Single, intra-articular treatment with 6 ml hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: a randomised, multicentre, double-blind, placebo controlled trial

X Chevalier,1 J Jerosch,2 P Goupille,3 N van Dijk,4 F P Luyten,5 D L Scott,6 F Bailleul,7 K Pavelka8

ABSTRACT
Objectives: The primary objective was to compare a single, 6 ml, intra-articular injection of hylan G-F 20 with placebo in patients with symptomatic knee osteoarthritis. The safety of a repeat injection of hylan G-F 20 was also assessed.

Methods: Patients with primary osteoarthritis knee pain were randomly assigned to arthrocentesis plus a 6 ml intra-articular injection of either hylan G-F 20 or placebo in a prospective, double-blind (one injector/one blinded observer) study. Results were evaluated at 4, 8, 12, 18 and 26 weeks post-injection. The primary outcome criterion was change from baseline over 26 weeks in Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index A pain. Secondary outcome measures included WOMAC A1 and C, patient global assessment (PGA) and clinical observer global assessment (COGA) and Outcome Measures in Rheumatology, Osteoarthritis Research Society International responder rates. A 4-week, open, repeat treatment phase evaluated safety only.

Results: A total of 253 patients (Kellgren–Lawrence grade II or III) were randomly assigned. Patients receiving hylan G-F 20 experienced statistically significantly greater improvements in WOMAC A pain scores (−0.15, SE 0.076, p = 0.047), and several of the secondary outcome measures (WOMAC A1, PGA and COGA), than patients receiving placebo. There was no difference between the safety results of the two groups. No increased risk of local adverse events was observed in the open, repeat treatment phase.

Conclusions: This placebo-controlled study demonstrated that, in patients with knee osteoarthritis, a single 6 ml injection of hylan G-F 20 is safe and effective in providing statistically significant, clinically relevant pain relief over 26 weeks, with a modest difference versus placebo.

Trial registration number: NCT00131352.

Osteoarthritis is the most common joint disease and one of the most frequent causes of physical impairment.1 Osteoarthritis of the knee has been associated with a decrease in the elasticity and viscosity of the synovial fluid,2,4 which may alter the transmission of mechanical forces to the cartilage, possibly increasing its susceptibility to mechanical damage, or wear and tear. Viscosupplementation addresses the degradation of hyaluronic acid (HA) in the synovial fluid of patients with knee osteoarthritis by the addition of exogenous HA, or its derivatives, by intra-articular injection and is cited for the treatment of knee osteoarthritis in the guidelines of several professional societies.5–10

Hylan G-F 20 (Synvisc) is a high molecular weight (average 6000 kDa) HA product consisting of two cross-linked components. Approved in several countries for the treatment of pain associated with knee osteoarthritis, the recommended treatment regimen for the treatment of knee osteoarthritis pain is one 2 ml intra-articular injection per week for three consecutive weeks.11 12

In order to reduce the number of intra-articular injections (and potential related side effects) a pilot study was conducted, and the results suggested that at 6 months post-injection, one 6 ml injection performed at least as well as three 2 ml injections.13 A single 6 ml injection may represent an attractive alternative to the current treatment regimen, reducing the number of intra-articular injections required and thereby offering potential comfort and safety benefits to patients.

The current study was designed to assess the efficacy and safety of one 6 ml injection of hylan G-F 20 in a 26-week, pivotal, prospective, multicentre, double-blind, randomised, placebo controlled clinical trial.

METHODS
Ethics
The study was performed in accordance with the principles of good clinical practice guidelines. Ethics committee approvals and informed patient consents were obtained. The study was registered in the ClinicalTrials.gov National Institutes of Health trial register under the identification number NCT00131352.

Study design
At the screening visit patients gave their written, informed consent and a physical examination was performed on the knee to be treated (“target knee”). A radiographic assessment was also performed if no valid x ray had been taken within 3 months before screening was available. Demographic data and medical history information were collected.

Before commencing the study, a washout period of prohibited pain and osteoarthritis medications (analgesics and non-steroidal anti-inflammatory...
drugs with half lives of $\geq 5$ h and systemic corticosteroids) was required.

