The conservative treatment of ankle osteoarthritis
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A prospective multi-centre, open study of the safety and efficacy of hylan G-F 20 (Synvisc®) in patients with symptomatic ankle (talo-crural) osteoarthritis

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Abstract

Background: To evaluate the safety and efficacy of hylan G-F 20 in patients with ankle osteoarthritis.

Methods: A prospective, open study in patients with symptomatic (≥50 mm and ≤90 mm on a 100 mm VAS) ankle osteoarthritis. Patients received 1 ml x 2 ml intra-articular injection of hylan G-F 20, plus an optional, second injection if pain remained at baseline levels after 1, 2 or 3 months. The primary efficacy endpoint was the change from baseline in the pain VAS score at 3 months.

Results: Fifty-five patients received the first injection; 24 patients received a second. There were no serious or severe adverse events (AEs) related to the treatment. Seventeen patients experienced mild or moderate local, treatment-related AEs. The mean pain VAS score decreased from 68.0 mm (baseline) to 33.8 mm at 3 months (p < 0.001), which was maintained to 6 months (34.2 mm, p < 0.001).

Conclusions: Hylan G-F 20 is well-tolerated and effective for up to 6 months in the treatment of symptomatic ankle osteoarthritis.

Keywords: Osteoarthritis; Ankle; Viscosupplementation; Hylan G-F 20; Hyaluronan
Introduction

Osteoarthritis (OA) is a chronic, degenerative disorder associated with joint pain and loss of joint function. It is the most common disease to affect synovial joints and is one of the most frequently occurring chronic conditions.

OA can affect any synovial joint but is most frequently found in the knee, hip and hand, and the majority of these patients present with primary (idiopathic) disease[1]. Reliable figures on the prevalence of OA in other joints are not readily available but estimates suggest that symptomatic ankle OA is found in <1% of the adult population[2]. In contrast to knee and hip OA, about 70% of patients with ankle OA present with secondary, post-traumatic disease[3]. As ankle trauma is often sports-related, patients suffering from OA are, on average, relatively young. Ankle OA can often prevent these young, otherwise healthy patients from working or participating in sports activities[3,4].

The choice of treatment of ankle OA depends on the severity of the disease, the patient’s age, medical and social history and the level of physical activity expected to be demanded of the joint.

A group that is difficult to treat are those patients suffering from milder, Grade II[5] ankle OA (joint space narrowing ≤50%). Although, usually, these patients are not yet surgical candidates, they are often relatively young and wish to be active without the burden of chronic pain medications with their associated adverse side-effects. Viscosupplementation (intra-articular supplementation of hyaluronic acid) could potentially provide a useful alternative in treating such patients with painful ankle OA.

Viscosupplementation is a well-established treatment option in knee OA and is included in the professional guidelines for treatment of the disease in this joint[6,7]. The potential for treating osteoarthritis of the ankle joint by viscosupplementation has been suggested in the literature[8,9]. Evidence for efficacy and safety in this setting is limited but two recent studies showed that five weekly HA injections in the ankle joint seem to be well-tolerated and can improve pain and function[10,11].

Dosing in the ankle joint remains an area for discussion as no dosing studies have been published to date. Anecdotal evidence suggests that some clinicians simply follow the dosing regimen for knee OA, which varies from 3 to 5 weekly injections of 1–2 ml. However, published evidence on the use of hylan G-F 20 in hip OA shows that a single,
2 ml injection, with an optional second injection between 1 and 3 months after the first, can be safe and effective\textsuperscript{[12,13]}. The aim of this study was therefore to evaluate the safety and efficacy of a single, 2 ml injection of hylan G-F 20, with an optional, second injection between 1 and 3 months after the first, in patients with symptomatic ankle (talo-crural OA).

**Materials and methods**

**Trial design**

This was a prospective, multi-centre, open study conducted in adult patients with symptomatic ankle OA between November 2003 and January 2006. To be considered symptomatic patients had to score $\geq 50$ and $\leq 90$ mm on the Ankle OA Pain visual analogue scale (VAS) (0–100 mm) at the baseline visit. Patients must have undergone at least 6 months of conservative treatment modalities (rest, physical therapy, NSAIDs etc.), and failed to achieve adequate symptomatic relief from these treatments, to be considered eligible.

