# Comparative efficacy and safety of two different molecular weight (MW) hyaluronans F60027 and Hylan G-F20 in symptomatic osteoarthritis of the knee (KOA). Results of a non-inferiority, prospective, randomised, controlled trial

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## Abstract

### Objectives

*To compare the efficacy and safety of a "medium" molecular weight (MW) hyaluronan product (F60027, Structovial®) with a "high" MW (Hylan G-F20, Synvisc®).*

### Methods

*Prospective, randomised, multicentre, double-blind, active controlled, parallel-group study with a non-inferiority design. Patients with symptomatic KOA, global pain ≥40 mm (VAS, 0–100), Lequesne index (LFI, 0–24) score >7 and radiological Kellgren-Lawrence grade 2/3 were centrally randomised to receive F60027 or Hylan G-F20, administered via three weekly injections, with regular follow-up evaluations up to week 24 (W24). The primary outcome was LFI score change over 24 weeks. Secondary outcomes comprised pain VAS, quality of life, patient's and physician's global assessments, rescue medication consumption and OMERACT-OARSI responders rate.*

### Results

*276 patients were analysed in the full analysis dataset (FAS), 236 in the Per Protocol dataset (PP). In the main efficacy analysis (PP), the difference of the LFI score change over 24 weeks between F60027 (-4.67 (0.27)) and Hylan G-F20 (-4.54 (0.28)) was 0.132 [95%CI: -0.598, 0.861] which met the predefined non-inferiority margin. Analyses of secondary efficacy criteria showed clinically relevant improvements of all outcomes at W24 for each treatment on both PP/FAS populations. Changes of LFI score between baseline and W24 were -5.73 in the F60027 and -5.57 in the Hylan G-F20 group (PP dataset). Few local reactions were reported: 3.6% of patients in each group.*

### Conclusion

*F60027 and Hylan G-F20 were equally effective in reducing functional impairment and relieving pain in KOA patients, and well-tolerated.*

**Key words**

hyaluronans, non-inferiority comparative trial, intra-articular treatment, molecular weight, knee OA

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## Introduction

Osteoarthritis (OA) is a widespread disease and the world leading rheumatologic cause of disability (1). Symptomatic OA of the knee may affect 40% of individuals aged 50 years old and over (2). As a result of pain and functional impairment, OA may severely alter the quality of life of patients (3). Though many paths have been identified these past years, no physiopathologic (*i.e.* targeted) therapy able to stop or delay the pathologic process has been identified until today (4). Therefore OA treatment, notably knee OA treatment relies on various palliative therapeutic options which have been listed by several scientific international associations (4-6). Evidences supporting each of these options have been reviewed. Various international recommendations for the management of knee OA have been published in the recent past (4-6). They all emphasise the importance of non-pharmacologic therapies such as education, muscle strengthening exercise, weight reduction, physiotherapy, spa-therapy (7) and physical aids such as crutches. Besides, pharmacologic treatment is based on first line on pain reduction by analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), steroids injections and the so-called symptom modifying drugs for OA. Intra-articular injections of hyaluronic acid (HA) also called hyaluronan belongs to this latter category. Despite controversial results, five meta-analyses of the clinical trials performed with HA intra-articular injections in knee OA have been published and overall concluded that HA injections reduced pain and improved function significantly compared to the placebo (which has a high symptomatic effect in OA, as recently shown (8)) over a prolonged period of time: symptom reduction may last as long as 6 to 12 months (9-13).

Assertions have been made advocating a more potent symptomatic effect of the higher molecular weight HA preparations, as compared to those of "medium" or "low" molecular weight. Few trials have been conducted in this field. Analysis of the available literature provides conflicting data: five methodologically acceptable trials (randomised, prospective, double-blind with a blind independent observer different from the injector, three weekly HA injections) have been performed comparing face to face "high" and "medium/low" molecular weight HA. Karlsson *et al*. in a 3-arm trial found no difference between Artzal® (around 2 million Daltons (mDa)) and Hylan G-F20 (Synvisc®, 6–7 mDa) on the Lequesne index and pain on a visual analogue scale (14). Furthermore, there was no difference between the two HA products and the placebo, although when mixing both HA groups, a slight superiority of HA over placebo could be observed. Karatosum *et al*. comparing Orthovisc® (1.5 mDa) to Hylan G-F20 (Synvisc®) found no difference between groups with respect to pain and functional relief obtained (assessed by the Hospital for Special Surgery Knee Score Criteria) during a 52-week follow-up (15). Kirchner M *et al*. compared Euflexxa® (2.4–3.6 mDa) also to Hylan G-F20 (Synvisc®) in a non-inferiority trial and concluded in an intent-to-treat analysis of the 321 knee OA patients included in the non inferiority of Euflexxa® on the Western Ontario and McMaster Universities Osteoarthritis index (WOMAC) pain subscale improvement, with a better safety profile of the latter over Hylan G-F 20 which was responsible of a higher rate of post-injection effusion (16). Juni *et al*. in a three-arm trial compared Ostenil® (0.7 mDa), Orthovisc® and Hylan G-F20 (Synvisc®) in almost 600 patients followed up to 6 months and assessed on the WOMAC pain subscale improvement. They found no evidence for a difference in efficacy between Hylan and the 2 other HA, but observed also a trend toward more local adverse events in the Hylan group (17). On the contrary, Raman *et al*. comparing Hylan G-F 20 and Hyalgan® (0.5–0.73 mDa) in almost 400 knee OA patients reported a higher and faster effect on pain relief assessed on a VAS and by the WOMAC pain subscale in the Hylan group (18). This effect was maintained up to 12 months. More treatment-related adverse events were also noted in the Hylan G-F20 group. Finally, a meta-analysis performed by Juni's group concluded in a comparable effectiveness on knee

OA symptoms of all HA preparations including Hylan G-F20, but to an increased risk of local adverse events associated with Hylan G-F20 (19).

