

ORIGINAL RESEARCH

Three once-weekly intra-articular injections of Hylan G-F 20 significantly improve pain relief compared with placebo in patients with chronic idiopathic knee osteoarthritis: a single-centre, evaluator-blinded and patient-blinded, randomized controlled trial

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Abstract

Background: Clinical trials on the use of viscosupplementation with hyaluronic acid (HA) in patients with knee osteoarthritis (KOA) are inconsistent, making it challenging to determine its value in clinical practice. One issue is the availability of various HA products on the market; differences in their chemical features can impact patient outcomes. Herein, we assess the efficacy and safety of three once-weekly intra-articular (IA) injections of Hylan G-F 20, a high-molecular-weight and highly crosslinked HA product, in patients with KOA. We hypothesized that Hylan G-F 20 would provide significant pain relief with no increased safety risk compared with IA saline (placebo).

Methods: This was a 26-week, patient-blinded and evaluator-blinded, single-centre, randomized placebo-controlled trial. Men or women ≥ 18 years of age with Larsen grade II or III KOA were included. Patients received IA injections of either Hylan G-F 20 or placebo once a week for 3 weeks. The primary endpoints were the week 12 and 26 visits. Primary efficacy outcomes included visual analogue scale (VAS) pain scores, patient activity level and an overall assessment of clinical condition. Secondary outcomes included adverse events (AEs) that emerged during treatment. The primary analysis included the intention-to-treat population. An alpha level of 0.05 was used in the statistical analysis.

Results: Thirty patients were included in the intention-to-treat population (15 per group). All efficacy outcomes

were statistically significant in favour of Hylan G-F 20, except night pain and inactivity stiffness, for both patient-assessed (all $p=0.0001$ at week 12) and evaluator-assessed (all $p=0.0001$ at week 12 and $p=0.0004$ – 0.0180 at week 26) measurements. There was also a greater proportion of symptom-free patients and those with a $>50\%$ improvement in their VAS scores, except night pain, in the Hylan G-F 20 group ($p=0.001$ – 0.003 in patient-assessed scores and $p<0.0001$ to 0.002 in evaluator-assessed scores at week 12). Two patients, one in each group, experienced an AE; no sequelae occurred, and no special treatment was required for either AE. No patients withdrew from the study prematurely due to an AE.

Conclusion: In patients with chronic idiopathic KOA, Hylan G-F 20 provides significant improvements in pain relief compared with placebo with no added safety concerns.

Keywords: hyaluronic acid, Hylan G-F 20, knee, osteoarthritis, randomized controlled trial, Synvisc, viscosupplementation.

Citation

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Introduction

Osteoarthritis (OA) is a chronic and debilitating disease affecting patients worldwide. It is a major cause of disability, pain and poor quality of life, primarily characterized by diminished joint cartilage.¹⁻³ Osteoarthritis is the most common form of arthritis in the USA, with the knee being the most frequently affected joint.^{2,4,5} Together, osteoarthritis of the knee (KOA) or hip have been placed within the top 15 largest contributors to disability worldwide, and within the top 40 largest in disability-adjusted life years across nearly 300 disorders.⁶ The prevalence of KOA is anticipated to continuously increase with rising obesity rates, body mass index and life expectancy amongst general populations.^{2,4,6-9} Furthermore, KOA is associated with costs of over US\$27 billion annually.^{2,10}

