically significant differences between Hyalgan and mucopolysaccharide polysulfuric acid ester at 14 to 26 weeks postinjection either in the total number of withdrawals overall (RR 0.41; 95% CI 0.04 to 4.27, P value 0.5) or in the number of adverse events due to study medication (RR 2.45; 95% CI 0.54 to 11.19, P value 0.2).

#### Hyalgan versus NSAID

One RCT included was a comparison of Hyalgan and naproxen (Altman 1998).

#### Efficacy

No statistically significant difference was found between Hyalgan and naproxen for pain after a 50 foot walk measured on a 100 mm VAS at any of the three assessment times: 1 to 4 weeks postinjection (WMD 0; 95% CI -5.99 to 5.99, P value 1); 5 to 13 weeks postinjection (WMD 2.00; 95% CI -4.33 to 8.33, P value 0.5); and 14 to 26 weeks postinjection (WMD -3.00; 95% CI -9.15 to 3.15, P value 0.3). There was no statistically significant difference in the number of patients with moderate to marked pain at 14 to 26 weeks postinjection (RR 0.90; 95% CI 0.63 to 1.28, P value 0.6) or in those with none to slight to mild pain (RR 1.06; 95% CI 0.87 to 1.30, P value 0.6).

#### Safety

There was a statistically significant difference in the number of patients with gastrointestinal complaints reported in the Hyalgan group (29%) compared to the naproxen group (42%) (RR 0.70; 95% CI 0.52 to 0.95, P value 0.02). There was a statistically significant difference in the number of adverse events for injection site pain reported in the naproxen group (9%) compared to Hyalgan (23%) (RR 2.70; 95% CI 1.52 to 4.79, P value 0.0007). There were more adverse events due to local joint pain and swelling reported in the Hyalgan group (13%) than the naproxen group (6%) (RR 2.09; 95% CI 1.01 to 4.29, P value 0.05).

There were no statistically significant differences for the other safety outcome measures: total withdrawals overall (RR 1.17; 95% CI 0.86 to 1.60, P value 0.3), withdrawals due to lack of efficacy (RR 1.69; 95% CI 0.80 to 3.58, P value 0.17), number of adverse events of local skin rash (RR 0.79; 95% CI 0.48 to 1.30, P value 0.4), or pruritis (RR 1.70; 95% CI 0.69 to 4.22, P value 0.2).

#### Hyalgan versus conventional therapy

One RCT included was a comparison of Hyalgan and conventional therapy (Listrat 1997).

#### Efficacy

There were no statistically significant differences between Hyalgan and conventional care at 45 to 52 weeks postinjection in overall pain (measured on 0 to 100 mm VAS) (WMD -14.40; 95% CI

-31.86 to 3.06, P value 0.11) or in function (measured by the Lequesne Index) (WMD -0.90; 95% CI -3.81 to 2.01, P value 0.5). Since the arthroscopic outcome measures were chosen a priori as the primary efficacy variables in this trial, their results are also reported. Joint space width, measured in mm, was greater at 45 to 52 weeks postinjection, in the [Hyalgan](#) group (WMD 1.10; 95% CI -0.01 to 2.21, P value 0.05). A statistically significant difference in favour of [Hyalgan](#), at 45 to 52 weeks postinjection, was found for both the arthroscopy overall assessment (0 to 100 mm VAS) (WMD -22.30; 95% CI -40.52 to -4.08, P value 0.02) and the SFA system score (0 to 100 mm VAS) (WMD -18.20; 95% CI -31.27 to -5.13, P value 0.006). Therefore, [Hyalgan](#) was 14 to 22% more effective than conventional therapy in improving these arthroscopy parameters at 45 to 52 weeks postinjection. This trial also utilised a quality of life outcome measure, the Arthritis Impact Measurement Scales (AIMS), based on the total of 12 items. There was no statistically significant difference between groups (WMD -0.20; 95% CI -0.98 to 0.58, P value 0.6).

The RevMan analysis differed from the [Listrat 1997](#) analysis. The publication reported a statistically significant difference in favour of [Hyalgan](#) for AIMS (P value 0.047) at 45 to 52 weeks postinjection whereas the RevMan analysis detected no difference.

#### *Safety*

Safety, as assessed by total withdrawals overall, was similar in the two groups (RR 0.48; 95% CI 0.05 to 4.82, P value 0.5). One patient in the [Hyalgan](#) group withdrew because of lack of pain while two patients in the conventional therapy group withdrew: one because of osteotomy performed on the study knee and one because of relocation.

#### [Hyalgan](#) versus homeopathic treatment

Readers are directed to the [Zeel](#) section for results based on a comparison of [Zeel](#) compositum and [Hyalart](#) ([Nahler 1998](#)).

#### [Hyalgan](#) versus [Hyalgan](#)

One RCT included was a schedule comparison of [Hyalgan](#) ([Karras 2001](#)).

#### *Efficacy*

There was no statistically significant difference in the number of patients assessing the response as satisfactory between the five injection [Hyalgan](#) schedule (67%) and the three injection [Hyalgan](#) schedule (79%) (RR 0.85; 95% CI 0.70 to 1.03, P value 0.10).

#### *Safety*

From the abstract it was not possible to ascertain to which group the patients belonged that experienced three cases of local pain.

#### [Hyalgan](#) versus other hyaluronans

Readers are directed to the [Adant](#) and [Fermathron](#) product results for comparisons of [Hyalgan](#) against these two HA products, respectively.

One RCT included was a comparison of [Hyalgan](#) and [Hylan G-F 20](#) ([Brown 2003](#)). This trial was discontinued on ethical grounds due to the frequency of acute inflammatory reactions with [Hylan G-F 20](#) (21%) compared to [Hyalgan](#) (0%) (RR 0.09; 95% CI 0.01 to 1.50, P value 0.09). No efficacy data were extracted from the abstract.

#### **Product - [Hylan G-F 20](#) ([Synvisc](#))**

##### *Description of studies*

Eighteen RCTs were included ([Adams 1995](#); [Ardic 2001](#); [Auerbach 2002](#); [Bayramoglu 2003](#); [Brown 2003](#); [Caborn 2004](#); [Dickson 2001](#); [Groppa 2001](#); [Kahan 2003a](#); [Karlsson 2002](#); [Leopold 2003](#); [Moreland 1993](#); [Raynauld 2002](#); [Scale 1994a \(2 inj\)](#); [Scale 1994b \(3 inj\)](#); [Thompson 2002](#); [Wobig 1998](#); [Wobig 1999](#)). Considering only the 14 trials in which [Hylan G-F 20](#) was designated the experimental intervention, the Jadad score ranged from 1 to 5 with an average quality of 3.1. One trial scored 5 ([Moreland 1993](#)), five scored 4 ([Dickson 2001](#); [Scale 1994a \(2 inj\)](#); [Scale 1994b \(3 inj\)](#); [Wobig 1998](#); [Wobig 1999](#)), four scored 3 ([Adams 1995](#); [Kahan 2003a](#); [Leopold 2003](#); [Raynauld 2002](#)), two scored 2 ([Auerbach 2002](#); [Caborn 2004](#)), and two scored 1 ([Ardic 2001](#); [Groppa 2001](#)). When considering all 18 trials, the average Jadad score was 2.9. Allocation concealment was adequate in nine trials and inadequate (not reported) in five trials ([Ardic 2001](#); [Auerbach 2002](#); [Caborn 2004](#); [Dickson 2001](#); [Groppa 2001](#)).

[Hylan G-F 20](#) has been compared against IA control treatment ([Ardic 2001](#); [Dickson 2001](#); [Groppa 2001](#); [Karlsson 2002b \(SvP\)](#); [Moreland 1993](#); [Scale 1994a \(2 inj\)](#); [Scale 1994b \(3 inj\)](#); [Wobig 1998](#); [Wobig 1999c \(NEhyl\)](#)), IA corticosteroid ([Caborn 2004](#); [Leopold 2003](#)), nonsteroidal anti-inflammatory drug ([Adams 1995](#); [Dickson 2001](#)), IA gaseous oxygen ([Auerbach 2002](#)), physiotherapy ([Bayramoglu 2003](#)), appropriate care ([Kahan 2003a](#); [Raynauld 2002](#)), and hyaluronan ([Bayramoglu 2003 \[Orthovisc\]](#); [Brown 2003 \[Hyalgan\]](#); [Karlsson 2002c \(AvS\) \[Artzal\]](#); [Thompson 2002 \[BioHy\(Arthrease\)\]](#); [Wobig 1999 \[Artz, Healon\]](#)). The draft manuscript for the abstract presented by [Moreland et al. \(Moreland 1993\)](#) was kindly provided by [Biomatix, Inc.](#) as were the Pre-Market Approval (PMA) data for the studies by [Adams et al. \(Adams 1995\)](#), [Scale et al. \(Scale 1994a \(2 inj\); Scale 1994b \(3 inj\)\)](#), and [Wobig et al. \(Wobig 1998; Wobig 1999\)](#). The trials were completed in eight countries: Canada ([Adams 1995](#); [Raynauld 2002](#)), England ([Dickson 2001](#)), France ([Kahan 2003a](#)), Germany ([Auerbach 2002](#); [Scale 1994a \(2 inj\)](#); [Scale 1994b \(3 inj\)](#); [Wobig 1998](#); [Wobig 1999](#)), Republic of Moldova ([Groppa 2001](#)), Scotland ([Dickson 2001](#)), Turkey ([Ardic 2001](#)), and the United States ([Caborn 2004](#); [Leopold 2003](#); [Moreland 1993](#)). They were published over an eleven-year period: 1993 through 2004. Sample size per group varied from 15 ([Scale 1994b](#)

(3 inj)) to 253 (Kahan 2003a) while sample size per trial varied from 30 to 518. One trial was eight weeks in duration (Ardic 2001), two trials were twelve weeks in duration (Dickson 2001; Wobig 1999), four trials were 12 weeks in duration with a telephone interview at 26 weeks (Adams 1995; Scale 1994a (2 inj); Scale 1994b (3 inj); Wobig 1998), one trial was 24 weeks in duration (Leopold 2003), one trial was 26 weeks in duration (Caborn 2004), one trial was 34 weeks in duration (Moreland 1993), one trial was 36 weeks in duration (Kahan 2003a), and three trials were 52 weeks in duration (Auerbach 2002; Groppa 2001; Raynauld 2002).

For the six trials that were included in the PMA P940015 (Adams 1995; Moreland 1993; Scale 1994a (2 inj); Scale 1994b (3 inj); Wobig 1998; Wobig 1999), control and Hylan G-F 20 treatments were prepared in syringes that had identical appearances and which were coded only by random numbers. All subjects participating in these trials received arthrocentesis with removal of effusion if present. All IA procedures were performed in an identical manner for treatment and control study groups in these trials. A screen, blinding the patient from the procedure, was utilised in four trials (Adams 1995; Dickson 2001; Moreland 1993; Wobig 1998).

Twenty-four studies were excluded (Bell 1999; Bruce 2004; Chhabra 2000; Clarke 2001; Evanich 2001; Goorman 2000; Ines 2002; Koyuncu 2003; Legre 2001; Lussier 1996; Magobotha 2001; Mathieu 2001; Miller 1999; Myburgh 2001; Olszynski 2002; Sripada 1999; Stambuk 2001; Torrance 2002; Vad 2000; Waddell 2001a; Waddell 2001b; Weiss 1999; Wobig 1999d; Wulwik 2001). Four trials are awaiting assessment (Atamaz 2004; Kotevogu 2002; Russell 2003; Shariati 2001). These trials have been published only as abstracts

with no extractable data, and at the closure of the database for this review no full length manuscripts have been published.

Adams et al. reported a 26-week, parallel-group RCT performed at six centres in Canada comparing three weekly injections of Hylan G-F 20 to either NSAID continuation plus three weekly control arthrocenteses or NSAID continuation plus three weekly injections of Hylan G-F 20 in 102 patients with OA of the knee (Adams 1995). All groups showed significant improvement from baseline at 12 weeks but did not differ from each other. The two groups receiving Hylan G-F 20 were significantly better than the NSAID alone group at Week 26.

Several design issues are noted for the Adams et al. RCT (Adams 1995). This trial was designed to evaluate viscosupplementation with Hylan G-F 20 as a replacement for continuous NSAID therapy. There was no washout period. The concomitant use of acetaminophen for analgesia was permitted and recorded by pill counts. However, usage was not reported since it was documented in different formats by the treating physicians and could not be standardised into a single format for purposes of uniform analysis. The resumption of NSAID between weeks 12 and 26 was

reported. 55.6% of patients in the Hylan G-F 20 group only resumed taking NSAID compared to 84.4% in the NSAID plus Hylan G-F 20 group and 96.8% in the NSAID group. Fifteen per cent of the included patients presented with effusion at the first visit. The Hylan G-F 20 only group may not have been blinded since they were instructed to discontinue their NSAID. The authors addressed this concern in the publication by commenting that, "if incomplete blinding introduced a bias, it would be against the Hylan G-F 20-only group in that patients recognized that they were discontinuing an active medication, and consequently may have expected their condition to worsen". The method of assessment at 26 weeks was by telephone follow-up which differed from that of baseline (i.e. office visit). A subsequent study showed that there was no significant difference in results obtained by telephone compared to office visits for the WOMAC 3.0 Osteoarthritis Index (Bellamy 2002).

Ardic et al. reported an eight-week, placebo-controlled RCT performed at one centre in Turkey comparing three weekly injections of Hylan G-F 20 to three weekly injections of saline in 17 patients with OA of the knee (Ardic 2001). The authors reported prominent clinical improvement in the Hylan G-F 20 group after eight weeks. No patients reported adverse events. Only safety data are used in the review since only p-values are reported for the clinical outcome measures.

The Ardic et al. trial reported results for only 17 patients (Ardic 2001). No explanation was given in the abstract for the unequal group allocation (i.e. 2.4:1 patients or 3:1 knees). Details regarding blinding and withdrawals/drop outs were not reported in the abstract. The 'need of drug' was an outcome measure in this trial.

Auerbach et al. reported a one-year, parallel-group RCT performed at a single centre in Germany comparing three weekly injections of Hylan G-F 20 plus an exercise programme to five weekly IA injections of gaseous oxygen (three days per week) plus an exercise programme in 111 patients with OA of the knee (Auerbach 2002; Auerbach 2002a). Both treatments were effective in relieving pain and improving joint function. Pain relief by Hylan G-F 20 and improvement in function by oxygen treatment were shown for more severe levels of cartilage damage.

The Auerbach trial was one of the few trials not published in English. Both the thesis (Auerbach 2002a) and the journal article (Auerbach 2002) were published in German. An English abstract was provided in the journal article. It was the only trial in which HA was compared to IA injection of gaseous oxygen. The authors studied the relation between treatment effect and severity of cartilage damage.

Caborn et al. reported a 26-week, parallel group, single-blind RCT performed at 14 centres in the United States comparing three weekly injections of Hylan G-F 20 to one IA injection of triamcinolone hexacetonide (Aristospan) in 218 patients with OA of the knee (Caborn 2003; Caborn 2004; Lanzer 2002). Treatment

with Hylan G-F 20 resulted in a longer duration of effect than triamcinolone hexacetonide. Both treatments were well tolerated with 10% of patients in each group reporting an adverse event that resulted in withdrawal from the trial.

The Caborn et al. trial was single-blind and details regarding the method of randomisation were not published (Caborn 2004). The triamcinolone hexacetonide group received only one injection compared to the three injections administered to the Hylan G-F 20 group. Analgesic and NSAID usage were monitored throughout this trial. Patients with effusion of greater than 10 ml were excluded. Almost 30% of each treatment group had severe radiological ratings while approximately 60% in each group had moderate ratings.

Dickson et al. reported a 12-week, parallel-group, double-blind RCT performed at 18 centres in England and Scotland comparing three weekly injections of Hylan G-F 20 and dummy capsules taken once daily to either Diclofenac retard 100 mg taken once daily and three weekly arthrocenteses or dummy capsules taken once daily and three weekly arthrocenteses in 165 patients with OA of the knee (Dickson 2001). Patients, completing the 12-week study, could enter an open-label study in which they received treatment with up to four additional courses of Hylan G-F 20 over a one-year period. Hylan G-F 20 was significantly better than either diclofenac or arthrocentesis in reducing WOMAC pain. The diclofenac group had significantly more total and gastrointestinal adverse events than the Hylan G-F 20 or control groups.

The Dickson et al. trial was one of the few trials conducted in general practice (Dickson 2001). To ensure blinding, all three arms of the trial received arthrocentesis. The diclofenac sodium dosage of 100 mg daily may be considered by some as subtherapeutic but the Diclomax Retard 1993 product label indicated this to be the recommended adult dosage. The mean number of paracetamol tablets taken for analgesic rescue medication (3000 mg daily permitted) was published.