Given the conflicting results, other prospective trials are warranted to compare the effectiveness of "low"/ "medium" MW HA *versus* "high" MW HA. This was part of the rationale of the present study.

The other objective was to answer the request formulated by the French National Authority of Health (HAS), which asked each HA preparation marketed in France to provide clear individual efficacy data by conducting a randomised clinical trial (either *versus* placebo or an active comparator such as Hylan G-F 20), in order to sustain any demand to be listed as a reimbursed product by the French Health System (20).

Since it was deemed unethical and not feasible to conduct a placebo-controlled trial in a country where 13 HA preparations were currently available and frequently used in daily rheumatologic ambulatory clinical practice, a non-inferiority design was preferred to assess the efficacy of this new HA compound F60027 (2.2–2.7 mDa, obtained by biofermentation).

The objective of the present study, therefore, was to demonstrate the non-inferiority in efficacy of F60027 compared to Hylan G-F20, a widely used HA, on functional improvement in patients with symptomatic knee OA over 24 weeks and to compare the efficacy of the 2 products in terms of pain reduction, patient's global assessment, health related quality of life impact and safety issues.

## Patients and methods

*Trial design*

This was a multicentre, prospective, randomised, controlled *versus* an active comparator, double-blind (patient and observer blinded to treatment) trial performed in patients with symptomatic knee OA with a 24 week duration. The trial was designed as a non-inferiority trial (21).

*Patients*

Patients were recruited across five different countries (Belgium, Czech Republic, Estonia, France, Poland). The study protocol and informed consent form received approval from local or national institutional Review Boards or Ethics Committees before the start of the study. The trial was conducted in accordance with the Good Clinical Practice (CPMP/ICH/135/95), standard ISO14155 and to the principles of the Declaration of Helsinki (1966, and its successive amendments including Escocia 2000).

To be included in the trial, patients having given their informed consent had to fulfill the following criteria: patients from either sex, aged 50–75, presenting with medial and/or lateral femoro-tibial OA of the knee (according to the American College of Rheumatology (22)), symptomatic for more than 6 months, with a baseline level of symptoms as follows, global pain score on a visual analogue scale of at least 40 millimetres (mm) and a Lequesne index score greater than 7 (23). Patients had to show radiographic OA as defined by a Kellgren-Lawrence grade II or III (24) on an antero-posterior weight-bearing view of both knees taken during the twelve months prior to inclusion. They had to fail to respond to analgesics / non-steroidal anti-inflammatory drugs (NSAIDs) and/or to be intolerant to these drugs. Patients could not be included in the study in the case of one of the following: secondary knee OA (post-traumatic; metabolic [haemochromatosis, ochronosis, haemophilia]; inflammatory [rheumatoid or psoriatic arthritis, ankylosing spondylitis] or post-infectious arthritis; Paget's disease, chondromatosis, or villonodular synovitis), ipsolateral painful hip OA, isolated or predominant femoro-patellar knee OA, presence of knee effusion at baseline, planned surgery of the target knee within the following 6 months. Patients were also excluded if they received systemic steroids during the previous month, or an intra-articular corticosteroid injection during the two months prior to inclusion, or if they took symptomatic slow-acting drugs for OA (Sy-SADOA, *i.e*. diacerhein, glucosamine, chondroitin sulfate, avocado/soybean unsaponifiables) or a neutraceutical unless dose regimen had been stabilised for at least 3 months, or if they had HA injections during the 12 previous months prior to beginning the study. They were also excluded if they had undergone surgery of the target knee, or knee lavage during the past three months, or if they took NSAIDs in the two days prior to inclusion or if they took an anticoagulant therapy or had a prior known allergy to any of the components of the study treatment. Any major medical history and/or uncontrolled study likely to interfere with the on-going study or current inclusion in another trial excluded the patient from the trial. Pregnancy and breast feeding were additional causes of exclusion for women, who had, in addition, to use effective contraception in case of child-bearing potential.

*Interventions*

Both products were administered as a course of three injections of a 2-millilitre (ml) syringe performed at a weekly intervals, each 2 ml syringe containing either 20 mg of sodium hyaluronate for F60027 or 16 mg of Hylan G-F20. In both cases, the commercially available formulation was used. For each product, the three syringes were packed together in an individual opaque study box sealed by a retractable polypropylene envelope. In accordance with European guidelines, a specific labelling was made for the trial, which could be adapted to national requirements.