Given the known safety profile of hylan G-F 20, its intra-articular residence time, and the volume of the ankle space, it was thought that an injection regimen of one 2 ml injection would be appropriate and would not pose major safety concerns. Patients whose AOAP VAS score remained $\geq 50$ and $\leq 90$ mm at 1, 2 or 3 months follow-up were deemed not to have achieved adequate symptomatic relief from the first injection and were offered an optional second (and final) injection.

A washout period of 1–3 weeks was applied (adapted to half-life), commencing at the screening visit, if patients had been taking analgesics, NSAIDs or COX-2 inhibitors. Once any required washout was completed and eligibility confirmed patients received one intra-articular 2 ml injection of hylan G-F 20 in the ankle. The injection, using strict aseptic administration technique, was placed in the anteromedial portal of the ankle joint as described for ankle arthroscopy\textsuperscript{[14]}. Patients were supine, the ankle was dorsiflexed to a neutral position and the injection site was manually located. Intra-articular placement of the needle was deemed determined if no resistance was felt when injecting local anaesthetic (bupivacaine). Any fluid or effusion present in the joint was removed prior
to the injection of hylan G-F 20. The second injection, if required, was performed in the same manner, by the same physician who had administered the first injection.

Medication for pre-existing conditions was permitted, in addition to: acetaminophen (≤4 g/day) except on the day before, and the day of, follow-up visits; analgesics and NSAIDs with a clearance time of <8 h for pain other than OA in the study ankle, or for post-injection pain management but not for more than three consecutive days or more than 10 days per month, nor on the day before, or the day of, a study visit; aspirin (≤325 mg/day) for anti-thrombotic prophylaxis, topical corticosteroids for skin problems, except at the study ankle, inhaled corticosteroids for asthma and allergic disease; non-pharmacological therapy (e.g. physical therapy) if begun at least 3 months before study entry.

Prohibited medications were: analgesics and aspirin except as described above; COX-2 inhibitors; oral corticosteroids; corticosteroid injections in any joint; topical analgesics at the study ankle; oral or parenteral anticoagulant therapy; glucosamine, chondroitin sulphate and diacerein, except if the patient was on a stable dose prior to inclusion and no changes to treatment were envisaged in the next 9 months. The use of all rescue and concomitant medications and therapies were recorded in the patient notes.

All patients were followed for 6 months after the last injection, with follow-up visits at 7 days, 1 month, 2 months, 3 months and 6 months after each injection. The study period for each patient therefore varied from 6 months, if receiving one injection, up to a maximum of 9 months if receiving two injections.

The study protocol was designed, conducted, recorded and reported in compliance with the principles of good clinical practice (GCP) and in accordance with the Declaration of Helsinki 1964.

Patients

Patients were enrolled at five centres across Europe: The Netherlands (1), Germany (2) and Italy (2). The study protocol, patient information and patient consent form were approved by the Independent Ethics Committee of each investigating centre. Written, informed consent was obtained from each patient prior to enrolment in the study.

The study was open to patients of either gender, presenting with OA pain in the ankle (the “study ankle”), ≥18 years of age with an active lifestyle and in general good health.
Criteria for inclusion were: a clinical diagnosis of primary or secondary talo-crural OA; a standard X-ray, taken within the 3 months prior to screening, confirming the clinical diagnosis and showing grade II OA (joint space narrowing with or without osteophytes, joint space narrowing ≤50%) according to the van Dijk et al. scale\textsuperscript{[5]}; patient willingness to comply with any required washout period; no planned surgical intervention in the next 9 months.