Groppa and Moshneaga reported a one-year, blind CT performed at a single centre in The Republic of Moldova comparing three weekly injections of Hylan G-F 20 to three weekly injections of placebo in 25 patients with OA of knee (Groppa 2001). Courses were repeated at six and 12 months. After the first course, one-third of the patients treated with Hylan G-F 20 had decreased pain and improved joint function compared to none in the placebo group. After three courses, 87% of the Hylan G-F 20 patients had moderate or very good effect compared to only 20% of the patients in the control group who had moderate effect. No safety data were reported in the abstract.

The Groppa trial randomised a sample size of 25 patients (Groppa 2001). However, the control group was matched by gender, disease duration and x-ray date. The study was designed to address the important issue of repeat treatment with a second and third course repeated at six and 12 months, respectively. Radiography,

ultrasonography and scintigraphy with Te 99m were all utilised in evaluation.

Kahan et al. reported a nine-month, open-label, parallel-group, RCT performed with 81 rheumatologists (21 hospital based, 60 office based) in France comparing three weekly injections of Hylan G-F 20 to conventional treatment in 518 patients with OA of the knee (Kahan 2003 [article published in French]; Kahan 2003a). The authors reported that Hylan G-F 20 viscosupplementation was more effective than conventional treatment at no additional cost.

The Kahan et al. trial provided medicoeconomic data on viscosupplementation for OA (Kahan 2003a; Kahan 2003). The design was very similar to the Raynauld et al. trial (Raynauld 2002). The study was completed under conditions of actual practice.

Leopold et al. reported a six-month, single-blind, parallel-group, RCT performed at a single centre in the United States comparing three weekly injections of Hylan G-F 20 to one injection of betamethasone sodium phosphate-betamethasone acetate (Celestone Soluspan), which could be repeated during the study, in 100 patients with OA of the knee (Leopold 2003; Redd 2003). No differences in pain or function were found between the two groups at the six months follow-up. Neither treatment worked well in females. One patient in the Hylan G-F 20 group withdrew because of an acute local reaction. One-fifth of the study population withdrew because of a lack of treatment efficacy. Only safety data have been extracted from this trial. Since the outcome variables had results that were not normally distributed, nonparametric statistical methods were used to analyze the data (e.g. change in median outcomes scores).

The Leopold et al. trial was an independent trial not funded by the manufacturer of the hyaluronate-based product under study (Leopold 2003). The injection procedure was standardised by: 1) patient was in the supine position, 2) the injection was made superolaterally into the suprapatellar notch, and 3) patients were encouraged to refrain from strenuous activity for a day. However, effusions were aspirated in the HA group whereas they were not in the corticosteroid group. In addition, patients in the corticosteroid group were permitted to have one more injection any time during the study. The authors chose not to use the Ahlback radiographic grading system, "because three of the four stages include knees with a completely obliterated joint space". This was the only trial to find a gender difference in treatment response.

Moreland et al. reported a 34-week, parallel-group, double-blind RCT performed at five centres in the United States comparing three weekly injections of Hylan G-F 20 to three weekly arthrocenteses in 94 patients with OA of the knee (Moreland 1993). This trial had two phases. Phase I lasted 10 weeks, after which patients could enter Phase II in which all patients received treatment with Hylan G-F 20. For this analysis, the Phase II data were not included because, although patient blinding was maintained

during this Phase, treatment was not randomised. Analyses were based on the week eight evaluation endpoint which was two weeks after the third injection in Phase I. A statistically significant difference, in favour of Hylan G-F 20, was detected in overall pain only in a predefined 'flare' population but not in the 'intent-to-treat' population. During the two phases approximately 7% of patients receiving Hylan G-F 20 discontinued treatment due to local adverse reactions (pain or swelling) in the injected knee.

The Moreland et al. trial was only published as an abstract but an in-house unpublished manuscript allowed this trial to be included in the review (Moreland 1993). This trial examined the "clinimetric utility" of identifying a flare population. Despite a four-week washout of all anti-inflammatory medication, only 30% of patients demonstrated a flare in pain symptoms. However, patients were randomised regardless of flare criteria. The authors noted that the final evaluation for Phase I of the trial was only two weeks after completing treatment. This may have minimised any between-group differences, and could have maximised the short-term effect of arthrocentesis. Acetaminophen usage was permitted throughout the entire trial duration but there was no significant difference between the groups in daily usage.

Raynauld et al. reported a one-year, open-label, parallel-group, RCT performed at 14 centres in Canada comparing appropriate care with Hylan G-F 20 (AC + H) to appropriate care without Hylan G-F 20 (AC) in 255 patients with OA of the knee (Raynauld 2002). For all the primary and secondary effectiveness outcome measures the AC + H group was superior to the AC group. Safety differences favoured the AC + H group.

The Raynauld et al. trial was an effectiveness study that also included an economic evaluation (Torrance 2002). The study was strengthened by the expertise of an independent, academic Steering Committee. This 'pragmatic' study operated under 'a real world scenario'. The trial highlighted the difference between radiologic grading completed by a central reader and that done by site investigators. Although Kellgren and Lawrence Grade 4 was an entry exclusion criteria, 20% of the appropriate care plus Hylan G-F 20 group and 33% of the appropriate care without Hylan G-F 20 group were rated as Grade 4 by the central reader. However, when Grade 4 was used as a covariate there was no significant difference in the analysis results. Repeat treatment was permitted to either or both knees as required during the trial.

The publication by Scale et al. reported two separate trials (Scale 1994a (2 inj); Scale 1994b (3 inj)). One was a comparison of two biweekly injections of Hylan G-F 20 versus two biweekly injections of saline in 50 patients with OA of the knee (Scale 1994a (2 inj)), and the other was a comparison of three weekly injections of Hylan G-F 20 versus three weekly injections of saline in 30 patients with OA of the knee (Scale 1994b (3 inj)). Both studies were 26-week, parallel-group, double-blind RCTs performed at a single centre in Germany. Patients were excluded if effusion was present in the

joint. For most outcome measures, the Hylan G-F 20 treatment showed statistically significant superiority over saline treatment for both treatment regimens. The three-injection treatment regimen was statistically more effective than the two-injection treatment regimen. One local, treatment-related, adverse event represented 1% of all the Hylan G-F 20 injections or 2.5% of all the knees treated with Hylan G-F 20 in this study.

Scale et al. published the first RCTs of Hylan G-F 20. Continuous outcome measures were transformed into categorical scores. "Successful treatment" (i.e. responder) was defined as a score of 0 to 20 mm on the VAS for the pain and activity reduction outcome measures, and a score of 80 to 100 mm for the improvement of the most painful knee movement. Although the journal publication reported results based on a combined control group, the PMA report provided results based on the separate randomised control groups which were used in this review. The three-injection trial randomised 30 patients in total.

Wobig et al. reported a 26-week, parallel-group, double-blind RCT performed at four centres in Germany comparing three weekly injections of Hylan G-F 20 to three weekly injections of saline in 110 patients with OA of the knee (Wobig 1998). Statistically significant differences between Hylan G-F 20 and saline treatment were reported for all outcome measures. No adverse events were observed in the injected joint after Hylan G-F 20 treatment.

In the Wobig et al. RCT, patients with effusion were excluded (Wobig 1998). Again a categorical analysis was completed based on the same responder criteria as Scale et al. above. 98% of the randomised patients completed all follow-up visits. Only one Hylan G-F 20 patient did not participate in the telephone interview and one saline patient, who missed the visits at weeks eight and 12, did participate in the telephone interview at week 26.

The 1999 Wobig publication reported the results of two arms (Hylan G-F 20 versus Artz) of a four-arm trial (Artz, Healon, Hylan G-F 20, nonelastoviscous hylan) (Wobig 1999). This was a 12-week, parallel-group, double-blind RCT performed at six centres in Germany comparing three weekly injections of Hylan G-F 20 to either three weekly injections of Artz (Wobig 1999b (Artz)), three weekly injections of Healon (Wobig 1999a (Healon)), or three weekly injections of nonelastoviscous (denatured) hylan (Wobig 1999c (NEhyl)) in 109 knees. Considering only the published Hylan G-F 20 versus Artz comparison, significantly greater pain-relieving effects were detected in favour of Hylan G-F 20. No statistically significant differences in the incidence of adverse events between these two groups were detected.

In an attempt to explain the mechanism of action of viscosupplementation, the objective of the Wobig et al. trial (Wobig 1999b (Artz)) was to determine if a correlation existed between clinical effectiveness and elastoviscosity. Patients were once again categorised as 'symptom-free' based on the Scale et al. criteria above.



Descriptions of the four RCT in which Hylan G-F 20 was the control treatment are found in the other product results sections: BioHy (Arthrease) (Thompson 2002), Artz (Artzal, Supartz) (Karlsson 2002), Hyalgan (Brown 2003), and Orthovisc (Bayramoglu 2003).

Hylan G-F 20 (Synvisc) versus placebo

Nine RCTs included were comparisons of Hylan G-F 20 and placebos (Ardic 2001; Dickson 2001; Groppa 2001; Karlsson 2002b (SvP); Moreland 1993; Scale 1994a (2 inj); Scale 1994b (3 inj); Wobig 1998, Wobig 1999c (NEhyl)). Control treatments included IA saline, arthrocentesis, arthrocentesis and placebo capsules taken once daily, and nonelastoviscous (NE) denatured hylan fluid. The current product monograph for Synvisc (Synvisc Hylan G-F 20) indicates administration by IA injection once a week (one week apart) for a total of three injections.

### *Efficacy*

Statistically significant differences in favour of Hylan G-F 20 compared to placebo were found in pain on weight bearing (measured on 0 to 100 mm VAS) at 1 to 4 weeks postinjection (WMD (random-effects model) -12.54; 95% CI -20.39 to -4.69, P value 0.002) (Karlsson 2002b (SvP); Moreland 1993; Scale 1994a (2 inj); Scale 1994b (3 inj); Wobig 1998; Wobig 1999c (NEhyl)). With the exception of the Karlsson RCT (Karlsson 2002b (SvP)), Hylan G-F 20 was 4 to 24% more effective than placebo. With five trials, a statistically significant difference in favour of Hylan G-F 20 compared to placebo was found at 5 to 13 weeks postinjection (WMD (random-effects model) -22.46; 95% CI -35.24 to -9.68, P value 0.0006) (Karlsson 2002b (SvP); Scale 1994a (2 inj); Scale 1994b (3 inj); Wobig 1998; Wobig 1999c (NEhyl)). Hylan G-F 20 was 1 to 43% more effective than placebo. At 14 to 26 weeks postinjection, there was a statistically significant difference in favour of Hylan G-F 20 compared to placebo (WMD (random-effects model) -20.70; 95% CI -35.56 to -5.83, P value 0.006) (Karlsson 2002b (SvP); Scale 1994a (2 inj); Scale 1994b (3 inj); Wobig 1998). Hylan G-F 20 was 1 to 49% more effective than placebo.

Statistically significant differences in favour of Hylan G-F 20 compared to placebo were found in pain at night (measured on 0 to 100 mm VAS) at 1 to 4 weeks postinjection (WMD -7.22; 95% CI -12.01 to -2.42, P value 0.003) (Moreland 1993; Scale 1994a (2 inj); Scale 1994b (3 inj); Wobig 1998; Wobig 1999c (NEhyl)). Hylan G-F 20 was 13 to 31% more effective than placebo. With four trials, a statistically significant difference in favour of Hylan G-F 20 compared to placebo was found at 5 to 13 weeks postinjection (WMD (random-effects model) -10.64; 95% CI -18.55 to -2.73, P value 0.008) (Scale 1994a (2 inj); Scale 1994b (3 inj); Wobig 1998; Wobig 1999c (NEhyl)). Hylan G-F 20 was 28 to 50% more effective than placebo. At 14 to 26 weeks postinjection, based on three trials, there was a statistically significant difference in favour of Hylan G-F 20 compared to placebo (WMD -17.12;

95% CI -23.22 to -11.02, P < 0.00001) (Scale 1994a (2 inj); Scale 1994b (3 inj); Wobig 1998). Hylan G-F 20 was 28 to 96% more effective than placebo.

No statistically significant difference was detected at 1 to 4 weeks postinjection in pain walking (0 to 100 mm VAS) (WMD -3.00; 95% CI -15.55 to 9.55, P value 0.6), pain at rest (0 to 100 mm VAS) (WMD -5.00; 95% CI -18.86 to 8.86, P value 0.5), pain overall (0 to 100 mm VAS) (WMD -2.00; 95% CI -13.09 to 9.09, P value 0.7) (Moreland 1993), or at 5 to 13 weeks postinjection in WOMAC pain (WMD -8.00; 95% CI -17.80 to 1.80, P value 0.11) (Dickson 2001).

The RevMan analysis differed from the publication analysis (Dickson 2001). The publication reported a statistically significant difference in favour of Hylan G-F 20 compared to the double dummy placebo at 5-13 weeks postinjection for WOMAC pain (P value 0.04) whereas RevMan detected no statistically significant difference (P value 0.11).

A statistically significant difference in favour of Hylan G-F 20 was detected in the WOMAC physical function subscale at 5 to 13 weeks postinjection, (WMD -9.00; 95% CI -16.07 to -1.93, P value 0.01) and in the Lequesne Index (WMD -1.60; 95% CI -2.99 to -0.21, P value 0.02) (Dickson 2001). Hylan G-F 20 was 7 to 13% more effective than placebo. No significant difference was detected in the Lequesne Index at 14 to 26 weeks postinjection (WMD 0.10; 95% CI -1.38 to 1.58, P value 0.9) (Karlsson 2002b (SvP)).

The RevMan analysis differed from the publication analysis (Dickson 2001). The publication reported no difference in the Lequesne Index at 5 to 13 weeks (P value 0.17) whereas RevMan detected a statistically significant difference in favour of Hylan G-F 20. The publication reported no difference in WOMAC physical function at 5 to 13 weeks (P value 0.05) whereas RevMan detected a statistically significant difference in favour of Hylan G-F 20.

A statistically significant difference in favour of Hylan G-F 20 compared to placebo was detected in improvement in the most painful knee movement (0 to 100 mm VAS) both at 1 to 4 weeks postinjection (WMD 19.29; 95% CI 12.16 to 26.31, P < 0.00001) and at 5 to 13 weeks postinjection (WMD (random-effects model) 33.87; 95% CI 21.19 to 46.55, P < 0.00001) (Scale 1994a (2 inj); Scale 1994b (3 inj); Wobig 1998; Wobig 1999c (NEhyl)).

When patient global assessment data were dichotomised into improved or not improved by classifying responses of 'very poor', 'poor' and 'fair' as 'not improved' and 'good' and 'very good' as 'improved', more patients in the Hylan G-F 20 group were either 'very good' or 'good' (69%) than in the double control group (48%) at 5 to 13 weeks postinjection (RR 1.44; 95% CI 1.01 to 2.06, P value 0.05) (Dickson 2001).

A statistically significant difference in favour of Hylan G-F 20 compared to placebo was detected for patient global assessment of treatment efficacy (0 to 100 mm VAS) both at 1 to 4 weeks postinjection (WMD 21.94; 95% CI 14.94 to 28.94,  $P < 0.00001$ ) and at 5 to 13 weeks postinjection (WMD (random effects) 34.66; 95% CI 21.27 to 48.06,  $P < 0.00001$ ) (Scale 1994a (2 inj); Scale 1994b (3 inj); Wobig 1998; Wobig 1999c (NEhyl)).

No statistically significant difference was noted in the number of clinical failures at 14 to 26 weeks postinjection: Hylan G-F 20, 7% and Saline 11% (RR 0.66; 95% CI 0.23 to 1.87,  $P$  value 0.4) or at 45 to 52 weeks postinjection: Hylan G-F 20 46% and saline 54% (RR 0.84; 95% CI 0.59 to 1.22,  $P$  value 0.4) (Karlsson 2002b (SvP)), or in the number of survivors (i.e. patients not requiring additional treatment to study knee): Hylan G-F 20 44% and saline 33% (RR 1.33; 95% CI 0.87 to 2.0,  $P$  value 0.18) (Karlsson 2002b (SvP)).