Patients were randomly assigned to receive arthrocentesis plus a 6 ml intra-articular injection of either hylan G-F 20 or buffered physiological sodium chloride solution (PBS) (placebo) on day 0.

Patients completed the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index Likert and patient global assessment (PGA) questionnaires and a blinded evaluator completed the clinical observer global assessment (COGA).

Safety assessments (including physical examination findings), usage of concomitant medications and treatments and vital signs were recorded until study completion. It was left to the judgement of the clinical evaluator to decide whether each target knee adverse event (AE) was related to the study procedure (ie, expected with any intra-articular injection procedure) or to the study material.

Patients were followed up 1, 4, 8, 12, 18 and 26 weeks after injection.

To assess the safety of a repeat injection of 6 ml hylan G-F 20, patients from both groups were permitted to enter a 4-week open-label repeat treatment phase 26 weeks after their initial injection if they had no major safety concerns during the first course of treatment and an average WOMAC A score of at least 1.

**Patient selection**

Patients were required to meet the American College of Rheumatology criteria for osteoarthritis (knee pain for most days of the previous month and osteophyte(s) at the joint margin visible on x ray).14

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**Figure 1** Study flow chart. AE, adverse event; ITT, intent-to-treat.

**Table 1** Baseline characteristics for all randomly assigned patients (ITT population)

<table>
<thead>
<tr>
<th></th>
<th>Hylan G-F 20 (N = 124)</th>
<th>Placebo (N = 129)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>63.6 (9.64)</td>
<td>62.5 (9.17)</td>
</tr>
<tr>
<td>Mean BMI, kg/m² (SD)</td>
<td>29.08 (4.81)</td>
<td>29.77 (5.74)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>32/92</td>
<td>41/88</td>
</tr>
<tr>
<td>Tibiofemoral compartment with the most severe features of osteoarthritis, N* (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial</td>
<td>93 (75.6)</td>
<td>103 (79.2)</td>
</tr>
<tr>
<td>Lateral</td>
<td>30 (24.4)</td>
<td>27 (20.8)</td>
</tr>
<tr>
<td>Modified Kellgren–Lawrence grade in most severe tibiofemoral compartment, N* (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade II</td>
<td>63 (51.2)</td>
<td>51 (39.2)</td>
</tr>
<tr>
<td>Grade III</td>
<td>60 (48.8)</td>
<td>78 (60.0)</td>
</tr>
<tr>
<td>Grade IV</td>
<td>0</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Previous corticosteroids in the target knee, N* (%)</td>
<td>40 (32)</td>
<td>31 (24)</td>
</tr>
<tr>
<td>Previous arthroscopy in the target knee, N* (%)</td>
<td>26 (21)</td>
<td>28 (22)</td>
</tr>
<tr>
<td>Total WOMAC score (0–4), mean (SD)</td>
<td>2.30 (0.44)</td>
<td>2.28 (0.39)</td>
</tr>
<tr>
<td>WOMAC A score (0–4), mean (SD)</td>
<td>2.30 (0.43)</td>
<td>2.25 (0.41)</td>
</tr>
<tr>
<td>Symptomatic osteoarthritis that was responsive to paracetamol and did not require other therapy, N* (%)</td>
<td></td>
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</tr>
<tr>
<td>In the contralateral knee</td>
<td>68 (55.3)</td>
<td>76 (58.5)</td>
</tr>
<tr>
<td>In either hip</td>
<td>12 (9.8)</td>
<td>18 (13.8)</td>
</tr>
<tr>
<td>Mean time since osteoarthritis diagnosis, months* (SD) (median, range)</td>
<td>77.38 (76.44)</td>
<td>70.01 (64.43)</td>
</tr>
<tr>
<td></td>
<td>(51.94, 3.1–350.9)</td>
<td>(47.34, 3.6–241.9)</td>
</tr>
</tbody>
</table>

*Safety population.