Exclusion criteria were: Grade I or III talo-crural OA\textsuperscript{[5]}; patients with post-traumatic OA if induced by trauma within the past 24 months; flare patients eligible for corticosteroid injection; chronic ankle instability; chronic anterior or posterior impingement syndrome in the study ankle requiring surgical treatment; current osteochondrosis dissecans in the study ankle; significant valgus/varus requiring corrective osteotomy; prior viscosupplementation in the study ankle; physical therapy if begun within the 3 months before study entry; history of sepsis in the study ankle; arthroplasty in the study ankle at any time, or any other surgery in the study ankle within the 6 months prior to study enrolment; clinically significant venous or lymphatic stasis in the study leg; any contraindication to acetaminophen; systemic or intra-articular injection of corticosteroid in any joint within the 3 months prior to enrolment; patients with related hypersensitivities to avian protein or any components of hyaluronan-based injection devices; concomitant inflammatory arthropathy; any history of, or active infection at the injection site; any significant chronic skin disorder at the injection site; any significant neuromuscular disease or musculoskeletal condition that would impede efficacy measurement; symptomatic peripheral vascular disease; current malignancy or treatment within the past 5 years; women who were pregnant or nursing, or women of childbearing potential not using a medically acceptable form of birth control; use of an investigational drug or device in the 90 days before entering the study or plans to use such a drug or device during the study; other factors assessed by the investigators that may limit the ability of the patient to perform necessary study evaluations.
Outcome measures

Safety
The safety assessment of hylan G-F 20 was based on reports of adverse events (AEs) collected between the signing of the informed consent form and the completion of the final follow-up visit for each patient. Study ankle and other (non-study ankle) AE reports were collected at each visit. Additionally, patients provided an overall evaluation of safety at each visit by using a four-point scale indicating the severity of any side effects experienced (none, mild, moderate, severe).

Efficacy
The primary efficacy hypothesis was evaluated by the change from baseline (immediately prior to the last injection) to 3 months after the last injection, using the patient’s assessment of his/her Study Ankle OA Pain within the past 48 h as measured by the patient-completed Study Ankle OA pain 100 mm VAS.

The secondary efficacy endpoints were the change from baseline (immediately prior to the last injection) in: the patient-completed Study Ankle OA Pain 100 mm VAS (at all other time-points); the total Ankle OA scale scores [15]; the patients’ Global OA Assessment VAS score; the physicians’ Global OA Assessment VAS score; the health related quality of life (SF-36). Patients were defined as responders if their Study Ankle OA Pain 100 mm VAS score decreased by ≥50% from baseline.

Statistical methods

Safety
AEs were classified using the Medical Dictionary for Regulatory Activities (MedDRA, Version 8.1) coding dictionary. AEs manifesting at the time of, or after, injection of hylan G-F 20 (treatment-emergent AEs) were tabulated. Patient-assessed evaluation of side-effects was summarised by the number and percentage of patients in each category at each scheduled visit.
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Efficacy

All efficacy analyses were performed on the intent-to-treat (ITT) population, which was defined as all patients who received the first injection and had at least one post-baseline efficacy assessment. All outcome measures were analysed on the ITT population using a paired t-test. If the data did not meet the appropriate assumptions for the paired t-test to be valid, the Wilcoxon Signed Rank test was used.

Clinical data were captured using electronic data capture technology from eTrials®. Statistical analysis was performed on validated systems including Clintrace® and SAS® Version 8.2.