Considering only the two most homogeneous trials, i.e., the three-injection trial of Scale (Scale 1994b (3 inj)) and the Wobig trial (Wobig 1998), a statistically significant difference in favour of Hylan G-F 20 compared to saline was detected in pain on weight bearing (0 to 100 mm VAS) at 1 to 4 weeks postinjection (WMD -22.00; 95% CI -29.13 to -14.87,  $P < 0.00001$ ), at 5 to 13 weeks postinjection (WMD -35.68; 95% CI -42.81 to -28.55,  $P < 0.00001$ ) and at 14 to 26 weeks postinjection (WMD -21.62; 95% CI -30.84 to -12.39,  $P < 0.00001$ ). A statistically significant difference in favour of Hylan G-F 20 compared to saline was detected in pain at night (0 to 100 mm VAS) at 1 to 4 weeks postinjection (WMD -10.64; 95% CI -17.29 to -3.99,  $P$  value 0.002), at 5 to 13 weeks postinjection (WMD -15.50; 95% CI -21.38 to -9.62,  $P < 0.00001$ ), and at 14 to 26 weeks postinjection (WMD -16.20; 95% CI -22.85 to -9.55,  $P < 0.00001$ ). A statistically significant difference in favour of Hylan G-F 20 compared to saline was detected in improvement in the most painful knee movement (0 to 100 mm VAS) both at 1 to 4 weeks postinjection (WMD 23.97; 95% CI 14.34 to 33.60,  $P < 0.00001$ ) and at 5 to 13 weeks postinjection (WMD 40.56; 95% CI 31.11 to 50.01,  $P < 0.00001$ ). A statistically significant difference in favour of Hylan G-F 20 compared to saline was detected for the variable treatment efficacy (improvement on 0 to 100 mm VAS) both at 1 to 4 weeks postinjection (WMD 26.62; 95% CI 17.39 to 35.84,  $P < 0.00001$ ) and at 5 to 13 weeks postinjection (WMD 43.85; 95% CI 34.62 to 53.07,  $P < 0.00001$ ).

### Safety

No statistically significant differences were detected in the total number of withdrawals overall at 1 to 4 weeks postinjection (RR 0.70; 95% CI 0.12 to 3.97,  $P$  value 0.7) (Moreland 1993) or at 5 to 13 weeks (RR 1.40; 95% CI 0.64 to 3.06,  $P$  value 0.4) (Dickson 2001; Wobig 1998; Wobig 1999c (NEhyl)). No significant differences were detected in the number of withdrawals due to adverse events (RR 13.55; 95% CI 0.79 to 233.96,  $P$  value 0.07). The

number of local reactions was significantly higher in the Hylan G-F 20 plus arthrocentesis group compared to arthrocentesis (RR 30.23; 95% CI 1.86 to 492.59,  $P$  value 0.02).

No significant differences were detected in the number of patients with local reactions (RR 1.17; 95% CI 0.48 to 2.83,  $P$  value 0.7) (Dickson 2001; Wobig 1998; Wobig 1999c (NEhyl)), number of patients with local adverse reaction at 1 to 4 weeks postinjection but study drug continued (RR 3.00; 95% CI 0.13 to 68.26,  $P$  value 0.5) (Scale 1994b (3 inj)), number of patients with adverse events at 5 to 13 weeks postinjection ( $P$  value 1) (Ardic 2001), number of patients with one or more probable or possible related systemic adverse events at 5 to 13 weeks postinjection (RR 1.98; 95% CI 0.79 to 4.96,  $P$  value 0.14) (Dickson 2001) or number of patients reporting systemic adverse reactions at 5 to 13 weeks postinjection (RR 7.60; 95% CI 0.39 to 139.45,  $P$  value 0.18) (Wobig 1998; Wobig 1999c (NEhyl)).

Hylan G-F 20 (Synvisc) versus corticosteroid

Two RCTs included were comparisons of Hylan G-F 20 and IA corticosteroid.

One RCT was a comparison of Hylan G-F 20 and betamethasone sodium phosphate - betamethasone acetate (Leopold 2003). One RCT was a comparison of Hylan G-F 20 and triamcinolone hexacetonide (Caborn 2004).

### Efficacy

The efficacy outcome measure results in the Leopold trial (Leopold 2003) were presented as changes in median scores because the data were not normally distributed. Therefore, only safety data for this RCT are reported.

A statistically significant difference in favour of Hylan G-F 20 compared to triamcinolone hexacetonide was found for WOMAC pain walking on a flat surface (scored 0 to 4) in the Caborn trial (Caborn 2004) (WMD -0.40; 95% CI -0.65 to -0.15,  $P$  value 0.002) at 5 to 13 weeks postinjection and (WMD -0.40; 95% CI -0.68 to -0.12,  $P$  value 0.005) at 14 to 26 weeks postinjection. Hylan G-F 20 was 17% more effective than triamcinolone hexacetonide. A statistically significant difference in favour of Hylan G-F 20 compared to triamcinolone hexacetonide was found for the WOMAC physical function subscale (scored 0 to 68) (WMD -5.00; 95% CI -8.86 to -1.14,  $P$  value 0.01) at 5 to 13 weeks postinjection and (WMD -5.20; 95% CI -9.10 to -1.30,  $P$  value 0.009) at 14 to 26 weeks postinjection. Hylan G-F 20 was, on average, 17% more effective than triamcinolone hexacetonide. A statistically significant difference in favour of Hylan G-F 20 compared to triamcinolone hexacetonide was found for WOMAC total score (scored 0-96) (WMD -7.40; 95% CI -12.74 to -2.06,  $P$  value 0.007) at 5 to 13 weeks postinjection and (WMD -7.30; 95% CI -12.76 to -1.84,  $P$  value 0.009) at 14 to 26 weeks postinjection. Hylan G-F 20 was 15% more effective than triamcinolone hexacetonide. A statistically significant difference in favour of Hylan

G-F 20 compared to triamcinolone hexacetonide was found for for patient global assessment (scored 0 to 100 mm VAS) (WMD -13.40; 95% CI -20.03 to -6.77, P value 0.00007) at 5 to 13 weeks postinjection and (WMD -15.10; 95% CI -22.17 to -8.03, P value 0.00003) at 14 to 26 week postinjection. Hylan G-F 20 was approximately 23% more effective than triamcinolone hexacetonide.

In the Caborn trial (Caborn 2004) there was no statistically significant difference in the number of responders defined as at least a one-point improvement in the WOMAC pain walking on a flat surface at 1 to 4 weeks postinjection (RR 1.21; 95% CI 0.96 to 1.53, P value 0.11). However, there was a statistically significant difference in favour of Hylan G-F 20 at 5 to 13 weeks postinjection (RR 1.44; 95% CI 1.09 to 1.90, P value 0.01). The NNT for the number of responders was 5. At 14 to 26 weeks postinjection, the RR was 1.44 (95% CI 1.00 to 2.09) P value 0.05. There was no statistically significant difference in analgesic usage between week 0 and prior to week 12 (RR 1.01; 95% CI 0.97 to 1.06, P value 0.6) or between week 12 and prior to week 26 (RR 0.84; 95% CI 0.64 to 1.11, P value 0.2).

#### *Safety*

With respect to the Leopold trial (Leopold 2003), there were no statistically significant differences in the safety outcomes: total withdrawals overall (RR 1.56; 95% CI 0.74 to 3.26, P value 0.2), withdrawals due to lack of efficacy (RR 1.50; 95% CI 0.67 to 3.35, P value 0.3) and withdrawals due to acute local reactions (RR 3.31; 95% CI 0.14 to 78.84, P value 0.5).

With respect to the Caborn trial (Caborn 2004), there was a statistically significant difference in favour of Hylan G-F 20 compared to triamcinolone hexacetonide in the number of withdrawals due to lack of efficacy (RR 0.03; 95% CI 0.00 to 0.48, P value 0.01). There were no statistically significant differences in the total number of withdrawals overall (RR 0.78; 95% CI 0.52 to 1.17, P value 0.2) or the number of withdrawals due to adverse events (RR 1.00; 95% CI 0.44 to 2.26, P value 1).

Hylan G-F 20 (Synvisc) versus NSAID

Two trials included were comparisons of Hylan G-F 20 and NSAID (Adams 1995; Dickson 2001). In the Adams trial (Adams 1995), the early 5 to 13 weeks postinjection follow-up assessment was reported as change (improvement) scores, while the 14 to 26 week follow-up was based on difference scores. The Dickson trial (Dickson 2001) results were reported as change (improvement) scores.

#### *Efficacy*

There were no statistically significant differences in any of the efficacy measures at either 5 to 13 or 14 to 26 weeks postinjection (Adams 1995): pain on motion (0 to 100 mm VAS) (WMD -6.00; 95% CI -17.09 to 5.09, P value 0.3) at 5 to 13 weeks and

(WMD -12.00; 95% CI -24.55 to 0.55, P value 0.06) at 14 to 26 weeks postinjection; pain at rest (0 to 100 mm VAS) (WMD -3.00; 95% CI -14.09 to 8.09, P value 0.6) at 5 to 13 weeks and (WMD -3.00, 95% CI -12.80 to 6.80, P value 0.5) at 14 to 26 weeks postinjection; pain at night (0 to 100 mm VAS) (WMD -7.00; 95% CI -19.55 to 5.55, P value 0.3) at 5 to 13 weeks and (WMD -3.00; 95% CI -15.55 to 9.55, P value 0.6) at 14 to 26 weeks postinjection; pain overall (0 to 100 mm VAS) (WMD -5.00; 95% CI -18.86 to 8.86, P value 0.5) at 5 to 13 weeks and (WMD -5.00; 95% CI -16.09 to 6.09, P value 0.4) at 14 to 26 weeks postinjection.

The RevMan analysis differed from the Adams publication (Adams 1995) analysis. The publication reported a statistically significant difference (P value 0.05) in favour of Hylan G-F 20 over NSAID in pain at rest at 5 to 13 weeks whereas the RevMan analysis detected no difference.

There was a statistically significant difference in favour of Hylan G-F 20 compared to NSAID in the WOMAC pain subscale (0 to 100 mm VAS) (WMD -12.00; 95% CI -23.09 to -0.91, P value 0.03) at 5 to 13 weeks postinjection (Dickson 2001). Hylan G-F 20 was 16% more effective than NSAID. There were no statistically significant differences in physical function measured either on the WOMAC physical function subscale (0 to 100 mm VAS) (WMD -4.00; 95% CI -11.07 to 3.07, P value 0.3) or on the Lequesne Index (0 to 24) (WMD -1.00; 95%

CI -2.39 to 0.39, P value 0.16) at 5 to 13 weeks postinjection (Dickson 2001).

There were no statistically significant differences in the patient global assessment, measured as the number of patients assessing the treatment as excellent, very good or good, either at 5 to 13 weeks postinjection (RR 0.83; 95% CI 0.65 to 1.06, P value 0.13) (Dickson 2001) or at 14 to 26 weeks postinjection (RR 1.63; 95% CI 0.96 to 2.76, P value 0.07) (Adams 1995).

#### *Safety*

There were no statistically significant differences in the following safety outcome measures: total withdrawals overall (RR 0.80; 95% CI 0.38 to 1.66, P value 0.5) at 5 to 13 weeks postinjection (Dickson 2001) and (RR 1.46; 95% CI 0.36 to 6.02, P value 0.6) at 14 to 26 weeks postinjection (Adams 1995); withdrawals due to adverse events (RR 3.28; 95% CI 0.14 to 77.69, P value 0.5) at 14 to 26 weeks postinjection (Adams 1995); or the number of patients with local reactions (RR 1.82; 95% CI 0.57 to 5.84, P value 0.3) at 5 to 13 weeks postinjection (Dickson 2001). There was a statistically significant difference in favour of Hylan G-F 20 compared to NSAID for the number of patients with possible or probable related systemic adverse events at 5 to 13 weeks postinjection (RR 0.46; 95% CI 0.25 to 0.83, P value 0.01) (Dickson 2001). The NNT was 4.

Hylan G-F 20 (Synvisc) + NSAID versus NSAID alone

The second comparison that was made from the Adams trial (Adams 1995) was Hylan G-F 20 plus NSAID and arthrocentesis versus NSAID and arthrocentesis alone.

#### *Efficacy*

There were no statistically significant differences between the two groups at 5 to 13 weeks postinjection for: pain on motion (0 to 100 mm VAS) (WMD -10.00; 95% CI -21.09 to 1.09, P value 0.08); pain at rest (0 to 100 mm VAS) (WMD -6.00; 95% CI -17.09 to 5.09, P value 0.3); pain at night (0 to 100 mm VAS) (WMD -11.00; 95% CI -22.09 to 0.09, P value 0.05); and pain overall (0 to 100 mm VAS) (WMD -12.00; 95% CI -24.55 to 0.55, P value 0.06). There were statistically significant differences in favour of Hylan G-F 20+NSAID+arthrocentesis compared to NSAID + arthrocentesis at 14 to 26 weeks postinjection for pain on motion (WMD -15.00; 95% CI -26.09 to -3.91, P value 0.008); pain at rest (WMD -11.00; 95% CI -19.31 to -2.69, P value 0.01); pain at night (WMD -19.00; 95% CI -30.09 to -7.91, P value 0.0008); and pain overall (WMD -15.00; 95% CI -26.09 to -3.91, P value 0.008). Hylan G-F 20+NSAID+arthrocentesis was approximately 10% more effective than NSAID + arthrocentesis. There was no statistically significant difference in the number of patients reporting that they were 'excellent, very good, or good' (RR 1.12; 95% CI 0.73 to 1.70, P value 0.6).

#### *Safety*

There was no statistically significant difference in the total withdrawals overall (RR 1.53; 95% CI 0.40 to 5.93, P value 0.5).

Hylan G-F 20 (Synvisc) + physiotherapy versus physiotherapy alone

One RCT included a comparison of Hylan G-F 20 plus physiotherapy to physiotherapy alone (Bayramoglu 2003).

#### *Efficacy*

There was no statistically significant difference in the Lequesne Index (scored 0 to 24) either at the end of treatment (WMD -0.70; 95% CI -3.25 to 1.85, P value 0.6) or at 5 to 13 weeks post injection (WMD -0.80; 95% CI -3.95 to 2.35, P value 0.6).

#### *Safety*

There was no statistically significant difference in the number of total withdrawals overall at 5 to 13 weeks postinjection (RR 0.50; 95% CI 0.15 to 1.64, P value 0.3).

Hylan G-F 20 (Synvisc) versus IA gaseous oxygen

One RCT was a comparison of Hylan G-F 20 plus an exercise programme to IA gaseous oxygen plus an exercise programme (Auerbach 2002; Auerbach 2002a).

#### *Efficacy*

A between-group difference was found for pain under load (0 to 100 mm VAS) at 5 to 13 weeks postinjection in favour of the oxy-

gen group (WMD 12.83; 95% CI 1.96 to 23.70, P value 0.02) but no statistically significant differences were found at the other assessments: end of treatment (WMD 9.14; 95% CI -2.23 to 20.51, P value 0.12); 14 to 26 weeks postinjection (WMD 8.02; 95% CI -2.91 to 18.95, P value 0.15); and 45 to 52 weeks postinjection (WMD 6.52; 95% CI -3.76 to 16.80, P value 0.2). There were no statistically significant differences between the groups for pain at rest (0 to 100 mm VAS) at any of the assessments: end of treatment (WMD 1.41; 95% CI -7.83 to 10.65, P value 0.8); 5 to 13 weeks postinjection (WMD 6.90; 95% CI -3.10 to 16.90, P value 0.18); 14 to 26 weeks postinjection (WMD 2.94; 95% CI -8.08 to 13.96, P value 0.6); and 45 to 52 weeks postinjection (WMD 0.09; 95% CI -9.04 to 9.22, P value 1). There were no statistically significant differences between the groups for WOMAC pain (0 to 20) at any of the assessments: end of treatment (WMD 1.30; 95% CI -0.15 to 2.75, P value 0.08); 5 to 13 weeks postinjection (WMD 1.40; 95% CI -0.10 to 2.90, P value 0.07); 14 to 26 weeks postinjection (WMD 0.60; 95% CI -1.04 to 2.24, P value 0.5); and 45 to 52 weeks postinjection (WMD 0.80; 95% CI -0.72 to 2.32, P value 0.3). There were no statistically significant differences between the groups for WOMAC physical function (0 to 68) at any of the assessments: end of treatment (WMD 3.30; 95% CI -1.83 to 8.43, P value 0.2); 5 to 13 weeks postinjection (WMD 2.80; 95% CI -2.29 to 7.89, P value 0.3); 14 to 26 weeks postinjection (WMD 4.10; 95% CI -1.51 to 9.71, P value 0.15); and 45 to 52 weeks postinjection (WMD 4.00; 95% CI -1.63 to 9.63, P value 0.16).

The RevMan analysis differed from the Auerbach publication (Auerbach 2002) analysis. In the publication, statistically significant differences were found at 45 to 52 weeks postinjection in favour of Hylan G-F 20 compared to IA gaseous oxygen for pain under load (P value 0.001), WOMAC pain (P value 0.003), and WOMAC function (P value 0.001) whereas the RevMan analysis did not detect any significant differences.

#### *Safety*

There was no statistically significant difference in the total number of withdrawals overall (RR 1.42; 95% CI 0.25 to 8.16, P value 0.7) or in the number of patients having total knee replacements (RR 2.84; 95% CI 0.30 to 26.45, P value 0.4).

Hylan G-F 20 (Synvisc) + appropriate care versus appropriate care alone

Two trials included were comparisons of the combination of Hylan G-F 20 and appropriate care (AC) to appropriate care alone (Kahan 2003a; Raynauld 2002).