Rescue medication was acetaminophen/paracetamol, up to 3 gm per day. A decoding list was safeguarded at the sponsor's Clinical Pharmacy Department. The investigator and (if applicable) the pharmacist were each provided with a set of individual sealed decoding envelopes each corresponding to a treatment number.

An envelope could be opened only in case of absolute emergency. As far as possible, the decision for doing so was to be taken upon a joint decision between the investigator and the sponsor. Should a decoding envelope be opened, the investigator had to inform the Study Manager as soon as possible.

*Randomisation, concealment and implementation*

Patients were centrally randomised to

receive either F60027 (namely Structovial® in France, Pierre Fabre Médicament, Boulogne, France) or Hylan G-F 20 (Synvisc® a cross-linked hyaluronan preparation, Genzyme Corporpation, Cambridge, MA, USA). A computer-generated randomisation number was centrally assigned to each box of studied treatment. The randomisation code was established by the sponsor's Department of Clinical Pharmacy (Pierre Fabre Labs.) and centrally maintained by the sponsor and concealed from all study sites. Randomisation was performed in blocks of four.

At the second visit (randomisation visit), the investigator called a vocal server which allocated a treatment number to each patient according to the treatment number provided by the centralised randomisation. This number was linked to either the studied or the reference drug following the randomisation procedure.

*Blinding procedure*

The blind-observer technique was used in order to maintain "double-blind" conditions. Therefore injections were performed by a separate "injecting physician" different from the investigator in charge of patient's clinical assessments (including physical evaluation, various pain scores, and safety assessments). Both the patient and the investigator remained blinded throughout the entire study. All study case report forms recorded only the randomisation number to identify the patient.

*Outcome measures and clinical assessments*

The primary criterion to assess effectiveness in this study was the Lequesne index score, which ranges from 0 to 24 (23). The primary outcome measure was the comparison between the F60027 and Hylan G-F20 groups of the mean variation of Lequesne index over 24 weeks. Secondary efficacy criteria included between-groups comparisons of the mean variation of global pain score rated on a 100 mm visual analogue scale (VAS) over 24 weeks, mean change of IAF score and VAS pain at weeks 12 and 24, mean changes on investigator's global assessment scores at weeks 12 and 24 (on a VAS, where 0 is the worst and 100 the best assessment), mean changes of Physical Component Summary (PCS) and Mental Component Summary (MCS) of SF12 (ranges 0–100) (25) between baseline and weeks 12 and 24, percentages of responders (defined as patients with high improvement in pain or function) according to OARSI-OMERACT criteria (26) at weeks 12 and 24, and the consumption of analgesic medications (including NSAIDs) over 24 weeks. These outcomes covered the core set proposed by the OMERACT for OA clinical trials (27). Pain and the Lequesne index were recorded at baseline, week 6, 12, 18 and 24. Investigator's global assessments and SF12 were collected at baseline, week 12 and 24. For OARSI-OMERACT response criteria, we used the high definition of response, *e.g*. improvement in pain or function of at least 50% and a decrease of at least 20 mm on the pain VAS or of 20 on a normalised to a 0–100 scale Lequesne index (26).

Safety was assessed by collecting adverse events spontaneously reported by the patient or identified by the investigator. Any sign, symptom or event occurring during the trial duration was considered as an adverse event and reported in the CRF, whether it was related or unrelated to the study treatment. In addition, investigators performed a physical examination. Any adverse event having been reported during the study for a given patient was classified by preferred term and corresponding system organ class using the MedDRA terminology. Adverse events were classified as: treatment emergent adverse events, *i.e*. any adverse event which occurs or worsens on study treatment during the randomised period, or non treatment emergent adverse events, *i.e*. any adverse event that occurs during the screening period or is reported as concomitant disease with the same intensity. Numbers and percentages of patients with at least one reported treatment emergent adverse event have been tabulated by treatment group. Local reactions have been presented separately.

*Statistical methods*

Analyses were conducted on the following patient datasets: The Full Analysis Set (FAS): patients having received at least one administration of the product and having at least one evaluation of the primary criterion post administration. The "Per Protocol" (PP) dataset: subset of the FAS composed of all patients without any major protocol deviations. The primary analysis was conducted on the PP dataset. The Safety dataset: composed of all randomised patients having received one administration of the product. This dataset has been used to perform the analysis of safety.

The number and percentage of patients who withdrew from the study after randomisation were given in each treatment group for all treated patients. All withdrawn patients have been further described regarding the time to dropout and reasons for withdrawal. Particular attention was paid to the description of adverse events leading to premature withdrawal during the treatment period. No extrapolation of missing data has been performed for the Lequesne index, if one or several missing items prevented to calculate the score. For the analysis of the primary criterion on the FAS population, in case of drop-out, the last available assessment has been carried forward. If one value was missing for the Lequesne index, the mean of previous and following data was used.