Results

Patients

Patient disposition for the study is shown in Fig. 1. The ITT population consisted of 55 patients. Fifty-one of the 55 patients (93%) completed the study. Baseline demographics for the ITT population are presented in Table 1. Patients were predominantly male (60%) and the mean age was 41 years.
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Table 1: Baseline Summary of patient demographics (ITT population)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Summary statistic</th>
<th>One injection</th>
<th>Two injections</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients in ITT population</td>
<td>N</td>
<td>31</td>
<td>24</td>
<td>55</td>
</tr>
<tr>
<td>Gender</td>
<td>n (%)</td>
<td>18 (58.1)</td>
<td>15 (62.5)</td>
<td>33 (60.0)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>13 (41.9)</td>
<td>9 (37.5)</td>
<td>22 (40.0)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean (S.D.)</td>
<td>42.9 (12.0)</td>
<td>38.5 (12.6)</td>
<td>41 (12.3)</td>
</tr>
<tr>
<td></td>
<td>Median (Min., Max.)</td>
<td>40.9 (25.5, 70.6)</td>
<td>37.9 (19.0, 70.3)</td>
<td>40.2 (19.0, 70.6)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Mean (S.D.)</td>
<td>76.9 (18.3)</td>
<td>81.4 (15.1)</td>
<td>78.9 (16.9)</td>
</tr>
<tr>
<td></td>
<td>Median (Min., Max.)</td>
<td>75 (50.0, 140.0)</td>
<td>81 (50.0, 115.0)</td>
<td>80 (50.0, 140.0)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>Mean (S.D.)</td>
<td>175 (11.2)</td>
<td>176.6 (8.1)</td>
<td>175.7 (9.9)</td>
</tr>
<tr>
<td></td>
<td>Median (Min., Max.)</td>
<td>173 (150.0, 195.0)</td>
<td>178 (154.0, 187.0)</td>
<td>176 (150.0, 195.0)</td>
</tr>
<tr>
<td>Body Mass Index (kg/m2)</td>
<td>Mean (S.D.)</td>
<td>24.9 (4.4)</td>
<td>26 (4.0)</td>
<td>25.4 (4.2)</td>
</tr>
<tr>
<td></td>
<td>Median (Min., Max.)</td>
<td>23.9 (18.1, 42.3)</td>
<td>24.8 (19.8, 34.7)</td>
<td>24.6 (18.1, 42.3)</td>
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<tr>
<td>Cause of OA</td>
<td>Idiopathic (%)</td>
<td>9 (29.0)</td>
<td>4 (16.6)</td>
<td>13 (23.6)</td>
</tr>
<tr>
<td></td>
<td>Secondary (%)</td>
<td>22 (71.0)</td>
<td>20 (83.3)</td>
<td>42 (76.4)</td>
</tr>
<tr>
<td>Time since OA diagnosis (months)</td>
<td>Mean (S.D.)</td>
<td>19.4 (31.8)</td>
<td>32.7 (48.7)</td>
<td>25.0 (39.9)</td>
</tr>
<tr>
<td></td>
<td>Median (Min., Max.)</td>
<td>10.0 (0.0, 152.6)</td>
<td>8.8 (0.0, 170.8)</td>
<td>9.4 (0.0, 170.8)</td>
</tr>
<tr>
<td>Joint space narrowing (%)</td>
<td>Mean (S.D.)</td>
<td>26.7 (9.2)</td>
<td>26.9 (7.7)</td>
<td>26.8 (8.5)</td>
</tr>
<tr>
<td></td>
<td>Median (Min., Max.)</td>
<td>28.6 (4.8, 40.0)</td>
<td>25 (10.0, 40.0)</td>
<td>25 (4.8, 40.0)</td>
</tr>
<tr>
<td>Ankle OA Pain VAS at baseline (mm)</td>
<td>Mean (S.D.)</td>
<td>68.1 (11.8)</td>
<td>67.8 (15.7)</td>
<td>68.0 (13.5)</td>
</tr>
<tr>
<td></td>
<td>Median (Min., Max.)</td>
<td>68.0 (26.0, 90.0)</td>
<td>68.5 (9.0, 86.0)</td>
<td>68.0 (9.0, 90.0)</td>
</tr>
</tbody>
</table>
Safety

Thirty-five patients (63.6%) experienced a total of 89 study ankle AEs during the study (Table 2). Of these, 17 patients (30.9%) experienced 28 treatment-related AEs of the study ankle. The majority consisted of arthralgia, injection site pain and joint swelling. All were mild or moderate in intensity and transient in nature. One of the study ankle AEs (pain in extremity) was indicated as severe but was unrelated to treatment.

Only one serious adverse event (SAE) was reported during the study: an occurrence of osteochondrosis dissecans in the study ankle 4 months after study treatment. This adverse event was not considered to be treatment-related by the investigator. Fifteen (27.3%) of the 55 patients treated experienced 22 other, non-study ankle AEs. None of these were treatment-related and all were of mild or moderate intensity.

Two patients discontinued the study due to the occurrence of AEs. The first was the patient with the recurrence and worsening of osteochondrosis dissecans described above. The second was a patient who received a second injection at month 2 and experienced arthralgia of the study ankle, which was of moderate intensity and considered unrelated to study treatment.