#### *Efficacy*

A statistically significant difference in favour of Hylan G-F 20 and AC compared to AC alone was found in the WOMAC OA Index pain subscale (0 to 20 Likert) at 45 to 52 weeks postinjection (WMD -3.16; 95% CI -4.17 to -2.15, P < 0.00001) (Raynauld

2002). The combination group was 22% more effective than AC alone group. A statistically significant difference in favour of Hylan G-F 20 and AC compared to AC alone was found in the WOMAC OA Index physical function subscale (0 to 68 Likert) at 45 to 52 weeks postinjection (WMD -9.61; 95% CI -13.09 to -6.13,  $P < 0.00001$ ) (Raynauld 2002). The combination group was 22% more effective than AC alone group. The patient global assessment, based on the number of patients improved in the study knee, was statistically better for the Hylan G-F 20 and AC group (73%) compared to AC alone (27%) (RR 2.68; 95% CI 1.98 to 3.62,  $P < 0.00001$ ) (Raynauld 2002). The NNT for patient global assessment was 2.

A statistically significant difference in favour of Hylan G-F 20 and AC compared to AC alone was found in the WOMAC OA Index pain subscale (0 to 100 mm VAS) (WMD -12.70; 95% CI -16.41 to -8.99,  $P < 0.00001$ ) (Kahan 2003a). The combination group was 25% more effective than AC alone. A statistically significant difference in favour of Hylan G-F 20 and AC compared to AC alone was found in the WOMAC OA Index physical function subscale (WMD -13.20; 95% CI -17.02 to -9.38,  $P < 0.00001$ ) (Kahan 2003a). The combination group was 24% more effective than AC alone. A statistically significant difference was found in favour of Hylan G-F 20 and AC compared to AC alone in the Lequesne Index (0 to 24) (WMD -2.20; 95% CI -2.98 to -1.42,  $P < 0.00001$ ) (Kahan 2003a). The combination group was 18% more effective than AC alone. The patient global assessment, based on effectiveness rated as good or satisfactory, was statistically better for the Hylan G-F 20 and AC group (74%) compared to AC alone (51%) (RR 1.44; 95% CI 1.25 to 1.66,  $P < 0.00001$ ) (Kahan 2003a). The NNT for patient global assessment was 4. The number of responders, defined as those patients with at least a 20% decrease in pain on walking, was significantly higher in the Hylan G-F 20 and AC group (88%) compared to AC alone (68%) (RR 1.30; 95% CI 1.18 to 1.43,  $P < 0.00001$ ) (Kahan 2003a).

#### *Safety*

There was no statistically significant difference in the total withdrawals overall (RR 0.30; 95% CI 0.08 to 1.08,  $P$  value 0.07) (Kahan 2003a; Raynauld 2002). There was no statistically significant difference in the number of patients reporting side effects from baseline (RR (random-effects model) 0.94; 95% CI 0.44 to 2.02,  $P$  value 0.9) (Kahan 2003a; Raynauld 2002). There was no difference in the number of patients withdrawn due to adverse events in the Kahan trial (Kahan 2003a) (RR 2.00; 95% CI 0.18 to 21.92,  $P$  value 0.6). The number of patients reporting mild, moderate or severe side effects at the end of the study was significantly higher in the AC alone group (68%) compared to the Hylan G-F 20 and AC group (52%) (RR 0.76; 95% CI 0.61 to 0.94,  $P$  value 0.01) (Raynauld 2002). There was a statistically significant difference in the number of patients with gastrointestinal adverse events in favour of the Hylan G-F 20 and AC group compared to AC alone (RR 0.38; 95% CI 0.25 to 0.60,  $P$  value 0.00002)

(Kahan 2003a; Raynauld 2002). Significantly fewer patients withdrew due to lack of effectiveness in the Hylan G-F 20 and AC group (2%) compared to the AC alone group (7%) (RR 0.35; 95% CI 0.14 to 0.88,  $P$  value 0.03) (Kahan 2003a).

#### Hylan G-F 20 (Synvisc) versus other hyaluronan

Five RCTs have been comparisons of Hylan G-F 20 and hyaluronan: 1) Artzal (Karlsson 2002) - readers are directed to the Artz product results, 2) Artz (Wobig 1999b (Artz)) and Healon (Wobig 1999a (Healon)), 3) Hyalgan (Brown 2003) - readers are directed to the Hyalgan product results, 4) Orthovisc (Bayramoglu 2003) - readers are directed to the Orthovisc product results, and 5) Arthrocare (Thompson 2002) - readers are directed to the BioHy (Arthrocare) product results.

The Wobig 199 trial had two active arms: Artz (Wobig 1999b (Artz)) and Healon (Wobig 1999a (Healon)). Since Healon is not indicated for the treatment of knee OA we have completed the analysis both including and excluding this arm.

#### *Efficacy*

There was no statistically significant difference in pain on weight bearing (0 to 100 mm VAS) at 1 to 4 weeks postinjection (WMD -2.06; 95% CI -7.45 to 3.32,  $P$  value 0.41) (Karlsson 2002c (AvS), Wobig 1999a (Healon), Wobig 1999b (Artz)) or at 14 to 26 weeks postinjection (WMD -5.00; 95% CI -14.98 to 4.98,  $P$  value 0.3) (Karlsson 2002c (AvS)). There was a statistically significant difference in favour of Hylan G-F 20 compared to other hyaluronans at 5 to 13 weeks postinjection (WMD -6.59; 95% CI -12.46 to -0.73,  $P$  value 0.03) (Karlsson 2002c (AvS); Wobig 1999a (Healon); Wobig 1999b (Artz)). There was a statistically significant difference in favour of Hylan G-F 20 in pain at night (0-100 mm VAS) at 1 to 4 weeks postinjection (WMD -7.07; 95% CI -13.41 to -0.73,  $P$  value 0.03), but no difference at 5 to 13 weeks postinjection (WMD -3.50; 95% CI -11.34 to 4.34,  $P$  value 0.4) (Wobig 1999a (Healon); Wobig 1999b (Artz)). There was no significant difference in improvement in knee movement (0 to 100 mm VAS) at 1 to 4 weeks postinjection (WMD -0.50; 95% CI -10.30 to 9.30,  $P$  value 0.9), but there was a statistically significant difference in favour of Hylan G-F 20 at 5 to 13 weeks postinjection (WMD 12.50; 95% CI 2.70 to 22.30,  $P$  value 0.01). There was no significant difference in the patient global evaluation of treatment efficacy (0 to 100 mm VAS) at 1 to 4 weeks postinjection (WMD 2.00; 95% CI -7.80 to 11.80,  $P$  value 0.7), or at 5-13 weeks postinjection (WMD 9.50; 95% CI -0.30 to 19.30,  $P$  value 0.06).

When excluding the Healon arm, there was no statistically significant difference in pain on weight bearing at 1 to 4 weeks postinjection (WMD -0.23; 95% CI -6.39 to 5.92,  $P$  value 0.9) or at 5 to 13 weeks postinjection (WMD (random-effects model) -8.11; 95% CI -22.79 to 6.57,  $P$  value 0.3) (Karlsson 2002c (AvS), Wobig 1999b (Artz)). There was no statistically significant difference in

pain at night at 1 to 4 weeks postinjection (WMD -3.00; 95% CI -12.80 to 6.80, P value 0.5) or at 5 to 13 weeks postinjection (WMD -4.00; 95% CI -15.09 to 7.09, P value 0.5) (Wobig 1999b (Artz)). There was no significant difference in improvement in knee movement (0-100 mm VAS) at 1 to 4 weeks postinjection (WMD -1.00; 95% CI -14.86 to 12.86, P value 0.9). There was a significant difference in improvement in knee movement in favour of Hylan G-F 20 at 5 to 13 weeks postinjection (WMD 17.00; 95% CI 3.14 to 30.66, P value 0.02). There was no significant difference in patient global evaluation of treatment efficacy at 1 to 4 weeks postinjection (WMD 5.00; 95% CI -8.86 to 18.86, P value 0.5). There was a statistically significant difference in patient global evaluation of treatment efficacy in favour of Hylan G-F 20 at 5 to 13 weeks postinjection (WMD 16.00; 95% CI 2.14 to 29.86, P value 0.02).

### *Safety*

The safety profile of the three groups (Artz, Healon and Hylan G-F 20) was very similar (Wobig 1999). No patients reported systemic reactions. Two Hylan G-F 20 patients and one Artz patient reported local reactions. One Hylan G-F 20 patient and two Healon patients withdrew from the trial.

### **Product - NRD-101**

#### *Description of studies:*

Two RCTs have been included (Pham 2003; Tsukamoto 1995 (abstract); Yamamoto 1994).

Pham et al. reported, as an abstract, a one-year, parallel-group, double-blind, placebo-controlled, multicentre RCT performed in France comparing three weekly injections of NRD-101 plus oral placebo to: 1) three weekly injections of saline solution plus Diacerein 50 mg twice daily, and 2) three weekly IA injections of saline solution plus oral placebo (Pham 2003). The objective was to evaluate long-term structural and symptomatic efficacy of three courses (every three months) of three weekly IA injections of NRD-101 over a one-year period. No statistically significant differences were found for pain. There was a statistically significant deterioration in joint space width but no difference between the three groups. The trial did not find any structural and/or symptomatic effect for NRD-101 and Diacerein.

Yamamoto et al. reported a five-week, parallel-group, double-blind RCT performed at 31 centres in Japan comparing five weekly injections of NRD-101 (produced by fermentation using *Streptococcus equi*, a type of lactobacilli, Denki Kagaku Kogyo) to five weekly injections of Artz in 203 patients with OA of the knee (Tsukamoto 1995; Yamamoto 1994). Statistically significant differences in favour of NRD-101 were reported for 'final global improvement' and 'usefulness' but not for evaluation of improvement in clinical symptoms. Adverse events were reported for 2 of 100 NRD-101 patients and 3 of 99 Artz patients.

This comparative HA trial was of short duration with the longest assessment only one week postinjection. The 31 trial sites were all Departments of Orthopedic Surgery. Almost all of the clinical evaluations were based on physician ratings rather than on patient ratings.

With respect to methodological quality, the average Jadad score was 4 out of 5; the Pham trial scoring 3 and the Yamamoto trial scoring 5. Allocation concealment was adequate for the Yamamoto trial but unclear for the Pham trial. One trial was excluded (Kurokawa 1994).

#### NRD-101 versus placebo

##### *Efficacy*

No efficacy data on the symptomatic outcome measures were extracted from the Pham trial as means and standard deviations were not published in the abstract (Pham 2003). Data were reported on the percentage of progressors (joint space narrowing greater than 0.5 mm). There was no statistically significant difference between NRD 101 + oral placebo 23 of 131 (17.6%) and saline injection + oral placebo 17 out of 85 (20.3%) (RR 0.88; 95% CI 0.50 to 1.54, P value 0.7).

##### *Safety*

There was no statistically significant difference in the number of completers: NRD 101 + oral placebo 123 of 131 (93.9%) and saline injection + oral placebo 79 of 85 (92.9%) (RR 1.01; 95% CI 0.94 to 1.09, P value 0.8) (Pham 2003).

NRD-101 versus corticosteroid: no trials included.

#### NRD-101 versus NSAID

##### *Efficacy*

Data were reported on the percentage of progressors (joint space narrowing greater than 0.5 mm) (Pham 2003). There was no statistically significant difference between NRD 101 +

oral placebo 23 of 131 (17.6%) and Diacerein + saline injection 16 of 85 (18.9%) (RR 0.93; 95% CI 0.52 to 1.66, P value 0.8).

##### *Safety*

There was no statistically significant difference in the number of completers: NRD 101 + oral placebo 123 of 131 (93.9%) and Diacerein + saline injection 80 of 85 (94.1%) (RR 1.00; 95% CI 0.93 to 1.07, P value 0.9) (Pham 2003).

#### NRD-101 versus other hyaluronans

##### *Efficacy*

For the NRD-101 comparison against Artz (Tsukamoto 1995; Yamamoto 1994) there were no statistically significant differences between the two products in any measure of efficacy at 1 to 4 weeks postinjection: spontaneous pain (RR 1.17; 95% CI 0.92 to

1.48, P value 0.2), pain on pressure (RR 1.12; 95% CI 0.88 to 1.42, P value 0.4), pain during the night (RR 0.98; 95% CI 0.78 to 1.24, P value 0.9), passive movement pain (RR 0.88; 95% CI 0.67 to 1.16, P value 0.4), passive flexion (WMD 1.00; 95% CI -2.73 to 4.73, P value 0.6), passive extension (WMD -0.20; 95% CI -1.79 to 1.39, P value 0.8), and patient global assessment (RR 1.03; 95% CI 0.80 to 1.33, P value 0.8).

### *Safety*

There was no statistically significant difference in the total number of withdrawals overall in the Artz group (15%) compared to the NRD-101 group (6%) (RR 0.40; 95% CI 0.16 to 1.00, P value 0.05) (Yamamoto 1994). There were a similar number of adverse events reported in the two groups: 2 of 100 in NRD-101 and 3 of 99 in the Artz group (RR 0.66; 95% CI 0.11 to 3.87, P value 0.6).

### **Product -Orthovisc**

#### *Description of studies*

Seven randomised controlled trials of Orthovisc (Anika Therapeutics, Inc., Woburn, MA) have been included. Four have been reported as journal articles (Bayramoglu 2003; Brandt 2001; Tascioglu 2003; Tekeoglu 1998), one was the basis of a specialisation thesis (Kalay 1997), one was presented as a poster at the 10th National Rheumatology Congress in Turkey (Guler 1996), and one remains unpublished (Hizmetli 1999). Orthovisc has been compared against placebo (Brandt 2001; Guler 1996; Hizmetli 1999), betamethasone (Tekeoglu 1998), 6-methylprednisolone acetate (Tascioglu 2003), IA hylan (Bayramoglu 2003), and physical therapy (Bayramoglu 2003; Kalay 1997). With the exception of the Brandt RCT (Brandt 2001), which was conducted in the United States, the other six RCT were conducted in Turkey. With respect to methodological quality, the average Jadad score was 2.7 out of 5, with two trials scoring 4 (Brandt 2001; Hizmetli 1999), one trial scoring 3 (Guler 1996), and four trials scoring 2 (Bayramoglu 2003; Kalay 1997; Tascioglu 2003; Tekeoglu 1998). Allocation concealment was adequately described in one trial (Brandt 2001) and unclear (not reported) in the remaining six trials. Seven trials were excluded (Ates 2001; Birbara 2004; Koyuncu 2002; Olszynski 2002; Oron 2003; Sepici 2002; Toh 2002; Toh 2003). Five trials are awaiting assessment (Gur 2002; Kilinc 2002; Kotevoglou 2002; Neustadt 2004; Renk[inodot]tepe 20). These trials have only been published as abstracts with no extractable data, and at the closure of the database for this review no full length manuscripts have been published.

Bayramoglu et al. reported a three-month, parallel-group RCT performed at a single centre in Turkey comparing three weekly injections of Orthovisc plus a physical therapy programme to three weekly injections of Hylan G-F 20 plus a physical therapy programme to a physical therapy programme alone (deep tissue heating with short wave diathermy, transcutaneous electrical neuromuscular stimulation and exercises) in 46 patients with OA of

the knee (Bayramoglu 2003). The authors were particularly interested in examining the effect of IA HA injection on muscular strength; testing the hypothesis that if patients were relieved of pain and disability then indirectly they would build stronger quadriceps muscles. They reported within-group improvement in the Lequesne score for all three groups but no between-group difference. No within- or between-group difference was detected in muscular strength. No between-group differences were reported for range of motion, knee instability, existing deformities and radiographic grade. No adverse events were associated with the IA hyaluronic acid injections.

The Bayramoglu et al. RCT had a small sample size. However, it was classified as a pilot study. The presence or absence of effusion, usage of rescue and concomitant medications, and OA diagnosis criteria were not reported. There was a difference in the number of patients with bilateral disease: 100% physical therapy (PT) group, 75% Orthovisc group and 67% Hylan G-F 20 group. No difference was found with respect to the MW of the HA products. Since PT is part of the first line nonpharmacologic therapy in the medical management of patients with OA of the knee, the designation of PT alone as a treatment group in comparison to the two combination groups (pharmacologic + nonpharmacologic groups) was a particular interest in this trial.

Brandt et al. reported a 27-week, placebo-controlled, double-blind RCT performed at 10 centres in the United States comparing three weekly injections of Orthovisc to three weekly injections of saline in 226 patients with OA of the knee (Brandt 2001). The authors examined the influence of contralateral knee pain in a post hoc analysis of patients who completed at least 15 weeks of the trial, had no major protocol violations, and a WOMAC OA Index pain score less than 12 in the contralateral knee. This 'effectiveness' population controlled for the severity in the contralateral knee. The authors concluded that, in patients with mild to moderate OA of the knee, Orthovisc produced statistically and clinically significant improvement. No side effects were attributed to treatment. The incidence of injection site reaction was similar in both groups: 2.1% Orthovisc and 1.5% saline.