BMI, body mass index; ITT, intent-to-treat; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
Main inclusion criteria were: age 40 years or greater; diagnosis of primary osteoarthritis of the target knee; radiographic evidence of osteoarthritis in the medial and/or lateral tibiofemoral compartment (one or more osteophyte(s) and a measurable joint space on a standard radiograph taken within 3 months before screening); continued osteoarthritis pain in the target knee despite conservative treatments. Patients were required to have a score of 2 or 5 (0 to 4 scale) on question 1 of the WOMAC (Likert version 3.1) pain (A) subscale (pain while walking on a flat surface) as this is the most commonly reported symptom in clinical practice and the protocol was designed to weight this symptom more heavily. Included patients required a mean score of 1.5–3.5 on the WOMAC A (total pain) subscore. Main exclusion criteria were: secondary osteoarthritis in the target knee; grade IV radiographic stage osteoarthritis (Kellgren–Lawrence grading system); clinically apparent tense effusion of the target knee; significant valgus/varus deformities; viscosupplementation in any joint in the past 9 months; surgery in the target knee despite conservative treatments. Other permitted treatments may be reviewed in supplementary material 1 available online only.

Randomisation
Randomisation was performed by a centralised, interactive, voice-response system and was done by site in computer-generated blocks of four. Unblinded injectors were strictly forbidden from discussing treatment allocation with patients and clinical observers.

Power and sample size
The sample size estimation was based on the mean intergroup difference in the WOMAC A pain subscale change from baseline over 26 weeks. The following assumptions were made to compute the sample size: anticipated overall treatment difference of 0.297; common SD of 0.725; dropout rate of 25%; two-sided significance level of 5%. A resulting sample size of approximately 250 patients (125 patients per group) provided greater than 80% power to detect a difference between the hylan G-F 20 and placebo groups over 26 weeks.

Concomitant medications and treatments
Paracetamol (<4000 mg/day) was permitted as rescue medication for the target knee. Other permitted medications were analgesics/non-steroidal anti-inflammatory drugs with a half-life of 5 h or less for indications other than osteoarthritis pain (not to be taken for more than five consecutive days or >10 days/month) and aspirin (≤325 mg/day). However, for 48 h before a study visit, patients were required to abstain from any paracetamol, pain or osteoarthritis medications.
placebo 130 patients). One patient was randomly assigned to the hylan G-F 20 group but received placebo in error and was therefore counted in the placebo group for safety and the hylan G-F 20 group for ITT efficacy.

A total of 252 patients (91.7%) completed the study. Nine patients (3.3%) randomly assigned to hylan G-F 20 and 12 patients (9.2%) randomly assigned to placebo failed to complete the study schedule as planned (fig 1).

There were no statistically significant, or clinically meaningful, differences between treatment groups in any baseline or demographic parameter (table 1).

**Treatment efficacy**

The treatment effect with hylan G-F 20 was statistically significantly superior to placebo for the primary endpoint, change in WOMAC A (pain) over 26 weeks (table 2 and fig 2).

Hylan G-F 20 demonstrated an estimated change (absolute change, adjusted for values, time and treatment) from baseline over 26 weeks of −0.84, a mean percentage change in pain from baseline of 36%. Patients in the placebo group had an estimated change from baseline over 26 weeks of −0.69, a mean percentage change in pain from baseline of 29%. The estimated treatment difference between the two treatment groups over the 26-week study was statistically significant (p = 0.047).

Some, but not all, of the secondary endpoints, including WOMAC A1 (walking pain), PGA and COGA, showed statistically significant differences between the two groups favouring hylan G-F 20 treatment (tables 3 and 4).

Seventy-one per cent (88/124) of the patients were WOMAC A1 responders at week 18 in the hylan G-F 20 group compared with 53% (69/129) in the placebo group (p = 0.003). At week 26, 64% (79/124) of patients in the hylan G-F 20 group were WOMAC A1 responders compared with 50% (64/129) in the placebo group (p = 0.028).

The change in WOMAC C (function) scores did not reach statistical significance. Further exploratory analyses of predefined covariates were carried out to understand better the lack of effect of hylan G-F 20 on the WOMAC C endpoint. In patients without any other lower limb osteoarthritis (defined as hip or contralateral knee involvement), those treated with Synvisc experienced a greater change in WOMAC C than those treated with placebo (−0.71 and −0.55, respectively).