The evaluation of the patient safety rating scale showed that patients reported increasingly fewer side effects as the study progressed. Of the patients receiving one injection, 86.6% and 93.6% reported none or mild side effects at day 7 post-injection and at month 1 respectively. At month 6, 100% of these patients reported no side effects. Of the patients who received two injections, 78.2%, 87.0% and 90.9% reported none or mild side effects at day 7, at month 1 and at month 6 respectively.

| Table 2: Incidence of Study Ankle Treatment-Emergent AEs |
|---------------------------------|-----------------|-----------------|-----------------|
| Parameter                       | One injection   | Two injections  | All patients    |
|                                 | N = 31          | N = 24          | N = 55          |
|                                 | n (%)           | n (%)           | n (%)           |
| Patients with any study ankle AEs | 14 (45.2)       | 15 (62.5)       | 35 (63.6)       |
| Patients with treatment-related AEs | 6 (19.4)       | 7 (29.2)        | 17 (30.9)       |
| Discontinuation due to AEs      | 1 (3.2)         | 1 (4.2)         | 2 (3.6)         |
| Patients with SAEs              | 1 (3.2)         | 0 (0.0)         | 1 (1.8)         |
Primary efficacy endpoint

There was a statistically significant decrease in the mean score of the patient-completed Study Ankle OA Pain VAS from 68.0 mm at baseline to 33.8 mm at month 3 (p < 0.001) (Fig. 2). Patients who received one injection had a mean change in VAS score of -42.5 mm (p < 0.001) and patients who received two injections had a mean change of -23.5 mm (p < 0.001).

Secondary efficacy endpoints

Study Ankle OA Pain VAS

The patient-completed Study Ankle OA Pain VAS scores at baseline, day 7, month 1, month 2, month 3 and month 6 after the final injection are shown in Fig. 2.

![Figure 2: Study Ankle OA Pain mean VAS score at each time-point (ITT population)](image)
Figure 3: (a) Ankle OA scale mean VAS score: pain (ITT population) (b) Ankle OA scale mean VAS score: disability (ITT population)
Ankle OA scale

The ankle OA scale\(^{[15]}\) consists of 18 questions (nine relating to pain, nine relating to disability) using a 100 mm VAS. Scores for pain and disability can therefore range from 0 to 100. At baseline, the mean VAS scores were 65.8 mm (pain) and 63.6 mm (disability). Three months after the last injection patients showed statistically significant mean changes in the pain score of -30.1 mm (p < 0.001) and in the disability score of -27.5 mm (p < 0.001) (Fig. 3a and b). Patients who received one injection showed mean changes at 3 months of -38.3 and -36.5 mm (both p < 0.001) in their pain and disability scores respectively. Patients who received two injections showed mean changes at 3 months of -19.5 mm (p < 0.001) and -15.7 mm (p = 0.008) in their pain and disability scores respectively.

Patient global assessment

The patients rated the overall status of their study ankle (pain, stiffness, function) using a 100 mm VAS. The mean VAS score showed a steady decrease from 64.9 mm at baseline to 34.6 mm at month 3 (p < 0.001). Patients who received one injection showed a statistically significant decrease in mean VAS score from 64.5 mm at baseline to 27.2 mm at month 3 (p < 0.001). Those patients who received a second injection also showed a statistically significant decrease from 65.4 mm at baseline to 44.3 mm at month 3 (p < 0.001).

Physician global assessment

The investigator rated the overall condition of the patient’s study ankle using a 100 mm VAS. Overall a statistically significant decrease in mean VAS score from 49.2 mm at baseline to 23.5 mm at month 3 (p < 0.001) was observed. Patients who received one injection showed a statistically significant decrease in mean VAS score from 54.8 mm at baseline to 20.6 mm at month 3 (p < 0.001). Those patients that received a second injection also showed a statistically significant decrease, from 42.0 mm at baseline to 27.2 mm at month 3 (p < 0.001).
Health related quality of life (SF-36 scale)

The physical and mental health states of patients were assessed by means of the SF-36 questionnaire at baseline, month 3 and month 6. The mean physical component increased from 36.2 at baseline to 43.9 at month 3 (p < 0.001) and to 44.6 at month 6 (p < 0.001). These increases were caused mainly by increases in the Role Physical and the Bodily Pain sub-scores. The mean mental component score increased from 49.9 at baseline to 54.3 at month 3 (p = 0.004) and 54.6 at month 6 (p = 0.002), due mainly to increases in the Social Functioning and Role Emotional sub-scores.

Responder analysis

The percentage of responders reached a maximum at month 3 when 29 of the 55 patients (52.7%) were responders (Fig. 4). At month 6, 50.9% of the ITT population were responders.