The Brandt et al. RCT did not report the presence or absence of effusion or disease duration (Brandt 2001). In this trial, acetaminophen was permitted at the recommended treatment dosage of 1 g four times daily, but was restricted 24 h before assessment visits. Patients in this trial had a high percentage of bilateral knee disease, but only the index knee received treatment. WOMAC OA Index questionnaires were completed by patients for each knee separately. The severity of pain in the contralateral knee confounded the outcome measurements in the index knee. The authors discussed how the pain response may be affected by severity of contralateral knee pain. They also noted the large placebo response detected in this trial. Although 78% of the patients randomised completed the trial, results were based only on the effectiveness population (i.e. 60%). It is of note that no sig-

nificant difference was detected in the intent-to-treat population between *Orthovisc* and placebo. The authors defined a clinically meaningful improvement as a decrease of at least three units in the WOMAC pain subscale score. They utilised a 1 to 5 scoring system for the Likert version of the WOMAC OA Index resulting in a score range of 5 to 25 for the pain subscale of the Index.

Guler et al. reported a 10-week, placebo-controlled, double-blind RCT performed at one centre in Turkey comparing three weekly injections of *Orthovisc* to three weekly injections of saline in 30 patients with OA of the knee (Guler 1996). Statistically significant improvement was reported in the *Orthovisc* group for the WOMAC pain and physical function subscales, walking time, and acetaminophen usage compared to the saline group. No adverse events were reported.

The small trial by Guler et al. demonstrated between-group differences (Guler 1996). Of particular note, there was a statistically significant decrease in the use of acetaminophen in the *Orthovisc* group. Although the abstract reported WOMAC OA Index subscale ranges with the minimum set at zero, it appeared that the score was based on 1 to 5.

Hizmetli et al. completed a one-year, placebo-controlled, double-blind RCT in Turkey comparing three weekly injections of *Orthovisc* to saline in 50 patients with OA of the knee (Hizmetli 1999). A fourth injection was given at six months. Statistically significant differences in all subscales of the WOMAC OA Index in favour of *Orthovisc* were reported. No local or systemic side effects were observed. This unpublished report was kindly provided by Anika Therapeutics Inc.

The Hizmetli et al. trial was one of a few unpublished trials included in this review (Hizmetli 1999). The manuscript did not report presence or absence of effusion, disease duration, or presence of uni/bilateral disease. The trial addressed repeat treatment at six months. Analgesics were restricted for the first four weeks of the trial.

Kalay reported a 56-day, parallel-group, open-label RCT performed at a single centre in Turkey comparing two weekly injections of *Orthovisc* plus a physical therapy programme to a physical therapy programme (paraffin, short wave, quadriceps exercises) in 40 patients with OA of the knee (Kalay 1997). Statistically significant improvement was reported in the *Orthovisc* group compared to the physical therapy alone group for the following clinical outcome measures: pain, paracetamol usage, walk time, and patient and investigator evaluation of treatment. Two patients in the *Orthovisc* group had local pain and swelling which resolved within 24 hours.

The Kalay trial utilised a two-injection schedule rather than a three-injection schedule (Kalay 1997). The publication did not report the presence or absence of effusion or disease duration. However, supplemental use of paracetamol as rescue medication

was graded and recorded. Statistically significant decreases in consumption were seen in both groups at the end of the study compared to baseline. As well, a statistically significant between-group difference in favour of *Orthovisc* was found at the eighth week.

Tascioglu and Oner reported a six-month, parallel-group, open-label RCT performed at a single centre in Turkey comparing three weekly injections of *Orthovisc* to three weekly injections of 6-methylprednisolone acetate (6-MPA) in 69 female patients with OA of the knee (Tascioglu 2003). A significant improvement was reported in both groups at week four in pain and Lequesne outcome measures. At three months, a significant improvement in pain and Lequesne was reported in favour of *Orthovisc* compared to 6-MPA. By six months, there was no difference between the two groups. No serious systemic adverse events were reported that could be related to the treatment. Similar percentages of patients reported knee pain after injection (*Orthovisc* 21%, 6-MPA 18%). There was no significant between-group difference with respect to adverse events.

In the Tascioglu and Oner trial paracetamol to a maximum of 3 g was permitted but with restriction 48 hours prior to an assessment (Tascioglu 2003). The percentage of patients with uni and bilateral disease was not reported.

Tekeoglu et al. reported a 15-week, parallel-group, open-label RCT performed in Turkey comparing three weekly injections of *Orthovisc* to three weekly injections of betamethasone in 40 female patients with OA of the knee (Tekeoglu 1998). In the short term (week 3), betamethasone was more effective than *Orthovisc*. In the long term (week 15), *Orthovisc* was more effective than betamethasone. No local or systemic reactions were reported.

The Tekeoglu et al. trial allowed patients to take paracetamol as well (Tekeoglu 1998). Again, the percentage of patients with uni and bilateral disease was not reported. In this RCT, patients were advised to rest for one day after injection 'to avoid overcharging the injected joint'.

#### *Orthovisc* versus placebo

##### *Efficacy*

Pain, as measured by the WOMAC OA Index (scored 5 to 25), improved significantly with *Orthovisc* versus placebo (Hizmetli 1999) (WMD -7.50; 95% CI -10.21 to -4.79,  $P < 0.00001$ ) at 1 to 4 weeks postinjection; (WMD -5.95; 95% CI -7.87 to -4.03,  $P < 0.00001$ ) at 5 to 13 weeks postinjection; (WMD -5.60; 95% CI -7.43 to -3.77,  $P < 0.00001$ ) at 14 to 26 weeks postinjection; and (WMD -5.30; 95% CI -7.02 to -3.58,  $P < 0.00001$ ) at 45 to 52 weeks postinjection. *Orthovisc* was between 32 and 45% more effective than saline in relieving pain as measured by the WOMAC OA Index pain subscale. Physical function, as measured by the WOMAC OA Index (scored 17 to 85), improved significantly with *Orthovisc* versus placebo at three of four follow-up assessments (WMD -12.25; 95% CI -20.83 to -3.67,  $P$  value 0.005) at 1 to 4



weeks postinjection; (WMD -10.15; 95% CI -17.72 to -2.58, P value 0.009) at 5 to 13 weeks postinjection; (WMD -9.30; 95% CI -17.00 to -1.60, P value 0.02) at 14 to 26 weeks postinjection; and (WMD -7.10; 95% CI -15.42 to -1.22, P value 0.09) at 45 to 52 weeks postinjection. *Orthovisc* was between 16 and 26% more effective than saline in improving physical function as measured by the WOMAC OA Index physical function subscale.

Patient satisfaction with treatment was similar in the *Orthovisc* (73%) and saline (33%) groups (Guler 1996); (RR 2.20; 95% CI 1.01 to 4.79, P value 0.05) at 5 to 13 weeks postinjection.

In Brandt's trial (Brandt 2001), results are presented only for the effectiveness population which represents approximately a 40% loss of the initially randomised population. *Orthovisc* was not statistically significantly different than saline in the number of patients who achieved a greater than five-unit improvement in the WOMAC pain score relative to baseline score by 25 weeks postinjection (*Orthovisc* 58%, saline 40%) (RR 1.42; 95% CI 1.00 to 2.02, P value 0.05). The RevMan analysis (P value 0.05) disagreed with the publication analysis where a statistically significant difference was detected in favour of *Orthovisc* (P value 0.04).

There was no statistically significant difference in the number of patients who improved in the WOMAC pain subscale score at 14 to 26 weeks postinjection: *Orthovisc* 92% versus saline 87% (RR 1.06; 95% CI 0.95 to 1.19, P value 0.3).

#### *Safety*

No local or systemic adverse events were observed in the Hizmetli trial (Hizmetli 1999). No complications (e.g. during or after intraarticular injection) were reported in the Guler trial (Guler 1996).

The safety data was based on the intention to treat population in the Brandt trial (Brandt 2001). There were no statistically significant differences between *Orthovisc* and saline in the safety profile.

#### *Orthovisc* versus corticosteroid

##### *Efficacy*

In the *Orthovisc*/betamethasone comparison (Tekeoglu 1998), at 1 to 4 weeks postinjection, there were no statistically significant differences for: WOMAC function (scored 17 to 85) (WMD 3.00; 95% CI -2.39 to 8.39, P value 0.3); the number of patients good or very good (RR 0.83; 95% CI 0.47 to 1.47, P value 0.5); and maximum flexion (WMD -4.90; 95% CI -14.69 to 4.89, P value 0.3). At 5 to 13 weeks postinjection, *Orthovisc* was significantly better than betamethasone for WOMAC function (WMD -9.00; 95% CI -14.15 to -3.85, P value 0.0006). *Orthovisc* was 20% more effective than betamethasone in improving physical function. *Orthovisc* was significantly better than betamethasone for patient global assessment (i.e. number of patients good/very good) (RR 1.88; 95% CI 1.04 to 3.39, P value 0.04). The NNT for

patient global assessment was 3. There was no between-group difference for maximum flexion at 5 to 13 weeks (WMD -7.05; 95% CI -15.48 to 1.38, P value 0.10).

In the *Orthovisc*/6-methylprednisolone acetate (6-MPA) comparison (Tascioglu 2003), there were no statistically significant differences between the two groups for any of the pain outcome measures (0 to 100 mm VAS), the Lequesne Index (0 to 24), or flexion outcome measures at 1 to 4 weeks postinjection. However, at 5 to 13 weeks postinjection, statistically significant differences were detected in all outcome measures, except flexion, in favour of the *Orthovisc* group: pain on weight bearing (WMD -15.64; 95% CI -24.51 to -6.77, P value 0.0006); pain at rest (WMD -7.70; 95% CI -13.50 to -1.90, P value 0.009); pain on walking (WMD -18.43; 95% CI -29.19 to -7.67, P value 0.0008); Lequesne Index (WMD -1.40; 95% CI -2.13 to -0.67, P value 0.0002). For flexion the WMD was 2.36 (95% CI -1.82 to 6.54) P value 0.3. *Orthovisc* was between 25 and 32% more effective than 6-MPA in relieving pain. *Orthovisc* was 18% more effective than 6-MPA in improving function (Lequesne). At 14 to 26 weeks postinjection, statistically significant differences in all outcome measures, except pain on rest, were detected in favour of the *Orthovisc* group: pain on weight bearing (WMD -15.40; 95% CI -25.91 to -4.89, P value 0.004); pain on walking (WMD -14.90; 95% CI -25.91 to -3.89, P value 0.008); Lequesne Index (WMD -1.14; 95% CI -2.16 to -0.12, P value 0.03), and flexion (WMD 5.00; 95% CI 0.19 to 9.81, P value 0.04). For pain at rest the WMD was -2.90 (95% CI -9.47 to 3.67) P value 0.4. *Orthovisc* was between 20 and 31% more effective than 6-MPA in relieving pain and between 4 and 15% more effective than 6-MPA in improving function.

The RevMan analysis differed from the publication analysis (Tascioglu 2003). The publication reported no statistically significant between-group difference at six months in pain on weight bearing whereas RevMan detected a statistically significant difference (P value 0.004) in favour of *Orthovisc* compared to 6-MPA. The publication reported no statistically significant between-group difference at six months in pain on walking whereas RevMan detected a statistically significant difference (P value 0.008) in favour of *Orthovisc* compared to 6-MPA. The publication reported no statistically significant between-group difference at six months in the Lequesne Index whereas RevMan detected a statistically significant difference (P value 0.03) in favour of *Orthovisc* compared to 6-MPA. The publication reported no statistically significant between-group difference at six months in flexion whereas RevMan detected a statistically significant difference (P value 0.04) in favour of *Orthovisc* compared to 6-MPA.

##### *Safety*

There were no adverse local (e.g. postinjection synovitis) or systemic reactions reported in either the *Orthovisc* or betamethasone group with all patients completing the trial (Tekeoglu 1998). There were no statistically significant differences in the safety pro-

file of **Orthovisc** compared to 6-MPA ([Tascioglu 2003](#)). A similar number of patients were withdrawn overall: **Orthovisc** 6.7% and 6-MPA 10% (RR 0.67; 95% CI 0.12 to 3.71, P value 0.6). One patient in each group withdrew due to increased pain (RR 1.00; 95% CI 0.07 to 15.26; P value 1). A similar number of patients reported musculoskeletal adverse events: **Orthovisc** 25% and 6-MPA 19% (RR 1.35; 95% CI 0.49 to 3.74, P value 0.6). A similar number of patients reported skin adverse events: **Orthovisc** 7% and 6-MPA 4% (RR 1.93; 95% CI 0.19 to 20.05, P value 0.6). A similar number of patients reported gastrointestinal adverse events: **Orthovisc** 11% and 6-MPA 7% (RR 1.45; 95% CI 0.26 to 7.99, P value 0.7). A similar number of patients reported general adverse events: **Orthovisc** 14% and 6-MPA 19% (RR 0.77; 95% CI 0.23 to 2.57, P value 0.7). A similar number of patients reported knee pain after injection: **Orthovisc** 21% and 6-MPA 19% (RR 1.16; 95% CI 0.40 to 3.35, P value 0.8).

**Orthovisc** versus NSAID: no trials included.

**Orthovisc** versus physiotherapy

#### *Efficacy*

In the **Orthovisc** plus physiotherapy versus physiotherapy comparison ([Kalay 1997](#)), there were no statistically significant differences at 1 to 4 weeks postinjection for: activity pain (VAS) (WMD -1.70; 95% CI -7.22 to 3.82, P value 0.5); spontaneous pain (VAS) (WMD 0.40; 95% CI -3.23 to 4.03, P value 0.8); night pain (VAS) (WMD -0.20; 95% CI -4.35 to 3.95, P value 0.9); 25 m walk time (sec) (WMD 0.75; 95% CI -1.09 to 2.59, P value 0.4); and flexion WMD was not estimable as the SD of the treatment group was zero. At 5 to 13 weeks postinjection, the combination of **Orthovisc** and physiotherapy was better than physiotherapy alone for activity pain (WMD -6.50; 95% CI -11.93 to -1.07, P value 0.02) and spontaneous pain (WMD -4.10; 95% CI -7.43 to -0.77, P value 0.02). **Orthovisc** plus physiotherapy was between 16 and 44% more effective than physiotherapy alone in relieving pain. No other significant differences were found: night pain (WMD -3.30; 95% CI -6.93 to 0.23, P value 0.07); walk time (WMD -1.15; 95% CI -2.83 to 0.53, P value 0.18); and flexion WMD was not estimable again due to the SD of the treatment group being zero. The number of patients rating the treatment as effective or very effective was significantly higher in the **Orthovisc** plus physiotherapy arm (95%) compared to the physiotherapy group (60%) (RR 1.58; 95% CI 1.09 to 2.30, P value 0.02). The NNT for patient global assessment was 3.

The RevMan analysis differed from the publication analysis. The publication reported a statistically significant difference in activity pain at day 21 (1 to 4 weeks postinjection) in favour of **Orthovisc** plus physiotherapy compared to physiotherapy alone (P value 0.03) whereas RevMan detected no difference. The publication reported a statistically significant difference in night pain at day 56 (5 to 13 weeks postinjection) in favour of **Orthovisc** plus physiotherapy compared to physiotherapy alone (P value 0.02) whereas

RevMan detected no difference. The publication reported a statistically significant difference in walk time both at day 21 (P value 0.0049) and day 56 (P value 0.0001) in favour of **Orthovisc** plus physiotherapy compared to physiotherapy alone whereas RevMan detected no difference.

In the **Orthovisc** plus physical therapy versus physical therapy comparison ([Bayramoglu 2003](#)), there were no statistically significant differences in the Lequesne Index at the end of treatment at three weeks (WMD -0.20; 95% CI -2.98 to 2.58, P value 0.9) or at three months (WMD -1.80; 95% CI -5.14 to 1.54, P value 0.3).

#### *Safety*

With respect to safety, two patients in the **Orthovisc** plus physiotherapy group ([Kalay 1997](#)) experienced local pain and swelling several hours after the IA injections which resolved in 24 hours with cold application; however, this difference was not statistically significant (RR 5.00; 95% CI 0.26 to 98.00, P value 0.3). In this trial the treatment schedule differed from the other four trials, in that only two injections were given on days 0 and 7. There were no adverse events associated with the IA hyaluronic acid injections in the second trial ([Bayramoglu 2003](#)). There was no statistically detectable difference in the number of withdrawals overall (RR 0.07; 95% CI 0.00 to 1.18, P value 0.07). No patients in either trial withdrew because of adverse events or experienced any systemic adverse events.

**Orthovisc** versus other hyaluronan

#### *Efficacy*

In the one trial included ([Bayramoglu 2003](#)), there were no statistically significant differences between **Orthovisc** plus a physical therapy programme versus Hylan G-F 20 plus a physical therapy programme in the Lequesne Index either at the end of the treatment schedule (WMD 0.50; 95% CI -1.58 to 2.58, P value 0.6) or at three months (WMD -1.00; 95% CI -3.30 to 1.30, P value 0.4).