Quantitative parameters have been described by treatment group using the following statistics: number of patients, mean, standard deviation, minimum, median and maximum values. Qualitative parameters have been described by treatment group using frequencies and percentages. The FAS and PP datasets were used to compare treatment groups at inclusion. No formal statistical testing for homogeneity between groups has been performed, since this was a randomised trial. Although the analysis of the primary criterion has been performed on the FAS and PP datasets, the analysis on the PP dataset was chosen as the primary analysis, as recommended by current guidelines (21). The 95% confidence interval of the difference F60027 - Hylan G-F20 has been calculated. F60027 was declared non-inferior to Hylan G-F20 if the lower limit of the 95% CI was

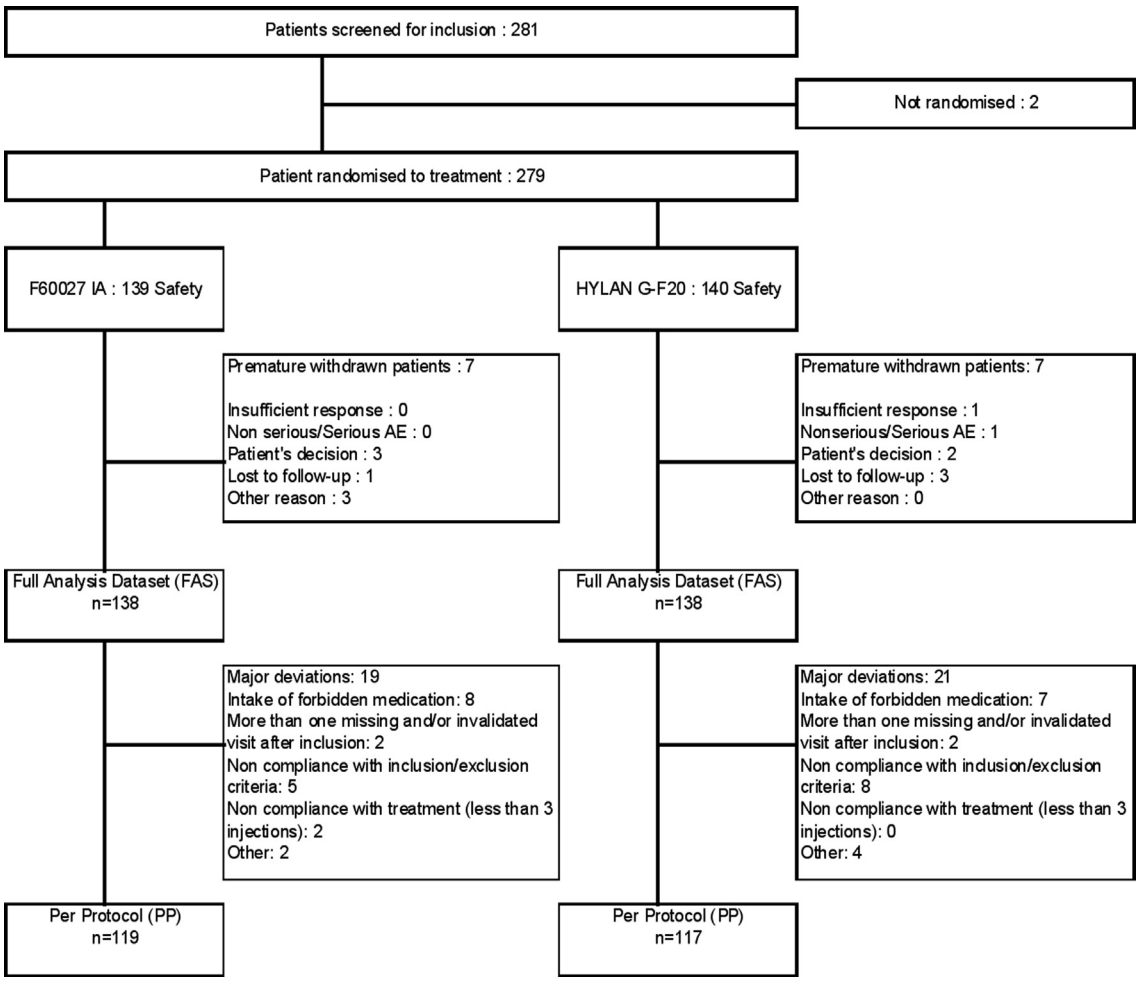


**Fig. 1.** Disposition of patients in the trial.

above -1.25. Analyses of the secondary criteria were performed on the FAS and PP datasets. The analysis of the mean variation of global pain score between baseline and Week 24 was performed using an analysis of covariance model with treatment and centre as fixed factors and baseline score as covariate. An evaluation of the improvement between baseline and Week 24 using a likelihood-based Mixed effects Model for Repeated Measures (MMRM) has been performed. The model included treatment, centre, and visit as categorical fixed factors, the interaction visit x treatment and the score at baseline as covariate. The same analysis was performed on the mean changes of PCS and MCS of SF12 scale and mean changes of investigator's global assessments between baseline and week 24. The Cochran-Mantel-Haenszel test stratified by centre (using the alternative hypothesis of general association) was used to compare the percentages of OARSI-OMERACT criteria responders at week 12 and week 24.

*Sample size calculation*

Based on an estimated non-inferiority margin of 1.25 between treatment groups on the Lequesne index, an estimated standard deviation of 2.6 based on published data (23) and a type one error ($\alpha$) risk of 2.5% (one-sided), the sample size required was 184 assessable patients (92 per group), providing a power of 90% for the primary analysis of the primary criterion on the Per Protocol dataset. Assuming around 25% of premature withdrawals and major protocol deviations, a minimum of 250 patients had to be randomised.