Intra-articular (IA) hyaluronic acid (HA) is a treatment option for patients with KOA who do not respond to initial pharmacological treatments and are either not suitable for surgery or prefer to avoid invasive procedures.^{1,11-13} Retrospective studies have shown that viscosupplementation with HA can decrease opioid, non-steroidal anti-inflammatory drug (NSAID) and corticosteroid use, reduce inflammation, and delay joint replacement surgery.^{5,14-19} However, current literature provides inconsistent results and conclusions regarding the use of HA, making it challenging to conclusively determine its value in clinical practice; various medical societies (including the American Academy of Orthopaedic Surgeons and the Osteoarthritis Research Society International (OARSI)) have come to differing conclusions and recommendations regarding its use.²⁰⁻²⁴ This may be explained by differences between clinical trials in terms of their study design methods and the quality of their reporting as well as by the number of HA products that are available in the market and how they may differ in their chemical features (e.g. crosslinkage or molecular weight).^{1,12,25,26} Previous studies have demonstrated that HAs that are crosslinked or have higher molecular weight are associated with better outcomes for the patient compared with non-crosslinked products or those with lower molecular weight.^{1,27,28}

Hylan G-F 20 (Synvisc*; Sanofi, Bridgewater, NJ, USA) is a high molecular weight (6000 kDa), highly crosslinked HA product that mimics the molecular weight of endogenous HA. The therapy involves weekly injections into the knee over three successive weeks (Synvisc-One*, which requires only one injection, is another option).^{29,30} The pivotal trials on the three-injection and single-injection Hylan G-F 20 formulations demonstrated that both products are safe and efficacious.^{29,31} To add to the literature on this

topic and to help address the uncertainty of the therapeutic value of HA products, this study was conducted to determine the efficacy and safety of three once-weekly injections of IA Hylan G-F 20 in patients with chronic KOA over 26 weeks. It was hypothesized that Hylan G-F 20 would provide significant pain relief with no increased safety risk compared with IA saline (placebo).

Methods

This study was not registered in any clinical trial registries and a Consolidated Standards of Reporting Trials (CONSORT) checklist is provided in the Appendix (available at: <https://www.drugsincontext.com/wp-content/uploads/2024/03/dic.2023-11-3-AppendixCONSORTChecklist.pdf>). This study was performed in accordance with the Declaration of Helsinki's ethical principles for medical research involving human participants and was approved by an ethics committee and institutional review board prior to enrolment. This study was conducted between April 1989 and December 1989, and results were reported on retrospectively.

Eligibility criteria

A detailed list of the inclusion and exclusion criteria of the study is presented in the Appendix Table 1 (available at: <https://www.drugsincontext.com/wp-content/uploads/2024/03/dic.2023-11-3-AppendixTables.pdf>). Eligible patients for this study included either men or women (≥ 18 years of age) who had chronic idiopathic KOA of Larsen grade II or III.

All patients who entered the study were considered eligible to complete the full 6-month programme. Any patient who desired to withdraw prematurely or was withdrawn for a protocol violation was dropped from the study, but these patients were included in the intention-to-treat (ITT) population.

Treatment details

Patients who were randomly allocated to the active treatment arm were given three IA injections of 2 mL of Hylan G-F 20 – a chemically altered and highly purified hyaluronan derived from an avian source – at intervals of once per week. Patients randomized to the placebo arm received injections of buffered physiological saline solution once weekly for 3 weeks.

Study design

The study took place at a single centre in Germany. Baseline was established at week 0 following a 2-week wash-out period in which treatment with NSAIDs, corticosteroids

* Synvisc and Synvisc-One are registered trademarks of Sanofi, Bridgewater, NJ, USA

or analgesics was prohibited. Patients were randomized in consecutive order of study entry. Syringes were then prepared and placed in boxes bearing preassigned numbers. A numbered box containing the syringes was randomly drawn for each patient at enrolment. Each syringe in the box contained the identical agent. Once assigned a treatment box, the patient's identification number was applied to the box. The box and syringes were used for that patient throughout the study. Injections were administered at weeks 0, 1 and 2. Concomitant medications were permitted only after the last injection, provided their usage was documented.

Blinding

Patients as well as outcome evaluators were unaware of the treatment allocation throughout the course of the study. Treating physicians who were responsible for injecting the patients were aware of the treatment being administered. Blinding was ensured by preparing and packaging both the experimental device and placebo in an identical fashion. Patient evaluation was carried out by an investigator who was unaware of which treatment each patient was assigned to. Communication between the treating physician and the evaluating investigator was not permitted regarding any aspect of the study.