![Figure 4: Percentage of responders (ITT population)](image-url)
Discussion

Although osteoarthritis of the ankle occurs infrequently in the general population, it remains of major clinical significance due to the limitations that the disease places on the everyday activities of affected individuals. These patients could benefit from additional non-surgical treatment options if the need for subsequent surgical intervention could be delayed or negated.

The objective of this study was therefore to evaluate the safety and efficacy (including duration of action) of intra-articular injections of hylan G-F 20 in patients with symptomatic ankle OA. The dosing regimen was one 2 ml injection, with the possible administration of a second and final 2 ml injection if insufficient pain relief was experienced during the initial 3-month follow-up period.

The safety profile of hylan G-F 20 is already supported by the clinical literature in patients with knee and hip OA\textsuperscript{[12,16,17]}. Adverse events consist typically of transient post-injection pain and/or swelling. Although the incidence of treatment-related AEs in this study is somewhat higher than that reported in the trials mentioned above, our results are consistent with findings in the literature where temporarily increased swelling and pain were reported as frequently observed adverse events after intra-articular injection of hyaluronans\textsuperscript{[18]}. Furthermore, the percentage of local adverse events in this study (30.9\%) is comparable to the results of a previous pilot study with another HA product in patients with ankle OA by Salk et al., which reported transient pain at the injection site in 29\% of patients\textsuperscript{[10]}.

The higher incidence of these injection site AEs in the ankle joint, in comparison to the knee and hip joints, may be due to the technical difficulty of injecting intra-articularly into the ankle joint due to its complex anatomy, and to the fact that no fluoroscopic or ultrasound guidance was used in this study. We consider it unlikely that these adverse events are correlated with the hyaluronic acid itself, since in the study by Salk et al. no significant difference was noted between the HA group and the saline solution group. In addition, similar adverse event profiles have been reported for both HA and saline injections in the knee\textsuperscript{[19–22]}. It is also important to note that there were no serious or severe, local, treatment-related safety concerns nor were any new safety concerns raised in this study. Most AEs experienced were transient ankle pain or injection site pain of
mild or moderate intensity, which lasted less than a week, and which were easily treated with simple oral analgesics. The use of appropriate imaging guidance, for example X-ray, may prevent such AEs as it would ensure consistent, accurate intra-articular placement of the injection.

Hylan G-F 20 was effective at significantly reducing the pain associated with ankle OA. Although it is difficult to draw definite conclusions about efficacy from an open-label study, the magnitude of the response seen in this study exceeded the expected placebo effect. The majority of patients (56%) responded adequately to only one injection. Even in those patients who did not respond adequately to one injection, and whose pain VAS scores remained ≥50 and ≤90 mm at months 1, 2 or 3 after the first injection, went on to obtain benefit from a second injection and demonstrated statistically significant decreases in pain at all time-points in the 6-month follow-up. No patient or disease characteristics were identified as predictive factors for response in our study.

In all patients, reduction in pain was apparent from as soon as 7 days after injection, was maximised at 3 months, and was maintained for up to 6 months. These results reflect those reported in patients with knee OA, where the symptomatic relief obtained by patients outlasts substantially the product’s residence time in the joint, thus supporting the hypothesis that viscosupplementation achieves its therapeutic effect by restoring the rheology of the joint temporarily\(^{[23]}\).

Previous trials of viscosupplementation in the ankle joint\(^{[10,11]}\) demonstrate comparable results to those presented here. However, both of these studies assessed a regimen of five weekly injections of low molecular weight sodium hyaluronate. Our study assessed a regimen of one single 2 ml injection of a high molecular weight hyaluronan derivative, with the possible administration of a second, and final, injection 1–3 months later. No dosing regimen studies have been published to date.

We conclude that viscosupplementation with hylan G-F 20 is well tolerated, and a regimen of one single 2 ml intra-articular injection, with the option of a second injection after 1–3 months if pain relief is inadequate, is an efficacious treatment of patients with symptomatic ankle OA.
**Conflict of interest statement**

This study was sponsored by Genzyme Europe B.V. There are no conflicts of interest.

**Acknowledgement**

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References

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17. Synvisc Product Label (USA).