## Results

Figure 1 provides the patient disposition throughout the study. Two hundred and eighty one patients were screened, 279 were randomised: 139 to F60027 group and 140 to hylan G-F20 group. FAS population included 276 patients. Two hundred and thirty-six patients, 119 in the F60027 group and 117 in the Hylan G-F20 group remained in the Per Protocol (PP) population.

Baseline characteristics in the PP population are given in Table I. Most of the patients were women (76%), aged 64 on average, with a mean BMI of 29.5, and a mean disease duration around 6 years. Almost 40% had a familial history of knee OA, more than 50% had OA at another site (mostly spinal OA). Knee OA was bilateral in 80% of cases, at a radiographic Kellgren-Lawrence grade II for 59% and III for 41%. Thirty-two percent had received previously an intra-articular steroid injection and only 11% a previous HA treatment.

Baseline clinical assessments of knee OA symptoms are presented in Table II. Baseline level of symptoms was high with a mean global pain on a VAS of 68 mm, a mean Lequesne index score of 13, and a mean SF12 physical score of 31.

**Table I.** Patient demographic and baseline characteristics [Per Protocol Dataset].

| | F60027 (n=119) | Hylan G-F20 (n=117) | All (n=236) |
|---|---|---|---|
| Sex n (%) Female | 87 (73.1) | 93 (79.5) | 180 (76.3) |
| Age at screening (years)* [Min., Max.] | 64.54 (7.13) [49.00, 77.00] | 63.00 (6.63) [50.00, 75.00] | 63.78 (6.91) [49.00, 77.00] |
| Weight (kg) males | 89.56 (14.25) | 89.85 (11.91) | 89.68 (13.18) |
| Weight (kg) females | 78.23 (14.26) | 78.99 (12.92) | 78.62 (13.55) |
| Height (cm) males | 174.31 (6.67) | 174.17 (7.02) | 174.25 (6.76) |
| Height (cm) females | 161.52 (5.91) | 162.38 (5.62) | 161.96 (5.76) |
| BMI (kg/m²) males* [1] [Min., Max.] | 29.43 (4.21) [20.94, 38.97] | 29.62 (3.67) [24.21, 38.10] | 29.51 (3.95) [20.94, 38.97] |
| BMI (kg/m²) females* [1] [Min., Max.] | 29.98 (5.26) [20.08, 44.74] | 30.01 (5.08) [18.00, 51.11] | 29.99 (5.15) [18.00, 51.11] |
| For females, post-menopausal status | 85 (97.7) | 92 (98.9) | 177 (98.3) |
| Disease duration (years) | 6.21 (6.02) | 5.61 (4.55) | 5.91 (5.34) |
| Family history of knee OA | 46 (38.7) | 43 (36.8) | 89 (37.7) |
| Knee OA bilateral | 89 (74.8) | 99 (84.6) | 188 (79.7) |
| If bilateral: study knee = left | 48 (53.9) | 60 (60.6) | 108 (57.4) |
| Hip OA | 16 (13.4) | 18 (15.4) | 34 (14.4) |
| Symptomatic hip OA | 3 (18.8) | 3 (15.8) | 6 (17.1) |
| Cervical spine OA | 18 (15.1) | 26 (22.2) | 44 (18.6) |
| Lumbar spine OA | 40 (33.6) | 34 (29.1) | 74 (31.4) |
| Hand OA | 12 (10.1) | 14 (12.0) | 26 (11.0) |
| Kellgren-Lawrence grade | | | |
| Grade II | 68 (57.1) | 71 (60.7) | 139 (58.9) |
| Grade III | 51 (42.9) | 46 (39.3) | 97 (41.1) |
| Non-pharmacological treatment (target knee) | 37 (31.1) | 45 (38.5) | 82 (34.7) |
| Previous IA corticosteroid injection | 34 (28.6) | 42 (35.9) | 76 (32.2) |
| Time since last IA corticosteroid injection(m) | 19.73 (18.52) | 28.26 (33.53) | 24.44 (28.00) |
| Previous HA injections | 13 (10.9) | 14 (12.0) | 27 (11.4) |
| Time since last HA injection (m) | 39.50 (24.48) | 26.60 (20.34) | 32.81 (22.94) |
| Intra articular effusion | 2 (1.4) | 1 (0.7) | 3 (1.1) |

All data are given as mean (SD) or n. (%).
*Calculated data; [1] BMI (kg/m²) *: weight (kg) / height (m²); OA: osteoarthritis ; IA: intra-articular; m: month; HA: hyaluronic acid.

**Table II.** Baseline level of symptoms [PP Dataset].

| Outcome parameter | F60027 (n=119) | Hylan G-F20 (n=117) | All (n=236) |
|---|---|---|---|
| Lequesne total index (0–24) | 13.62 (3.23) | 13.17 (2.85) | 13.40 (3.05) |
| Global pain VAS (0–100; mm) | 68.63 (13.24) | 67.47 (11.64) | 68.06 (12.46) |
| Global investigator assessment of severity of the disease (mm) | 47.19 (14.18) | 49.12 (13.74) | 48.14 (13.97) |
| SF12 Physical (0–100) | 30.17 (7.90) | 31.78 (6.88) | 30.96 (7.44) |
| SF12 Mental (0–100) | 45.72 (11.36) | 45.10 (10.39) | 45.41 (10.87) |

VAS: visual analogue scale; mm: millimetres; V2: second visit.