Follow-up details

Patients came to the clinic over 12 weeks, with visits at weeks 1, 2, 3, 8 and 12. A final telephone follow-up was conducted at 26 weeks. The primary endpoints of the study were the week 12 and 26 visits.

Outcomes

Efficacy

The following efficacy outcomes were measured throughout the study:

- Patient-assessed and evaluator-assessed:
 - Visual Analogue Scale (VAS) weight-bearing pain
 - VAS night pain
- Patient-assessed only:
 - VAS improvement in most painful knee movement
 - VAS assessment of treatment (an improvement measure)
- Evaluator-assessed only:
 - VAS decrease in activity
 - VAS overall improvement of clinical condition
 - Inactivity stiffness
 - Average value (in minutes) to the first rest period
 - Duration of average rest period
 - Number of rest periods per day
- Percentage of 'symptom-free' patients, defined as a VAS score <20 mm

- Percentage of patients with a >50% improvement from baseline

A minimal clinically important improvement of 20 mm was used as a reference for improvements in VAS pain.^{32–34}

Safety

Adverse events (AEs) were defined as signs and symptoms that emerged during treatment, including intercurrent illnesses and subjective complaints. Patients were assessed and asked about present or between-treatment AEs at each visit throughout the study, and all reported AEs were documented. The investigator's evaluation of whether the AE was related to the test device was included in this documentation as well as the need for remedial therapy, the time at which the AE began in relation to the injection, its duration, and its relationship to the continuance of the patient in the study. Any AEs that were considered by the investigator to be serious or life-threatening were immediately reported to the study sponsor.

Statistical methods

The last observation carried forward approach was used for statistical analyses carried out on the ITT population. Outcomes between groups were compared using least squares mean change from baseline in VAS scores. The mean and standard error of the mean were used to represent continuous outcomes. Baseline to endpoint improvements in VAS scores were compared between groups with a one-way analysis of variance (ANOVA). The Cochran–Mantel–Haenszel χ^2 analysis was used to analyse categorical outcomes. For each statistical analysis, a two-tailed test with an alpha of 0.05 was utilized.

Sample size

The study sample size was determined by assuming that a clinically significant difference between the improvements in means for the key outcome measures would be 25 mm with a standard deviation of 23. The calculation was based on a power level of 0.80 and a two-tailed alpha level of 0.05. A sample size of 15 patients per arm (i.e. 30 patients total) was therefore required.

Ethics

This study was approved by an ethics committee and institutional review board. The procedures in this study were performed in accordance with the Declaration of Helsinki's ethical principles for medical research involving human participants. Each patient's written or witnessed verbal informed consent was obtained prior to enrolment. The patients were informed of the

experimental nature of the device, the duration of the trial, alternative modes of treatment, potential risks associated with the treatment, and their right to withdraw from the study at any time.

Results

Patient characteristics

A total of 30 patients (15 per group) were enrolled in the ITT population between April and December 1989. A summary of the patient characteristics of the study sample is presented in Table 1. All 30 patients received all three IA treatments, and all were evaluated for efficacy and safety. Four patients deviated from the study protocol with respect to the study eligibility criteria, as they were diagnosed with Larsen grade IV KOA, and another patient had a rheumatoid factor titre indicative of rheumatoid arthritis. Of note, the analysis of an evaluable patient population was deemed unnecessary and was not undertaken because this sub-population was too small

to warrant a statistically valid sub-set analysis of efficacy. Additionally, all five patients received the three IA treatments and remained in the study for up to 26 weeks along with all other patients in the ITT population.