#### *Safety*

There were no adverse events associated with either of the IA hyaluronic acid injections ([Bayramoglu 2003](#)).

#### **Product - Ostenil**

##### *Description of studies*

One RCT was excluded: [Uebelhart 2003](#).

#### **Product - Replasyn**

##### *Description of studies*

One RCT has been reported.

Cohen et al. reported an eight-week, placebo-controlled, double-blind RCT performed at four centres in Canada and the United

States comparing three weekly injections of Replasyn to placebo (not specified) in 39 patients with OA of the knee (Cohen 1994). A significant within group difference was found for pain on walking by week 8 in the Replasyn group. However, no between-group differences were found in pain on walking, range of motion, the WOMAC functional index, or patient and physician global assessments. Transient joint pain or swelling was reported in 3 of 19 Replasyn and 6 of 20 placebo patients.

An abstract is the only publication of this trial.

Replasyn versus placebo

#### *Efficacy*

Since no measure of dispersion was reported in the abstract (Cohen 1994) this review does not report efficacy data.

#### *Safety*

There was no statistically significant difference in the number of patients with local adverse reactions: Replasyn 16% versus placebo 30% (RR 0.53; 95% CI 0.15 to 1.81, P value 0.3).

Replasyn versus corticosteroid: no trials included.

Replasyn versus NSAID: no trials included.

Replasyn versus other hyaluronan: no trials included.

### **Product - SLM-10**

#### *Description of studies*

One RCT has been included.

Kawabata et al. reported a five-week, parallel-group, single-blind RCT performed at 23 centres in Japan comparing five weekly injections of SLM-10 (developed and produced by fermentation with *Streptococcus zooepidemicus* of Lancefield's group C, Shiseido Co., Ltd.) to five-weekly injections of Artz in 172 patients with OA of the knee (Kawabata 1993). No statistically significant between-group differences were reported for patients' impression, final global improvement and utility, leading the authors to conclude that SLM-10 was as useful as Artz. Adverse events were reported in one SLM-10 patient and two Artz patients. The Jadad score for this trial was 2 out of 5; single-blind and no specific details regarding randomisation were reported. Allocation concealment was adequate.

This comparative HA trial was of short duration with the longest assessment only one week postinjection. In addition, it was single-blind because of differences in the HA; SLM-10 was provided in a syringe while Artz was provided in an ampoule. The 23 trial sites were all Departments of Orthopedic Surgery. Almost all of the clinical evaluations were based on attending physician or committee ratings rather than on patient ratings. The case study committee, as well as the attending physician, assessed overall severity, final global improvement, overall safety and usefulness. Differences in

results were noted in assessments made by the attending physician compared to those made by the committee. In the analysis method section of the publication, it reports that "cases which deviated from the protocol or those judged to be inappropriate as the subjects of assessment were excluded from the analysis of corresponding assessment item". However, no definition of appropriateness was reported.

Five trials were excluded (Minami 1993; Ono 1993; Ono 1993a; Suzu 1993; Taneda 1993).

SLM-10 versus placebo: no trials included.

SLM-10 versus corticosteroid: no trials included.

SLM-10 versus NSAID: no trials included.

SLM-10 versus other hyaluronan

#### *Efficacy*

Regarding the SLM-10 comparison against Artz (Kawabata 1993), significantly more patients improved on pain on pressure in the Artz group (82%) compared to the SLM-10 group (64%) (RR 0.78; 95% CI 0.64 to 0.96, P value 0.02). The NNT for pain on pressure was 2. No statistically significant between-group differences were found for pain in movement (RR 0.89; 95% CI 0.75 to 1.06, P value 0.18), pain when resting (RR 1.05; 95% CI 0.86 to 1.29, P value 0.6), and patient global assessment (RR 0.95; 95% CI 0.78 to 1.17, P value 0.7).

#### *Safety*

There was no statistically significant difference in the total number of withdrawals overall in the Artz group (12%) compared to SLM-10 group (3%) (RR 0.29; 95% CI 0.08 to 1.03, P value 0.06). The incidence of local adverse events related to study drug, resulting in withdrawal, was similar in the Artz (3%) and the SLM-10 (1%) groups (RR 0.46; 95% CI 0.04 to 5.03, P value 0.5). One patient in each group had a local adverse event with no specific causal relationship to the study drug and continued in the trial (RR 0.93; 95% CI 0.06 to 14.61, P value 1).

### **Product - Suplasyn**

#### *Description of studies*

One RCT has been included.

Petrella et al. reported a 12-week, placebo-controlled, double-blind RCT performed at a single centre in Canada comparing Suplasyn (a bacterial source HA) plus placebo (lactose), placebo (lactose plus saline), NSAID (Arthrotec plus saline), and Suplasyn plus NSAID in 120 patients with OA of the knee (Petrella 2002). The authors reported that Suplasyn was superior to placebo alone or NSAIDs alone for pain with physical activity and functional performance. Suplasyn was as effective as NSAID for resting pain relief. With respect to safety, Petrella reported that two patients had moderate gastrointestinal irritation resulting in their withdrawal,

and that most adverse events occurred in the NSAID plus saline group. No

serious adverse events occurred.

The efficacy outcome measures extracted from this trial were pain after walking (0 to 100 mm VAS), WOMAC pain (0 to 10 cm) and WOMAC function (0 to 10 cm), pain at rest (0 to 100 mm VAS), and walk time (seconds). Of the four groups, three comparisons are reported: (Suplasyn plus lactose) versus (saline plus lactose), (Suplasyn plus lactose) versus (NSAID plus saline), and (Suplasyn plus NSAID) versus (NSAID plus saline); not reporting the combination of (NSAID plus saline) versus placebo (lactose plus saline). With respect to methodological quality, it scored 5 out of 5 on the Jadad scale achieving bonus points for providing details of appropriate randomisation and blinding. Allocation concealment was adequate. An editorial reported the results obtained from this trial using a factorial design analysis (Felson 2002). Two trials were excluded (Olszynski 2002; Payne 2000).

Some design points were noted: 1) a medial approach was utilised for injections; 2) rescue medication with 2600 mg (650 g x 4) of acetaminophen was permitted; 3) a 10-minute home-based resistance exercise programme was part of the treatment and was monitored by a patient diary; 4) patients were recruited from a primary care referral centre; 5) no details were published regarding the presence or absence of effusion, disease duration, and OA diagnosis criteria. The only significant results reported were based on within-group comparisons. No information on rescue medication usage was reported.

A randomised, double-blind trial comparing three and six injections of Suplasyn is awaiting assessment (Petrella 2002). This trial has only been published as an abstract with no extractable data and at the closure of the database for this review no full length manuscript had been published. Three trials were excluded (Mazieres 2004; Petrella 2003a; Petrella 2003b).

Suplasyn versus placebo

#### *Efficacy*

No statistically significant differences were found between Suplasyn and placebo for the following outcome measures: pain after walking (WMD -0.67; 95% CI -1.61 to 0.27, P value

0.2); WOMAC pain (WMD -0.77; 95% CI -2.16 to 0.62, P value 0.3); WOMAC function (WMD -1.28; 95% CI -2.69 to 0.13, P value 0.08); and walk time (WMD 3.14; 95% CI -6.02 to 12.30, P value 0.5). A statistically significant difference, in favour of the placebo group (saline + lactose) compared to the treatment group (Suplasyn plus lactose), was found for the primary outcome measure, pain at rest (WMD 0.83; 95% CI 0.03 to 1.63, P value 0.04). Suplasyn plus lactose was 25% less effective than saline plus lactose in relieving pain at rest.

The RevMan analysis differed from the publication analysis. The publication reported that Suplasyn may be superior to placebo for pain with physical activity and functional performance whereas the RevMan analysis detected no difference.

#### *Safety*

There was no statistically significant difference in the number of withdrawals overall: Suplasyn 17% versus placebo 7% (RR 2.50; 95% CI 0.53 to 11.89, P value 0.2).

Suplasyn versus corticosteroid: no trials included.

Suplasyn versus NSAID

#### *Efficacy*

No statistically significant differences were found between Suplasyn and NSAID for: WOMAC pain (WMD -0.44; 95% CI -1.80 to 0.92, P value 0.5); WOMAC function (WMD -0.31; 95% CI -1.60 to 0.98, P value 0.6); walk time (WMD -1.49; 95% CI -10.38 to 7.40, P value 0.7); pain at rest (WMD 1.02; 95% CI -0.32 to 2.36, P value 0.14); and pain after walking (WMD 1.08; 95% CI -0.37 to 2.53, P value 0.15).

The RevMan analysis differed from the publication analysis. The publication reported that Suplasyn may be superior to NSAID alone for pain relief, pain with physical activity, and functional performance whereas the RevMan analysis detected no difference.

#### *Safety*

There was no statistically significant difference in the number of withdrawals overall: Suplasyn 17% versus NSAID 3% (RR 5.00; 95% CI 0.62 to 40.29, P value 0.13).

Suplasyn + NSAID versus NSAID alone

#### *Efficacy*

No statistically significant differences were found between Suplasyn plus NSAID versus NSAID alone for: pain after walking (WMD 0.24; 95% CI -1.09 to 1.57, P value 0.7); WOMAC pain (WMD -0.27; 95% CI -1.68 to 1.14, P value 0.7); WOMAC function (WMD -0.03; 95% CI -1.42 to 1.36, P value 1); pain at rest (WMD -0.02; 95% CI -1.26 to 1.22, P value 1); and walk time (WMD -3.48; 95% CI -12.14 to 5.18, P value 0.4).

#### *Safety*

There was no statistically significant difference in the number of withdrawals overall: Suplasyn plus NSAID 13% versus NSAID alone 3% (RR 4.00; 95% CI 0.47 to 33.73, P value 0.2).

Suplasyn versus other hyaluronan: no trials included.

#### *Product - Synject*

#### *Description of studies*

One trial was excluded: Alonge 2004.

## Product - Zeel compositum

### Description of studies

One RCT included was a comparison of Zeel compositum and Hyalart (Nahler 1996 [article published in German with English abstract]; Nahler 1998). With respect to methodological quality, the Jadad score was 4 out of 5. Allocation concealment was unclear.

Nahler et al. reported a five-week, parallel-group, single-blind RCT performed at twelve centres in Germany and Austria comparing 10 injections (two injections a week for five weeks) of Zeel compositum to five weekly injections of Hyalart in 121 patients with OA of the knee (Nahler 1998). Both treatments were equally effective in treating patients. Undesirable side effects were reported by 11% of Zeel patients and 23% of Hyalart patients; the most frequent being local inflammation or irritation following the injection. One patient withdrew from the study early due to suspected allergic reaction after injection with Hyalart. For this trial, Zeel was the treatment group and Hyalart was the control group.

This is the only RCT in the review comparing homeopathy drug therapy to HA. It was designed as a clinical equivalence study. The follow-up assessment was short, one week following the treatment. As the authors noted, the design was single-blind due to the imbalance in number of injections (Hyalart n = 5 versus Zeel n = 10). It was deemed 'unethical' to equalise the frequency of injections with additional injections of a placebo.

Zeel versus placebo: no trials included.

Zeel versus corticosteroid: no trials included.

Zeel versus NSAID: no trials included.

Zeel versus other hyaluronans

### Efficacy

At the end of treatment (i.e. last injection), there were no statistically significant between-group differences in any of the efficacy outcome measures: pain during movement (0 to 100

mm VAS) (WMD 5.00; 95% CI -3.14 to 13.14, P value 0.2); pain during the night (0 to 100 mm VAS) (WMD 2.00; 95% CI -6.15 to 10.15, P value 0.6); assessment of improvement (0 to 100 mm VAS) (WMD -4.00; 95% CI -13.12 to 5.12, P value 0.4); and assessment of tolerance (0 to 100 mm VAS) (WMD -3.00; 95% CI -10.09 to 4.09, P value 0.4). There was no statistically significant difference in the number of patients who reported noticeable improvement in symptoms: Zeel 87% versus Hyalart 93% (RR 0.94; 95% CI 0.83 to 1.06, P value 0.3).

### Safety

There was no statistically significant difference in the number of patients with side effects: Zeel 11% versus Hyalart 23% (RR 0.48; 95% CI 0.20 to 1.17, P value 0.11); or in the number of patients

withdrawn due to lack of efficacy: Zeel 4% versus Hyalart 2% (RR 2.00; 95% CI 0.19 to 21.44, P value 0.6).

### By-class (pooled) analysis

Thirty-seven trials included comparisons of hyaluronan/hylan and placebo (Altman 1998; Ardic 2001; Bragantini 1987; Brandt 2001; Bunyaratavej 2001; Carrabba 1995; Cohen 1994; Corrado 1995; Creamer 1994; Day 2004; Dickson 2001; Dougados 1993; Formiguera Sala 1995; Forster 2003; Grecomoro 1987; Groppa 2001; Guler 1996; Henderson 1994; Hizmetli 1999; Huskisson 1999; Jubb 2003; Karlsson 2002; Lohmander 1996; Moreland 1993; Petrella 2002; Pham 2003; Puhl 1993; Scale 1994a (2 inj); Scale 1994b (3 inj); Shichikawa 1983a; Shichikawa 1983b; St. J. Dixon 1988; Tamir 2001; Tsai 2003; Wobig 1998; Wobig 1999c (NEhyl); Wu 1997).

In this section, we report only analyses based on multiple studies. Analyses based on single products and/or studies can be found in the relevant by-product results section. This section is most informative when read in combination with the relevant by-product section(s).

There was a statistically significant difference in favour of HA compared to placebo for pain on weight bearing (0 to 100 mm VAS) at three assessments: at 1 to 4 weeks postinjection, based on 21 trials (WMD (random-effects model) -7.92; 95% CI -11.70 to -4.14, P value 0.00004); at 5 to 13 weeks postinjection, based on 16 trials (WMD (random-effects model) -12.97; 95% CI -18.00 to -7.93, P < 0.00001); at 14 to 26 weeks postinjection, based on 9 trials (WMD (random-effects model) -9.04; 95% CI -14.83 to -3.24, P value 0.002); but not at 45 to 52 weeks postinjection, based on 3 trials (WMD (fixed-effect model) (-2.60; 95% CI -7.40 to 2.19, P value 0.3).

There was no statistically significant difference in pain at rest (0 to 100 mm VAS) at 1 to 4 weeks postinjection, based on 7 trials (WMD (random-effects model) -3.54; 95% CI -9.21 to 2.13, P value 0.2). There was no statistically significant difference in WOMAC pain at 1 to 4 weeks postinjection (WMD -3.07; 95% CI -7.07 to 0.92, P value 0.13) (Petrella 2002; Tsai 2003). However, there were statistically significant differences in favour of HA versus placebo at 5 to 13 weeks (SMD -0.33; 95% CI -0.55 to -0.10, P value 0.004) (Dickson 2001; Hizmetli 1999; Tsai 2003); and at 14 to 26 weeks postinjection (WMD -5.66; 95% CI -10.06 to -1.26, P value 0.01) (Tsai 2003).

There was no statistically significant difference in WOMAC function at 1 to 4 weeks postinjection (WMD -2.24; 95% CI -6.29 to 1.80, P value 0.3) (Petrella 2002; Tsai 2003). However, at 5 to 13 weeks postinjection, there was a statistically significant difference in favour of HA versus placebo (SMD -0.56; 95% CI -0.89 to -0.24, P value 0.0007) (Dickson 2001; Hizmetli 1999). There was no statistically significant difference at 14 to 26 weeks postinjection (WMD -4.05; 95% CI -8.38 to 0.28, P value 0.07) (Tsai 2003).

There was a statistically significant difference in the Lequesne Index both at 1 to 4 weeks postinjection (WMD (random-effects model) -1.21; 95% CI -2.19 to -0.22, P value 0.02) (Carrabba 1995; Dougados 1993; Huskisson 1999; Puhl 1993); and at 5 to 13 weeks postinjection (WMD -1.30; 95% CI -1.93 to -0.67, P value 0.00005) (Carrabba 1995; Dickson 2001; Huskisson 1999; Puhl 1993). There was no statistically significant difference either at 14 to 26 or 45 to 52 weeks postinjection, (WMD 0.06; 95% CI -0.75 to 0.87, P value 0.9) (Huskisson 1999; Karlsson 2002; Lohmander 1996); and (WMD -1.11; 95% CI -2.70 to 0.48), P value 0.17) (Dougados 1993), respectively.

With respect to patient global assessment (expressed as the number of patients improved), there were no statistically significant differences between HA and placebo at any of the four assessment times: at 1 to 4 weeks post injection (RR (random-effects model) 1.07; 95% CI 0.84 to 1.35, P value 0.6) (Corrado 1995; Creamer 1994; Lohmander 1996; Shichikawa 1983a; Shichikawa 1983b); at 5 to 13 weeks postinjection (RR (random-effects model) 1.03; 95% CI 0.82 to 1.29, P value 0.8) (Corrado 1995; Dickson 2001; Guler 1996; Lohmander 1996; Puhl 1993); at 14 to 26 weeks postinjection (RR (random-effects model) 0.92; 95% CI 0.52 to 1.63, P value 0.8); and at 45 to 52 weeks postinjection (RR 1.17; 95% CI 0.85 to 1.62, P value 0.3).