*Main outcome analysis*

The results of the principal analysis (on the PP dataset) of the main criterion (Mean Lequesne index score) are provided in Table III. The mean LFI score over 24 weeks was 8.85 in the F60027 group and 8.66 in the Hylan G-F20 group. The unadjusted mean changes (standard deviation) between baseline and the mean index score over 24 weeks was 4.67 (0.27) in the F60027 group and 4.54 (0.28) in the Hylan G-F20 group. The between group difference was 0.132 with a 95% confidence interval ranging from -0.598 to +0.861. The lower limit of this confidence interval was -0.598, greater than the pre-selected non-inferiority margin of -1.25, allowing the conclusion of the non-inferiority of the two products.

*Secondary efficacy analyses*

The analysis of the primary criterion (mean LFI score over 24 weeks) gave the same results on the FAS dataset (between group difference between adjusted mean changes of -0.069 [95% CI: -0.753; + 0.614], with a lower limit of the 95% CI above the pre-determined non-inferiority margin. LFI score decreased by -5.7 (3.8) in the F60027 group and -5.6 (4.0) in the Hylan G-F20 group between baseline and week 24 (Fig. 2).

All results on secondary outcome parameters (given in Table IV) showed the same trends, without any intergroup difference. Mean global pain reduction between baseline and week 24 was -38.8 mm (24.7) in the F60027 group and -37.1 mm (25.4) in the Hylan G-F20 group. Adjusted mean changes between baseline and mean pain over 24 weeks were -33.6 mm (18.0) and -31.3 mm (19.7), respectively (intergroup difference = 1.686; $p$=0.46). Mean improvement of the investigator's assessment was +14.3 mm (29.4) and +14.4 mm (27.7), respectively, with a mean intergroup difference of -0.154 ($p$=0.95). Mean improvement of SF12 Physical Component Summary was +8.1(8.6) in the F60027 group and +6.7 (8.3) in the Hylan G-F20 group, showing an improvement in patient's global physical status. The intergroup comparison using the MMRM model did not show any significant difference. The response rate assessed by the OARSI-OMERACT responder criteria was high in this trial at week 12 and 24: 64.7% of patients for F60027 and 67.5% for Hylan G-F20 at week 24, without any statistical difference between the two groups (Fig. 3).

Twenty five percent of patients in the F60027 and 21.4% in the Hylan G-F20 group did not take any rescue paracetamol medication during the trial. Among those who did take rescue medication,

**Table III.** Results of the primary analysis on the main outcome (LFI score, PP Dataset).

| Description | Statistic | F60027 (n=119) | HYLAN G-F20 (n=117) | Difference, [95% CI] and *p*-value |
|---|---|---|---|---|
| Baseline (V2) | Mean (SD) | 13.62 (3.23) | 13.17 (2.85) | |
| | [95% CI] | [13.03, 14.21] | [12.65, 13.69] | |
| Mean over 24 weeks* | Mean (SD) | 8.85 (3.59) | 8.66 (3.54) | |
| | [95% CI] | [8.20, 9.50] | [8.02, 9.31] | |
| Change (Baseline - Mean over 24 weeks*) | Mean (SD) | 4.77 (2.79) | 4.51 (3.12) | |
| | [95% CI] | [4.27, 5.28] | [3.94, 5.08] | |
| Primary analysis model: | Adjusted mean (SE) | 4.67 (0.27) | 4.54 (0.28) | 0.132 [-0.598, 0.861] *p*-value = 0.7227 |
| | [95% CI] | [4.13, 5.20] | [3.99, 5.08] | |

*Calculated data.