Efficacy

Patients treated with Hylan G-F 20 improved significantly more than patients treated with placebo across all patient-assessed and evaluator-assessed efficacy outcomes measured on the VAS, except night pain, at weeks 12 and 26 (Figures 1 and 2; Appendix Tables 2 and 3; available at: <https://www.drugsincontext.com/wp-content/uploads/2024/03/dic.2023-11-3-AppendixTables.pdf>). There were no statistically significant differences between groups in inactivity stiffness variables. There were also a significantly higher number of patients treated with Hylan G-F 20 who achieved greater than 50% improvement in VAS scores for each of the efficacy outcomes, with the exception of night pain (Appendix Tables 4 and 5; available at: <https://www.drugsincontext.com/wp-content/uploads/2024/03/dic.2023-11-3-AppendixTables.pdf>).

Safety

Two patients, one in each group, experienced an AE. In the placebo group, the arthritis of a patient was diagnosed at the second visit as 'arthritis due to uric acid'. The investigator considered that the relationship of this AE to treatment was unlikely. In the Hylan G-F 20 group, one patient had muscle pain at each of the three injections. The study investigator considered this AE to be possibly related to treatment with Hylan G-F 20. No sequelae occurred, and no special treatment was required for either AE. No patients withdrew prematurely due to an AE.

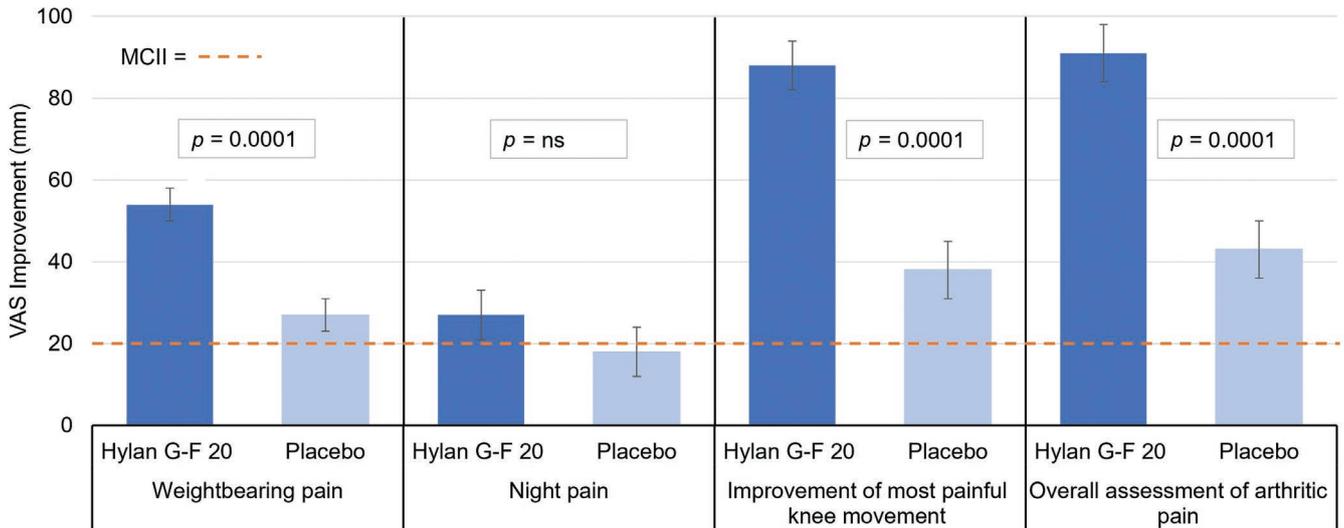
Discussion

The results of this trial showed that three once-weekly injections of Hylan G-F 20 significantly improves both patient-assessed and evaluator-assessed efficacy outcomes, except for night pain and inactivity stiffness, compared with placebo injections with no added safety risk. Statistically significant differences between Hylan G-F 20 and placebo were observed early (i.e. within the first 1–2 weeks) following the start of treatment up until the 26-week visit. Furthermore, improvements across all mean VAS scores after receiving Hylan G-F 20 were clinically meaningful (relative to a minimal clinically important improvement of 20 mm) at the primary endpoints of 12 and 26 weeks. It is important to note that night pain was not present or very mild at baseline across both treatment groups, and that both patient-assessed and evaluator-assessed night pain improved to a clinically relevant degree in the Hylan G-F 20 group only. Similarly, categorical analyses of the efficacy outcomes (i.e. patients who had >50% improvement