The OMERACT—OARSI responder analysis over 26 weeks approached statistical significance (p = 0.059). At week 26, 73 patients (59%) in the hylan G-F 20 group and 66 patients (51%) in the placebo group were responders.

Overall, patients consumed a mean daily dose of 0.26 g (SD 0.57 g) of paracetamol in the hylan G-F 20 group, and 0.28 g (SD 0.57 g) in the placebo group. Throughout the study there was no statistically significant difference in paracetamol consumption between the two groups (p = 0.370).

**AE and safety**

There were no target knee serious AE and no serious AE that were related to the study treatment or the study procedure. The overall frequency of AE was comparable between the two treatment groups (hylan G-F 20, n = 70, 56.9%; placebo, n = 79, 60.8%).

The most commonly reported AE were pain in the target knee (coded as “arthralgia”), joint stiffness, joint effusion and joint swelling. The incidence of AE was slightly higher in the hylan G-F 20 group (n = 7, 5.7%) than in the placebo group (n = 4, 3.1%) but this was not statistically significant (p = 0.366) (table 5). In addition, there were no statistically significant differences between the groups in treatment-related (p = 0.203)

### Table 2: Primary efficacy endpoint—WOMAC A (pain) change over 26 weeks (ITT population)

<table>
<thead>
<tr>
<th></th>
<th>Baseline mean (SE)</th>
<th>26-Week mean (SE)</th>
<th>Estimated change (SE)</th>
<th>Estimated difference between groups (SE)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hylan G-F 20 (n = 124)</td>
<td>2.30 (0.038)</td>
<td>1.43 (0.060)</td>
<td>−0.84 (0.060)</td>
<td>−0.15 (0.076)</td>
<td>0.047</td>
</tr>
<tr>
<td>Placebo (n = 129)</td>
<td>2.25 (0.036)</td>
<td>1.59 (0.058)</td>
<td>−0.69 (0.058)</td>
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ITT, intent-to-treat; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

### Table 3: Secondary efficacy endpoints (ITT population): estimated between-group differences

<table>
<thead>
<tr>
<th></th>
<th>Baseline mean (SE)</th>
<th>Week 26 mean/overall mean (SE)</th>
<th>Estimated change (SE)</th>
<th>Estimated between-group difference (SE)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOMAC A (pain) change from baseline at 26 weeks*</td>
<td></td>
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<tr>
<td>Hylan G-F 20</td>
<td>2.30 (0.04)</td>
<td>1.51 (0.074)</td>
<td>−0.76 (0.07)</td>
<td>−0.18 (0.097)</td>
<td>0.064</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.25 (0.04)</td>
<td>1.69 (0.073)</td>
<td>−0.58 (0.07)</td>
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<tr>
<td>WOMAC C (function) change from baseline over 26 weeks†</td>
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<tr>
<td>Hylan G-F 20</td>
<td>2.29 (0.04)</td>
<td>1.62 (0.061)</td>
<td>−0.66 (0.061)</td>
<td>−0.03 (0.077)</td>
<td>0.679</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.28 (0.04)</td>
<td>1.66 (0.059)</td>
<td>−0.63 (0.059)</td>
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<tr>
<td>WOMAC C (function) change from baseline at 26 weeks†</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Hylan G-F 20</td>
<td>2.29 (0.04)</td>
<td>1.69 (0.076)</td>
<td>−0.59 (0.076)</td>
<td>−0.11 (0.100)</td>
<td>0.266</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.28 (0.04)</td>
<td>1.80 (0.074)</td>
<td>−0.48 (0.074)</td>
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</tbody>
</table>

*Week 26 mean in column 3; †overall mean in column 3. ITT, intent-to-treat; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
or procedure-related \((p = 0.531)\) target knee AE, all of which were of mild or moderate severity.

**Repeat treatment phase**

A total of 160 patients was treated in the open, repeat treatment phase, of which 77 received a second injection of hylan G-F 20 and 83 received a first injection of hylan G-F 20, having received placebo during the initial treatment phase. There were no target knee serious AE. In the group receiving a second injection of hylan G-F 20 one patient \((1.3\%)\) experienced target knee AE related to the study treatment and four patients \((5.2\%)\) experienced target knee AE related to the study procedure.