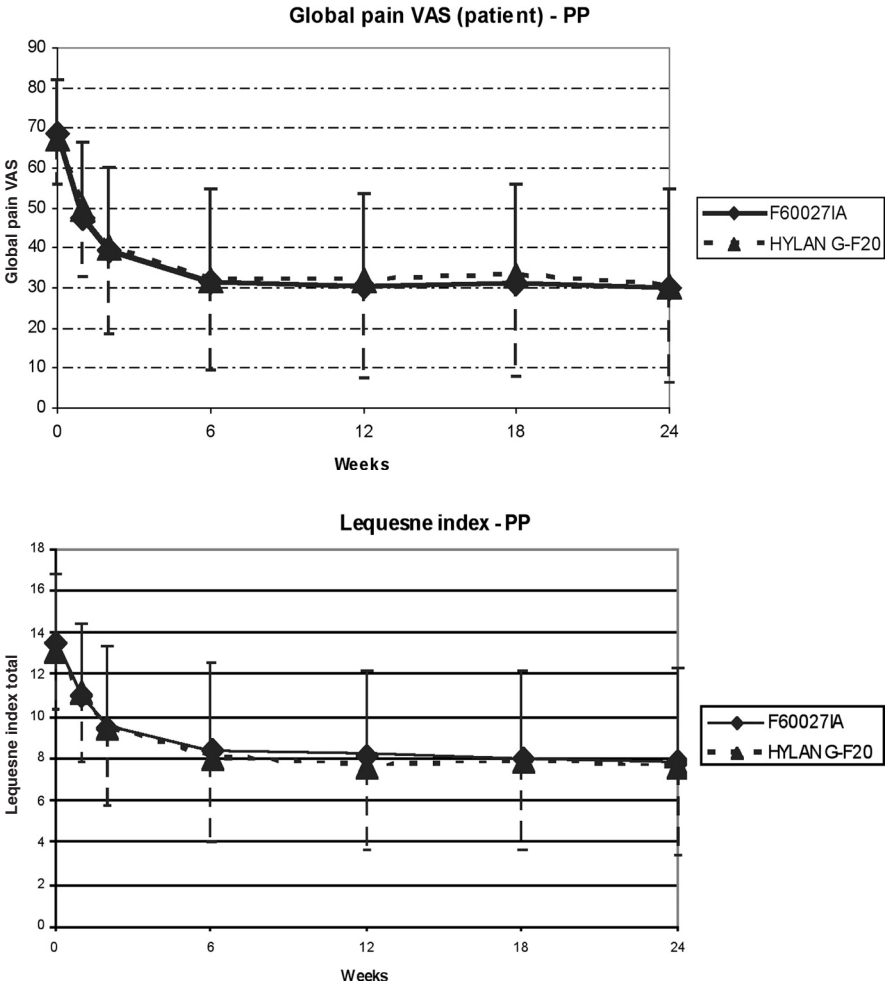


**Fig. 2.** Evolution of the Lequesne index score and global pain on VAS from baseline to week 24 in the per protocol population.

distributions of percentages of day with intake were similar in both groups, the majority of patients using few rescue paracetamol. No significant difference was observed between the two groups. 68.1% of patients in the F60027 group and 70.1% in the Hylan F-F20 group did not use any rescue NSAID (no difference between the groups).

No significant centre or country-treatment effect was observed in this trial (data not shown).

*Safety analysis*

Table V gives a summary of adverse events during the trial. Overall, 470 adverse events were reported by 123 patients (88.5%) in the F60027 group and 492 by 122 patients (87.1%) in the Hylan G-F20 group. A total of 102 treatment emergent adverse events (TEAE) were reported by 56 patients (40.3%) in the F60027 group and 120 TEAE were reported by 60 patients (42.9%) in the Hylan G-F20 group.

No AE led to study drug discontinuation, and only one event in the Hylan group led to premature withdrawal from the study. Six serious adverse events (SAE) were reported by 6 patients, 1 in the F60027 group and 5 in the Hylan group. Local tolerance of HA intra articular injections appeared satisfactory, with only 5 reports in each group (3.6%) of post-injection site pain. There was no pseudo-septic post-injection arthritis (28-30) reported during the trial.

Overall, treatment with both F60027 and Hylan could be considered as safe and well-tolerated.

## Discussion

This is the first report of a non-inferiority trial which compared the efficacy and safety of two HA preparations of various MW, F60027 a "medium" MW (Structovial®) and a "high" MW (Hylan G-F20, Synvisc®) on symptoms in the treatment of knee OA.

The results have clearly shown the non-inferiority of F60027 compared to Hylan G-F20 both on functional impairment, assessed by the Lequesne's index score which was the primary outcome, and on pain reduction in the per protocol analysis. The same results have been observed with respect to investigator's global disease assessment, quality of life (assessed by SF12), and responders rates using the OARSI-OMERACT response criteria either in the per protocol and the FAS analysis.

This study is, to our knowledge, the first study who fully complied with the current European recommendations for the conduct of non-inferiority trials (21), in particular using as main analysis the analysis performed on the per protocol population, as clearly stated by the EMEA guidelines (21). One previ-

**Table IV.** Secondary efficacy outcome measures analyses [PP dataset].

| Outcome [PP dataset] | Statistic | F60027 (n=119) | Hylan G-F20 (n=117) |
|---|---|---|---|
| LFI score (change Baseline - W24) | Mean (SD) [95% CI] | 5.73 (3.80) [5.04, 6.42] | 5.57 (3.97) [4.84, 6.30] |
| Global pain (change Baseline - W24) | Mean (SD) [95% CI] | 38.82 (24.67) [34.35, 43.30] | 37.12 (25.43) [32.46, 41.78] |
| Investigator's assessment (change Baseline - W24) | Mean (SD) [95% CI] | 14.29 (29.36) [8.82, 19.77] | 14.38 (27.74) [9.11, 19.64] |
| SF12 : Physical component (change Baseline - W24) | Mean (SD) [95% CI] | 8.14 (8.58) [6.55, 9.72] | 6.72 (8.34) [5.16, 8.27] |
| SF12 : Mental component (change Baseline - W24) | Mean (SD) [95% CI] | 1.66 (11.51) [-0.47, 3.79] | 1.91 (10.01) [0.04, 3.77] |
| OARSI OMERACT Responders rate at W12 | n (%) | 76 (63.9) | 70 (59.8) |
| OARSI OMERACT Responders rate at W24 | n (%) | 77 (64.7) | 79 (67.5) |
| Rescue medication: Patients who did NOT take Paracetamol during the study period | n (%)/0% | 30 (25.2) | 25 (21.4) |
| Rescue medication: Patients who did NOT take NSAIDs during the study period | n (%)/0% | 81 (68.1) | 82 (70.1) |

W: week; SD: standard deviation; CI: confidence interval; VAS: visual analogue scale; N: number; %: percentage.