There was no statistically significant difference in flexion (degrees) at 1 to 4 weeks postinjection (WMD 3.21; 95% CI -1.27 to 7.68, P value 0.16) (Corrado 1995; Shichikawa 1983a; Shichikawa 1983b). However, at 5 to 13 weeks postinjection there was a statistically significant difference in favour of HA versus placebo (WMD 7.60; 95% CI 0.46 to 14.74, P value 0.04) (Corrado 1995).

In safety analyses in HA versus placebo comparisons, no statistically significant differences were detected in the following: total withdrawals overall (1 to 4 weeks, 5 to 13 weeks, 14 to 26 weeks, 45 to 52 weeks postinjection), patients with local adverse reaction and study drug discontinued, number of patients with local adverse reaction but study drug continued, number of patients discontinued due to adverse events, withdrawals due to lack of efficacy, number of adverse events due to local skin reaction, number of patients with gastro-intestinal complaints, number of patients with treatment related adverse events, number of patients with possible study medication related events, number of serious adverse events, number of adverse events probably/possibly related to treatment, and number of patients reporting adverse events. A statistically significant event favouring placebo was noted in the number of adverse events for injection site pain (RR 1.70; 95%CI 1.19 to 2.44, P value 0.004).

In comparative studies of HA versus NSAID, no statistically significant differences were detected in pain on walking at 1 to 4 weeks post-injection (WMD 1.56; 95% CI -3.97 to 7.10, P value 0.6) or total withdrawals overall at 14 to 26 weeks (RR 1.19; 95%CI 0.88 to 1.61, P value 0.3).

In comparative studies of HA versus methylprednisolone acetate, statistically significant differences in favour of IA steroid were detected in range of motion (degrees of flexion) at 1 to 4 weeks postinjection (WMD 3.87; 95%CI 0.36 to 7.37, P value 0.03) and 5 to 13 weeks postinjection (WMD 3.66; 95%CI 0.48 to 6.83, P value 0.02).

In six comparative studies of selected HA products, no statistically significant differences were detected between the products concerned in: pain on movement (number of patients improved) (1 to 4 weeks postinjection), pressure pain (number of patients improved) (1 to 4 weeks postinjection), Lequesne Index (1 to 4 weeks and 5 to 13 weeks postinjection), or patient global assessment (1 to 4 weeks, 5 to 13 weeks, 14 to 26 weeks and 45 to 52 weeks postinjection).

## DISCUSSION

This review is current as of the second quarter of 2004, and contains both by-product and by-class analyses. It is comprehensive and more current than preceding systematic reviews and avoids limiting the review to a single product, variable or timepoint, or forcing different variables assessed using different instruments through a hierarchical algorithm in a reductionist manner, that attempts to obtain a single value capturing complex, dynamic, and heterogeneous phenomena. In developing a strategy for conducting this review, we have considered the complexity of the HA class of interventions, issues relating to the design, execution, analysis and interpretation of clinical trials, and the nuances of systematic reviews and meta-analytic techniques. It is recognized in combining studies using different designs that any resulting heterogeneity may be in part or in whole attributable to design elements, or characteristics of the patient population, rather than to variability in the efficacy of the HA product. This heterogeneity can in part be addressed by recognizing the presence and potential determinants of the heterogeneity and conducting the review in a manner that attempts to minimize the influence of any existent heterogeneity.

Previous systematic reviews by Lo et al. (Lo 2003) and Wang et al. (Wang 2004) have reached similar conclusions regarding the efficacy of HA products, although the magnitude of effect has differed. Lo et al. (Lo 2003), in particular, concluded that the effect size may be small at the class level. Bernstein (Bernstein 2004) has drawn attention to the discrepancy between the Lo et al. (Lo 2003) and Wang et al. (Wang 2004) commentaries on effect size. Hou and Wang (Hou 2004) have correctly asserted that the reviews differ in the approach to effect size estimation, search date and searching source, and in their interpretation of funnel plot distortion. Brandt (Brandt 2004) reported that Dieppe et al. (Dieppe (in press)) found a pooled effect size of -0.48 with a confidence interval of -0.72 to -0.23 in an analysis of 11 clinical trials. It appears, therefore, that the results of the meta-analyses may be, in part, method dependent and reviewers should be aware

of the nuances associated with the method used in this and other meta-analyses.

HA products differ in their origin, method of production, molecular weights (MW), biologic characteristics, rheologic properties, residence time in the joint and pharmacodynamic properties. As a consequence, any by-class analysis needs to be approached with due recognition that the products may differ in important respects, and that this may restrict the valuation of individual products, particularly where patients have not been randomised to receive the competing alternatives. The by-class analysis is also less informative to clinicians, since they generally seek to make evidence-based decisions in treating individual patients with specific products. In this review, we have presented both by-product

analyses and by-class analyses in order that readers can make their own judgement regarding individual products as well as the class as a whole.

The clinical epidemiology toolbox contains numerous alternative approaches to the design, execution and analysis of clinical trials. It is our understanding that traditionally, this class of intervention was considered as a device class and originally was not generally subject to the same evaluation guidelines that then existed for pharmacologic agents. This may explain, in part, the heterogeneity in research designs and outcome measurement techniques used, a phenomenon, however, not peculiar to this class of interventions. Our review detected differences in a least nineteen areas of trial design including: clinical environment, sample size, number of study arms, number of centres, nature of the placebo comparator, inclusion and exclusion criteria, washout period, retreatment opportunity, concomitant therapy, follow-up schedule, duration of follow-up, outcome measures, age, gender balance, disease duration, baseline pain severity, radiographic grade, treatment schedule, rescue medication. These differences were sometimes evident, even when comparing different trials involving the same HA product.

The nuances of systematic reviews and meta-analysis require due consideration of any assumptions, implicit or explicit that are made to combine information and data from diverse sources into valid and meaningful summary statistics. In particular, it is necessary to be familiar with a number of factors including, but not limited to the following: RevMan 4.1 software and its operations; assumptions, if any, regarding the value of  $\rho$  in imputations which require converting between change scores and post-test scores; the significance of the test for heterogeneity and its implications both on the appropriateness of combining studies and the use of fixed-effect versus random-effects models of analysis; the consequence of basing analyses on transformed data, for example where different outcomes (pain walking, pain at night, global pain) measured on different instruments, have been filtered through a hierarchical algorithm to obtain a single measure of pain suitable for meta-analysis. This latter issue is particularly concerning given the dif-

ferential impact of interventions on different components of the symptom complex and between-instrument differences in responsiveness (synonym: sensitivity to change). Other methodologic issues include the potential for publication bias, and the interpretation of the clinical importance of the observed treatment effects.

This review highlights the challenge of interpreting the results of clinical trials of intra-articular (IA) injections of hyaluronan and hylan in knee OA. Greater standardisation in methodology would facilitate assessment of these trials. Complete descriptions of blinding, randomisation, withdrawals and dropout would improve reporting quality. There was wide variation in the method of assessment of outcome. The distinction between primary and secondary outcome measures was infrequently reported. The utilisation of local anaesthetic also varied as well as description of the injection technique employed. The inclusion/exclusion criterion of presence of effusion at study entry was variable with some trials limiting the entry of subjects with a predefined volume of effusion. Different osteoarthritic populations were included in the trials; some subjects had unilateral disease while others had bilateral disease. Variability was noted in both timing and method (e.g. office versus telephone) of assessments, and in the opportunity for retreatment. In some trials, a per protocol rather than intent-to-treat statistical analysis was reported.

Safety was reported in variable formats, e.g. number of adverse events per number of injections, number of 'related' adverse events, number of subjects reporting adverse events, number of serious adverse events, number of local (injection site) reactions, number of systemic reactions, number of patients withdrawing due to adverse events. The denominator for safety analyses was frequently based on the intent-to-treat population. However, in some trials it was difficult to ascertain the denominator (patients versus injections). Ideally, the following should be reported: 1) withdrawals overall, 2) withdrawals due to all adverse events, 3) withdrawals due to system specific adverse events (e.g. gastrointestinal related grouped, cardiovascular grouped, etc.), and 4) withdrawals due to lack of efficacy.

Safety of hyaluronan and hylan in the general population for approved products in the U.S.A. can be examined by review of the U.S.A. Food and Drug Administration Manufacturers and User Device Experience (MAUDE) database available online at <http://www.fda.gov/cdrh/maude.html>. Large pharmacoepidemiologic databases are generally better sources of safety data than small individual clinical trials. An article by Hammesfahr, Knopf and Stitik reviews the safety data for the three products marketed in the United States, e.g. Hyalgan, Supartz and Synvisc (Hammesfahr 2003). They concluded that HA therapy is a safe treatment for OA of the knee. In addition, Hamburger et al. also concluded that HA therapy is a safe treatment for knee OA, but that there may be interproduct variability in safety profiles (Hamburger 2003).

The possibility of publication bias exists if reviewers choose to

exclude unpublished studies. McAuley et al. recommend the inclusion of all reports, grey and published, that meet predefined inclusion criteria in meta-analyses (McAuley 2000). In this review, nine included studies (Ardic 2001; Brown 2003; Cohen 1994; Groppa 2001; Guler 1996; Karras 2001; Moreland 1993; Pham 2003; Tsai 2003) were published only as abstracts. However, an in-house manuscript by Moreland (Moreland 1993) was provided. The articles by Hizmetli (Hizmetli 1999) and Lin (Lin 2004) were in-house publications. Two specialization thesis (Auerbach 2002a; Kalay 1997) were included. Published articles have the advantage of having undergone the peer review process. Frequently, abstracts do not provide enough information to be included in reviews, and, consequently, are excluded.

The method of statistical analysis can affect the result. The utilisation of follow-up (difference) scores, change (improvement) scores, or unadjusted post-test (synonym: final value) scores for continuous outcome measures can influence the result. Vickers and Altman (Vickers 2001), Norman (Norman 1989), Lund (Lund 1988) and Stucki et al. (Stucki 1996) have discussed this issue.

A high placebo effect has been noted in HA clinical trials (Bhagal 2000). This response may be attributed to a number of factors including: 1) removal of excess synovial fluid, 2) patient expectation, 3) Hawthorne effect of participating in a clinical trial, or 4) active treatment effect of saline and/or arthrocentesis (Kaptchuk 2000). The modulating effects of rescue analgesia and co-therapy with other OA treatments on outcome variables also should be considered.

The effect of treating both unilateral and bilateral disease in the same trial is problematic. Generally, efficacy results were based on analyses of the worse joint, while safety results were based on analyses of both joints. In some patients both knees received the same intervention, while for other patients they received one intervention in one knee and the comparative intervention in the other knee. The time between treatment of the knees varied considerably with some knees both being treated the same day, while other knees had a 210-day difference between initiation of treatment. The selection of a target joint (e.g. study knee) is one method of resolving this controversy. The problem of analysing the person versus the joint(s) has been reported in the literature (Sutton 1997; Zhang 1996).

Some trials used the Ahlback classification of knee OA. A recent publication, suggested that this classification had some 'major limitations' (Galli 2004). Even low grade Ahlback grades reflect substantial structural damage. Patients with higher grade structural damage may be generally less responsive to treatment (Barrett 2002; Evanich 2001; Lussier 1996; Magilavy 2003; Toh 2002; Vad 2003).

Limitations of this review are the omission of open trials and case series, the omission of studies that failed to meet inclusion criteria,

the lack of standard outcome measures restricting pooling opportunities, and restricted access to source data. Strengths of the review are the inclusion of only randomised controlled trials, the focus on four core OARSI and OMERACT outcome measures, and adherence to the principles of Cochrane systematic reviews.

A product-based discussion is followed by a class-based discussion. All comments are based on the trials that could be included in this review, the data that could be extracted and the analyses that could be performed, and should be interpreted and utilized by readers with the understanding that the review was conducted using the methodology described in the earlier part of this document, a methodology anchored to the Cochrane review process using RevMan 4.1 software, and limited potentially by restricted access to both unpublished studies and primary data. It should be recalled that HA products are not generally immediate in their onset, and that the 5 to 13 week time period may be one of the more relevant for single course studies, while later periods may be particularly relevant for studies allowing more than a single course. Statistically detectable differences seen in the 1 to 4 week postinjection period represent a relatively early onset of action and are not necessarily expected in all responding patients or all studies. It should also be noted that statistically detectable improvement may not necessarily be detected on all variables or at the same point in time. Function may improve more slowly than pain, and it may be more difficult to detect an effect on night pain than on walking pain. Finally, comparisons against other efficacious forms of treatment are likely to result in either no statistically detectable difference in efficacy or in relatively small differences (cf studies of HA products against placebo). The inability to show a statistically detectable difference between an HA product and placebo, in at least one key variable such as pain, function or patient global assessment from about 5 to 13 weeks onwards might be regarded with some degree of concern.

RevMan output for continuous data can be in the form of the WMD or SMD. The WMD provides a summary statistic whose magnitude is related to a number of factors including the treatment effect and the scale length of the instrument on which the underlying data were collected. What constitutes a minimum clinically important difference (MCID) is subject to ongoing debate (Bellamy 1993). The value for the minimum perceptible clinical improvement (MPCI) for the WOMAC Index is approximately 10 normalised units (0 to 100). This may serve as one indicator of the clinical importance of the WMD for pain, stiffness and function measured on 0 to 100 normalised unit scales. In contrast, the SMD provides a summary statistic adjusted by the variance, is of a different order of magnitude to the WMD and expresses the effect size as a unitless measure. What constitutes a small, medium, or large effect size is a matter for debate. We have used the proposals advanced by Cohen (Cohen 1977), and operationalised in a recent publications by Jordan et al. (Jordan 2003), and Mazieres et al. (Mazieres 2001) i.e. small effect size = 0.2, moderate effect size,



i.e. clinically recognisable = 0.5, large effect size = 0.8. Other measures of clinical value are the percentage superiority in response and the NNT. We are not aware of published critical values for these parameters in OA management. Nevertheless, tables have been provided for all the aforementioned parameters, in order that readers can make informed decisions. It should be noted that the magnitude of these parameters differs with product, comparison, variable and time period.

We have observed that in some analyses, the RevMan 4.1 output differs from the original publication (Table 36). Repeat analyses based on RevMan 4.2 produced comparable results, also disparate with the original publication. The discrepancies are likely due to the use of secondary data and the statistical methods available within the software programme. Reviewers are advised to consider these disparities when making product-based evaluations.

#### **Product - Adant**

No placebo-controlled trials were included in this review. The only data that could be included in the review suggested that Adant is not different to Hyalgan with respect to patient global assessment at 1 to 4 weeks, 5 to 13 weeks, and 14 to 26 weeks, or with respect to the risk of experiencing injection-related pain. This review provides some supportive evidence for the efficacy and safety of Adant, but is based on limited data, and does not include placebo-controlled trials.

#### **Product - Artz (Artzal)**

In comparative studies of Artz and placebo included in this review, several outcome measures (Lequesne Index, range of motion, WOMAC OA Index), failed to detect a statistically significant difference at 1 to 4 weeks, 5 to 13 weeks, 14 to 26 weeks and 45 to 52 weeks, with the exception of patient global assessment at 1 to 4 weeks and 5 to 13 weeks and pain and the number of clinical failures at 5 to 13 weeks postinjection. Given the inclusion of single course studies, and the time-dependent dynamics of HA therapy, the positive effects of Artz on pain and patient global assessment seen at 5 to 13 weeks postinjection are expected. It is of note that statistically significant differences were detected on one pain measure but not another at 5 to 13 weeks. Significant effects on physical function cannot be confirmed from these analyses. It should be noted that the original analyses give a more positive result than the RevMan analyses we have performed. Taken collectively, the data generally support the efficacy of Artz (Artzal).

Analyses supported the safety of Artz, with no statistically significant differences from placebo being detected for the majority of safety variables.

No trials of Artzal against either corticosteroid or NSAID therapy were reported and no comment can be made on the relative effectiveness or safety against these two classes of

interventions.

In comparative analyses of Artz and Hylan G-F 20, there were no statistically significant differences at any of the four time periods in any of the four efficacy or three safety variables. This analysis derives from an ostensibly negative study. The two products could not be differentiated based on this single study.

#### **Product - BioHy (Arthrease)**

The placebo-controlled study is inconclusive for efficacy, likely as a result of previously described methodologic issues. There was no statistically significant between-group difference in the proportion of patients experiencing postinjection pain, or in overall withdrawals and there were no systemic reactions in either group, providing some support for the safety of

BioHy within the limits of the available data.

No trials of BioHy against either corticosteroid or NSAID therapy were reported and no comment can be made on the relative effectiveness or safety against these two classes of interventions.