Patients who developed target knee AE during the initial phase of the study, and who subsequently received repeat treatment, did not experience target knee AE on repeat exposure to hylan G-F 20. All treatment-related and procedure-related target knee AE were of mild or moderate severity.

**DISCUSSION**

This study demonstrates that a single intra-articular injection of hylan G-F 20 is safe and effective in providing statistically...
significant, clinically relevant pain relief, as measured by WO
MAC A1 (walking pain) over 26 weeks, with a modest
difference compared with placebo. Several secondary efficacy
results also show the superiority of hylan G-F 20 over placebo.

Pain while walking is particularly medically relevant for the
assessment of symptomatic relief and has been selected as the
primary efficacy measure in other studies of hylan G-F 20 or
other hyaluronans.18–20 The OMERACT–OARSI responder
analysis also favoured hylan G-F 20 although statistical
significance was not reached (p = 0.059).

This trial had a large placebo effect (−0.69 change in mean
WOAMC A score over 26 weeks), which may explain why the
observed overall treatment difference (0.15) was weaker than
anticipated (0.297). The placebo effect in osteoarthritis treat-
ment has been re-evaluated in a recent meta-analysis showing
this contributed to the robust response in patients receiving
placebo. However, hylan G-F 20 was still significantly
superior to placebo in the primary and several of the secondary
endpoints.

Effect size is a way to measure effectiveness and to compare
clinical interventions.21 The effect size of hylan G-F 20 versus
control in this study was −0.23 for WOAMC A at week 26. In
chronic pain conditions such as osteoarthritis, this modest effect
size should be interpreted as clinically relevant on an individual
patient basis as recommended by the IMMPACT consensus.22,23

In addition, the accepted threshold for a minimum clinically
important improvement in osteoarthritis (12–18% improve-
ment in WOAMC A from baseline)24 was exceeded in this study.
Patients treated with one 6 ml injection of hylan G-F 20
experienced a 51.5% improvement in WOAMC A from baseline
(p<0.001) at week 26.

The WOAMC C (function) subscale findings in the current
study are inconsistent with those from previous controlled
studies of hylan G-F 20.18–20 However, our post-hoc analysis
showed that WOAMC C scores were improved in a subgroup
of patients without any other lower limb joint involvement,
suggesting that osteoarthritis occurring in other lower limbs
may contribute to substantial functional impairment, and may
confound the patient’s ability to detect improvement in the
target knee in a clinical trial setting.

Evaluation of the safety profile for the higher injected volume
(6 ml) of hylan G-F 20 was also a major objective of this study.
The similarity in the safety profiles of hylan G-F 20 and placebo
(PBS) is reassuring. No new, unrecognised AE were identified
during this study. The safety profile of hylan G-F 20 was
confirmed during the repeat treatment phase of the study,
indicating no increase in the risk of AE in the patients receiving
a second injection of hylan G-F 20. This finding contrasts with
previous reports of post-marketing studies, which suggest an
approximate threefold increased risk of local target knee AE
with a repeat course of hylan G-F 20.19 The excellent safety
profile of the increased 6 ml dose translates to an improved
benefit-risk ratio for the patient.

CONCLUSIONS

This placebo-controlled study demonstrated that, in patients
with knee osteoarthritis, a single 6 ml intra-articular injection of
hylan G-F 20 is safe and effective in providing statistically
significant, clinically relevant pain relief over 26 weeks, with a
modest difference compared with placebo.

In daily practice the favourable benefit-risk profile of a single
injection of 6 ml hylan G-F 20 has the major advantage of
decreasing the number of injections from three to five to only
one.

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Biosurgery, the manufacturer of hylan G-F 20, for attending symposia and have also
received speaker fees. JJ has received research funds from Genzyme Biosurgery. FB is
an employee of Genzyme Biosurgery working in the Clinical Research and Medical
Affairs Departments. NvD, PFL, DLS and KP have no conflicts of interest. All authors
actively participated in the conduct of this trial and in its analysis and interpretation.

Ethics approval: Ethics committee approvals were obtained.

Patient consent: Obtained.

Provenance and peer review: Not commissioned; externally peer reviewed.

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