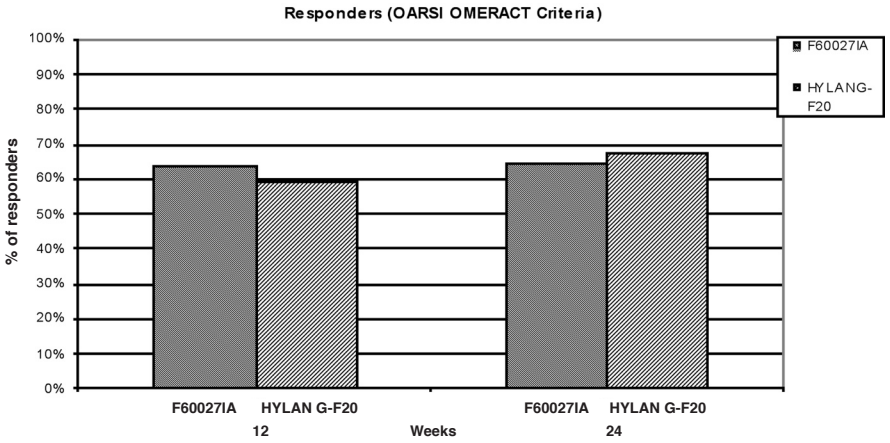


**Fig. 3.** Responders (OARSI-OMERACT Criteria) [PP].

**Table V.** Summary of adverse events on study drug [Safety Dataset].

| Safety Outcome | F60027 (n=139) | Hylan G-F20 (n=140) |
|---|---|---|
| Number of AEs on study drug | 470 | 492 |
| Number of TE AEs | 102 | 120 |
| Number of serious AEs on study drug | 1 | 5 |
| Patients with at least one AE on study drug | 123 (88.5%) | 122 (87.1%) |
| Patients with at least one TE AE | 56 (40.3%) | 60 (42.9%) |
| Patients with at least one AE leading to definitive study drug discontinuation [1] | 0 | 0 |
| Patients with at least one AE leading to withdrawal [1] | 0 | 1 (0.7%) |
| Patients with at least one serious AE | 1 (0.7%) | 5 (3.6%) |

[1] One patient discontinued the study follow-up on D47 due to an AE. He has not been discontinued from the study treatment. AE: adverse event; TE AE: treatment emergent adverse event.

ous study comparing two different HA, namely Euflexxa® (2.4–3.6 mDa) and Hylan G-F20 (Synvisc®), presented as a non-inferiority trial but provided as the principal analysis, the data obtained in the "intent-to-treat population" (16), which may be criticised by clinical biostatisticians.

The strengths of our study, besides the true non-inferiority design and relevant statistical analysis, were the clear pre-trial definition of the non-inferiority margin which allows for concluding or not to non-inferiority. This was settled on the main outcome, the LFI, as the lower limit of the 95% CI of the inter-group difference at endpoint above -1.25. According to Lequesne himself, the minimum clinically relevant difference is around 1.5 to 2 points on the LFI score in knee or hip OA (23). The difference observed in this trial is of 0.132 [-0.598, 0.861] *i.e*. close to zero. A third strength is the low number of patients "lost" between the number of randomised patients (safety dataset) and the number of patients in the per protocol dataset: 236 out of 279, well balanced between the groups. In addition, statistical analyses performed on the full analysis dataset as sensitivity analysis confirmed the results observed in the PP analysis. A fourth strength is the fact that all secondary outcomes gave the same consistent results.

The limitations of this study are of two kinds. The main limitation is the absence of a placebo group, deemed to be unethical and not feasible given the wide availability of various HA preparations in the countries where the trial was performed. In addition, published meta-analyses have established the clinical efficacy of HA intra-articular injections in knee OA (9-13). It must be added that the French Regulatory Authorities which required this trial to prove the efficacy of each HA asking for a reimbursement have admitted in their recommendations for conducting these trials that they could be performed using an "active" control (*i.e*. a HA preparation having produced positive trials *vs*. placebo) with a non-inferiority design. A second limitation lies in the absence of the patient global assessment of the disease as outcome.

This outcome was planned in the protocol, but could not be analysed since in some countries the VAS used to score was misused, thus leading to non-interpretable data.

The results obtained in this trial are in line with most of recent head-to-head published trials comparing HA preparations of various MW (14-18), and with a meta-analysis which concluded that high MW HA have no clinical superiority on knee OA symptoms over lower MW HA preparations (19). Besides, we did not observe any higher rate of acute post-injection arthritis, contrary to what Reichenbach *et al*. reported (19).

In conclusion, in this trial there was no clinical difference with respect to efficacy on knee OA symptoms between a "medium" MW HA, F60027 and a "high" MW HA, Hylan G-F20. It can be concluded that both HA are clinically effective in reducing symptoms, and safe in the treatment of knee OA, and that higher MW HA preparations are probably not superior to lower MW compounds.

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