In comparative analyses of BioHy and Hylan G-F 20, there were no statistically significant differences at either of the time periods in either efficacy variable, or one of the two safety variables. Joint effusion was significantly less likely in the BioHy group. The two products could not be differentiated based on this single study.

#### **Product - Fermathron**

No trials of Fermathron against placebo were reported and efficacy against placebo cannot, therefore, be assessed. No trials of Fermathron against either corticosteroid or NSAID therapy were reported and no comment can be made on the relative effectiveness or safety against these two classes of interventions.

In comparative analyses of Fermathron and Hyalart, there were no statistically significant differences at either of the time periods in any of the three efficacy variables, or in the safety variable. The two products could not be differentiated based on this single study.

#### **Product - Hyalgan**

In comparative studies of Hyalgan and placebo included in this review, statistically significant differences were detected at 1 to 4 weeks (pain on weight-bearing, spontaneous pain, pain at rest, Lequesne Index, number of joints improved for walking pain, number of joints improved for weight under load), 5 to 13 weeks (pain on weight-bearing, spontaneous pain, pain at rest, Lequesne Index, number of joints improved for walking pain, number of joints improved for weight under load, flexion, patient global assessment), 14 to 26 weeks (pain on weight-bearing, WOMAC pain), Statistically significant differences were not detected for pain at rest at 14 to 26 weeks, pain on weight bearing at 45 to 52 weeks, night pain, WOMAC pain at 1 to 4 weeks or 5 to 13 weeks, WOMAC function, Lequesne Index at 14 to 26 weeks, flexion at 1 to 4 weeks, or patient global assessment at 1 to 4 weeks, 14 to 26 weeks and 45 to 52 weeks. Many of the aforementioned sta-

tistically significant differences were highly significant, and clinically important (WMD (disregarding sign) for pain (0 to 100 mm) varying from 3.93 to 33.50). Overall, these analyses strongly support the evidence for efficacy of *Hyalgan*. No statistically significant differences from placebo were detected in the majority of safety variables although number of patients with local adverse events, number of patients with local adverse events that caused discontinuation, and number of patients with treatment-related adverse events was significantly greater with *Hyalgan*. Analyses of safety data also support the safety of *Hyalgan*.

Comparative studies of *Hyalgan* against IA methylprednisolone suggest that *Hyalgan* is superior to methylprednisolone at 5 to 13 weeks postinjection on spontaneous pain intensity, number of patients with moderate to severe pain under load, number of patients with moderate or greater rest pain, flexion, patient global assessment, but with the exception of flexion was not different at 1 to 4 weeks. No statistically significant differences were detected at 14 to 26 weeks or 45 to 52 weeks postinjection. These differences are probably due to the quick onset but often relatively short duration of the response to IA corticosteroid treatment. Overall, these analyses suggest that *Hyalgan* is comparable, or superior in efficacy to methylprednisolone, notwithstanding that the latter has a faster onset of action but the former a longer duration of action. Analyses of safety data also supported the safety of *Hyalgan*, with no statistically significant differences from IA methylprednisolone being detected in safety variables. The comparative study of *Hyalgan* against IA triamcinolone hexacetonide suggests that *Hyalgan* is not different in efficacy to triamcinolone hexacetonide, except in pain at night at 14 to 26 weeks. Analyses of safety data supported the safety of *Hyalgan*, with no statistically significant differences from IA triamcinolone hexacetonide being detected in safety variables. Collectively these data support the efficacy and safety of *Hyalgan*, and show some 5 to 13 week postinjection advantages in favour of *Hyalgan* over methylprednisolone.

The comparative study of *Hyalgan* against NSAID suggests that *Hyalgan* is comparable in efficacy to NSAID therapy at 1 to 4 weeks, 5 to 13 weeks, and 14 to 26 weeks postinjection, based on pain after a 50-foot walk and number of patients with moderate to marked pain. There were significantly fewer patients with gastrointestinal complaints, but more injection-site pain on *Hyalgan*; otherwise there were no statistically detectable differences in safety. Overall, these analyses suggest that *Hyalgan* is comparable in efficacy to NSAID therapy and similar in safety, with the exception of more injection-site pain events but fewer gastrointestinal adverse events than NSAID.

The comparative study of *Hyalgan* against mucopolysaccharide polysulfuric acid ester detected statistically significant differences in pain, Larson rating and patient global assessment, but no difference in function or range of motion. There was no difference in safety profile. The data are limited and no conclusion can be reached from this review regarding relative efficacy and safety.

The comparative study of *Hyalgan* versus conventional therapy detected statistically significant differences in arthroscopy score but not in clinical outcomes at 45 to 52 weeks. The data are limited, but are of interest in terms of potential structure modification effects.

#### *Product - Hylan G-F 20 (Synvisc)*

In comparative studies of Hylan G-F 20 and placebo included in this review, statistically significant differences were detected at 1 to 4 weeks (pain on weight-bearing, night pain, improvement in most painful knee movement, patient global assessment of treatment efficacy), 5 to 13 weeks (pain on weight-bearing, night pain, WOMAC function, Lequesne Index, improvement in most painful knee movement, patient global assessment of treatment efficacy), 14 to 26 weeks (pain on weight-bearing, night pain). Statistically significant differences were not detected for pain walking, pain at rest, pain overall or WOMAC pain. Many of the aforementioned statistically significant differences were highly significant, and clinically important (WMD (disregarding sign) for pain (0 to 100 mm) varying from 7.22 to 34.66). Overall, these analyses strongly support the evidence for efficacy of Hylan G-F 20. Analyses of safety data also support the safety of Hylan G-F 20, with no statistically significant differences from placebo being detected in the majority of safety variables.

Comparative studies of Hylan G-F 20 against corticosteroid suggest that Hylan G-F 20 is superior to triamcinolone hexacetonide at 5 to 13 weeks, and 14 to 26 weeks post injection on WOMAC pain walking on a flat surface, WOMAC function and total WOMAC score, but not at 1 to 4 weeks. This difference is probably due to the quick onset but often relatively short duration of the response to IA corticosteroid treatment. Overall, these analyses suggest that Hylan G-F 20 is comparable in efficacy to IA corticosteroid, notwithstanding that the latter has a faster onset of action but the former a longer duration of action. Analyses of safety data also supported the safety of Hylan G-F 20, with no statistically significant differences from IA corticosteroid being detected in the majority of safety variables.

Comparative studies of Hylan G-F20 against NSAID suggest that Hylan G-F 20 is comparable in efficacy to NSAID therapy at 5 to 13 weeks, and 14 to 26 weeks postinjection, based on the majority of variables. There were significantly fewer patients with possible or probable related systemic adverse events on Hylan G-F 20 but otherwise there were no statistically detectable differences in safety. Overall, these analyses suggest that Hylan G-F 20 is comparable in efficacy to NSAID therapy and similar or slightly superior in safety.

The comparative study of Hylan G-F 20 plus physiotherapy against physiotherapy alone detected no difference in Lequesne score or withdrawals but is limited in its scope and generalisability.

The comparative study of Hylan G-F 20 and intra-articular gaseous oxygen, detected no statistically significant differences on

the majority of variables. Indeed the only variable on which a difference was detected was pain under load at 5 to 13 weeks and was in favour of intra-articular gaseous oxygen. The two treatments could not be differentiated based on this single study.

Two comparative studies of Hylan G-F 20 plus appropriate care versus appropriate care alone both confirm the superiority of adding Hylan G-F 20 to appropriate care as assessed by the WOMAC OA Index, Lequesne Index and patient global assessment. Safety variables either detected no statistically significant difference or were in favour of Hylan G-F 20 plus appropriate care. These studies provide strong support for the incorporation of Hylan G-F 20 into routine clinical care treatment paradigms.

#### ***Product - NRD-101***

In the comparative analyses against Artz, no statistically significant differences were detected between the products in efficacy or safety. The two products could not be differentiated based on this single study. No comment can be made regarding the relative efficacy of NRD-101 and placebo, since efficacy data relevant to performing RevMan analysis, could not be extracted from the original publication.

#### ***Product - Orthovisc***

In comparative studies of Orthovisc and placebo included in this review, statistically significant differences in WOMAC pain and WOMAC function were detected at 1 to 4 weeks, 5 to 13 weeks, and 14 to 26 weeks postinjection. These analyses support the evidence for efficacy of Orthovisc. Analyses of safety data also supported the safety of Orthovisc, with no statistically significant differences from placebo being detected in the safety profile.

Comparative studies of Orthovisc against corticosteroid suggest that Orthovisc is superior to 6-MPA at 5 to 13 weeks and 14 to 26 weeks postinjection and superior to betamethasone at 5 to 13 weeks postinjection. No statistically significant differences were detected at 1 to 4 weeks against either corticosteroid. This time-dependent difference is probably due to the quick onset but often relatively short duration of the response to IA corticosteroid treatment. Overall, these analyses suggest that Orthovisc is comparable in efficacy to IA corticosteroids at 1 to 4 weeks and superior at 5 to 13 weeks and 14 to 26 weeks, notwithstanding that the latter have a faster onset of action but the former a longer duration of action. Analyses of safety data also support the safety of Orthovisc, with no statistically significant differences from either IA corticosteroid preparation being detected in the safety profile.

No trials of Orthovisc against either NSAID therapy were reported and no comment can be made on the relative effectiveness or safety against this class of intervention.

In the comparative study of Orthovisc plus physiotherapy against physiotherapy alone, no statistically significant differences in efficacy variables were detected at 1 to 4 weeks postinjection. Statistically significant differences in favour of Orthovisc were noted in

some, but not all, variables at 5 to 13 weeks postinjection. There were no statistically significant differences in safety profile. These analyses suggest that adding Orthovisc to physiotherapy may be beneficial with respect to activity pain and spontaneous pain, at 5 to 13 weeks postinjection.

In a comparative analysis of Orthovisc plus physical therapy versus Hylan G-F 20 plus physical therapy there were no statistically significant differences in efficacy or safety. The two products could not be differentiated based on this single study.

#### ***Product - Replasyn***

It was not possible to conduct informative analysis of Replasyn as part of this review, and therefore no conclusion can be reached regarding efficacy or safety, based on our review. The original publication, referred to previously, noted a significant difference in only one of six variables.

#### ***Product - SLM-10***

SLM-10 was comparable in efficacy to Artz on three outcome measures and statistically significantly inferior on pain on pressure. There was no difference in safety profile. This review provides some supportive evidence for the efficacy and safety of SLM-10, but is based on limited data, and does not include placebo-controlled trials or studies against NSAID, IA corticosteroid or appropriate care.

#### ***Product - Suplasyn***

No statistically significant differences were detected in our analyses between Suplasyn and placebo for four of the five efficacy measures and for the fifth favoured the control group. No statistically detectable differences were noted in the safety profile. The review does not incontrovertibly support the efficacy of Suplasyn, given negative outcomes for the majority of variables in our RevMan analyses, which are somewhat at variance with the original publication. However, Felson and Anderson (Felson 2002) published an editorial on HA injections for OA in the same issue of Archives of Internal Medicine in which the Petrella trial (Petrella 2002) was published. They re-evaluated the data of Petrella analysing it as a factorial experiment, and noted that Suplasyn had no "significant or important clinical effect on pain" and "there [were] null results for disability and other outcomes".

No statistically significant differences in efficacy or safety variables were detected between Suplasyn and NSAID. The two treatment strategies could not be differentiated based on this single study.

#### ***Product - Zeel compositum***

No statistically significant differences in efficacy or safety variables were detected between Zeel compositum and Hyalart. The two products could not be differentiated based on this study.

#### ***By-class analyses***

The pooled analyses address issues relating to class characteristics and may not be shared to the same extent by each individual HA product. Readers including practitioners, regulators and third party payers should be cautious in extrapolating from the class to an individual product or vice versa, as the class-based analysis may either under-estimate or over-estimate the performance of individual component products. For product-based information, readers are referred to the relevant preceding sections. Only comparisons against placebo are discussed, because of the relatively large number of studies available for some of these analyses. The other comparisons were limited, in some cases, by a relative paucity of studies.

Statistically significant differences were detected between HA and placebo at 1 to 4 weeks (pain on weight bearing, Lequesne Index), 5 to 13 weeks (pain on weight bearing, WOMAC pain, WOMAC function, Lequesne Index, flexion), and 14 to 26 weeks (pain on weight bearing, WOMAC pain) postinjection. Apart from a higher incidence of injection site pain, no statistically significant differences versus placebo were noted in the safety profile variables. These data generally support the evidence for the efficacy and safety (versus placebo) of the HA class of intervention.

## AUTHORS' CONCLUSIONS

### Implications for practice

The review presented is comprehensive and permits practitioners to more fully consider the therapeutic profile of HA products. Each analysis addresses a different issue, and practitioners are recommended to review those analyses specifically relating to their questions. This should involve examining the original publication, the methodology employed in conducting the review, the results for the product(s) of interest, with attention to the relevant variables and timepoints. Readers should consider the clinical importance as well as the statistical significance of any differences detected. Readers should be aware that the results of our review derive from a defined approach to the analysis of selected studies, that selected studies vary in quality and that the analyses do not consider studies excluded from consideration. Nevertheless, the approach is traditional, follows Cochrane guidelines and uses RevMan 4.1 software.

Controversy in the existing literature is part due to a combination of the heterogeneous time-dependant nature of the response to the HA class of products, diversity in protocol design in the contributing studies, and the different approaches taken to the conduct of systematic reviews. We have attempted to dissect out the effect of these issues by performing multiple analyses on a by-product, by-comparison, by-variable, by-timepoint basis. While this does not provide a single answer to questions of efficacy, effectiveness and safety, the analyses permit the complexity of the HA effect to be appreciated.

The analyses suggest that there is considerable heterogeneity in the clinical response, such that there are differential therapeutic effects by different HA products, on different variables and that the response is time dependent. For example, when pain on weight bearing at 5 to 13 weeks postinjection is considered the evidence is very supportive of therapeutic benefit over placebo, and the effect size (SRM) may be as high as 0.94 depending on the product and is 0.58 for the HA class in general. Given that effect sizes can be classified as small (0.2), medium (0.5) or large (0.8), these analyses suggest a range of effect sizes up to large product-based effect on pain on weight bearing, and a moderate class-based effect on pain on weight bearing.

The dynamics of the response are such that a statistically significant, clinically important, effect 1 to 4 weeks postinjection versus placebo is not necessarily achievable. Nevertheless, early responses are observed in some comparisons. In contrast, in comparisons against placebo there may be a more durable, albeit slower response compared to IA corticosteroids. In long-term studies, the effects of combining single course with repeat treatment studies in our analyses deserve due consideration, particularly when reviewing the late stage endpoints, for example 45 to 52 weeks. In single course studies the last course may have been almost one year prior when a persisting effect might not be expected, while in repeat-course studies the last course may have been recent, or even 5 to 13 weeks prior, when a clinical benefit might well be anticipated. These nuances deserve due recognition since they account for some of the diversity in the responses reported in the literature.

These issues notwithstanding, HA products generally appear superior to placebo on multiple efficacy variables, providing support for the use of those HA products for which the effect is not only statistically significant but also clinically important. These benefits appear to be achievable without attributable systemic adverse events but with occasional local reactions which tend, for the most part, to be relatively transient, resolving without sequelae either spontaneously or with simple intervention. It should be noted that this review is not the premier source of safety data, since sample sizes are relatively small in the trials reported, particularly for detecting less frequent or even rare adverse events. Readers are referred to the general literature and the surveillance literature for a more comprehensive appreciation of safety issues. Nevertheless, based on the evidence reviewed, HA products appear in general to be safe.

### Implications for research

The following types of studies would be informative: long-term trials (up to one year) including repeat course studies, head-to-head comparisons of different HA products, effectiveness, cost-effectiveness and cost-utility studies, studies of different OA subgroups, dissection of the determinants of the response to HA products, exploration of the apparently differential effect of HA products on different variables. The aforementioned studies should

follow OARSI and other similar guidelines for the conduct and design of OA studies. The use of standardized outcome measures is encouraged to facilitate meta-analyses and between trial comparisons.

## ACKNOWLEDGEMENTS

The authors are grateful to Jessie McGowan for conducting the search strategy. We acknowledge the assistance of former Musculoskeletal Review Group Co-ordinator Maria Judd and current Musculoskeletal Review Group Co-ordinator Lara Maxwell for their guidance in completing this review.

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\* Indicates the major publication for the study

## SOURCES OF SUPPORT

### External sources of support

- Genzyme Biosurgery (formerly Biomatrix Inc.) and Wyeth-Ayerst provided an unrestricted educational grant CANADA

### Internal sources of support

- Centre of National Research on Disability and Rehabilitation Medicine (CONROD) AUSTRALIA

## **INDEX TERMS**

### **Medical Subject Headings (MeSH)**

Hyaluronic Acid [\*analogs & derivatives; \*therapeutic use]; Osteoarthritis, Knee [\*drug therapy]; Randomized Controlled Trials

### **MeSH check words**

Humans