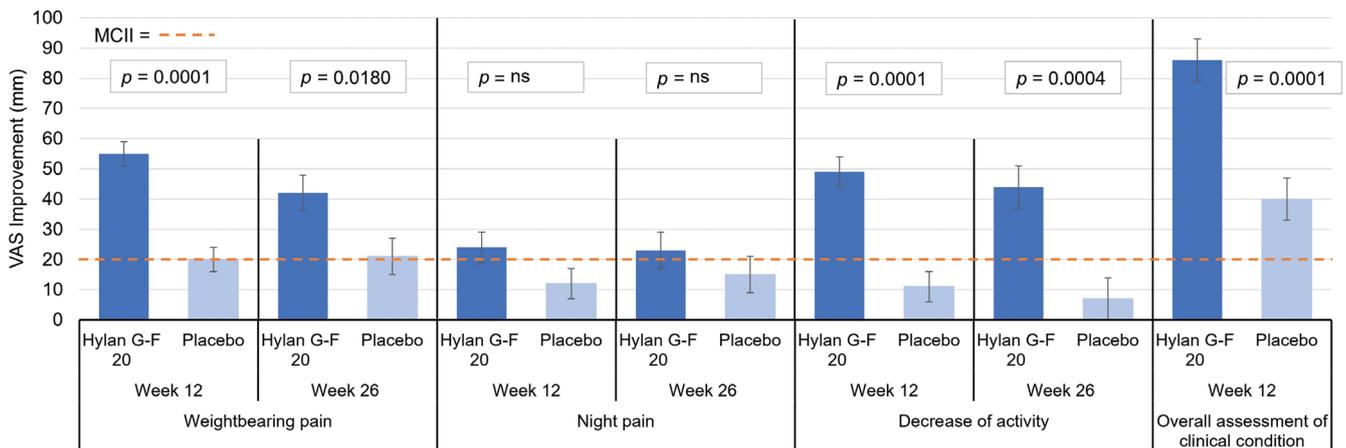
Table 1. Patient and disease characteristics of the intention-to-treat population.

Parameter	Hylan G-F 20	Placebo
Sex, n (%)		
Male	11 (73%)	8 (53%)
Female	4 (27%)	7 (47%)
Age, years		
Mean (SEM)	58 (2)	60 (2)
Median	59	58
Range	38–74	52–79
Height, cm		
Mean (SEM)	173 (2)	172 (2)
Median	174	173
Range	160–192	159–183
Weight, kg		
Mean (SEM)	79 (3)	83 (3)
Median	80	85
Range	60–102	63–100
Disease duration, years		
Mean (SEM)	2 (0.6)	2 (0.5)
<1 year, n (%)	4 (27%)	5 (33%)
1–5 years, n (%)	8 (53%)	7 (47%)
>5 years, n (%)	3 (20%)	3 (20%)
Larsen grade, n (%)		
I	0 (0%)	0 (0%)
II	6 (40%)	5 (33%)
III	8 (53%)	7 (47%)
IV	1 (7%)	3 (20%)

SEM, standard error of the mean.

Figure 1. Improvements in patient-assessed efficacy outcomes at week 12.

MCII, minimal clinically important improvement; ns, not significant; VAS, visual analogue scale.

Figure 2. Improvements in evaluator-assessed efficacy outcomes at weeks 12 and 26.

MCII, minimal clinically important improvement; ns, not significant; VAS, visual analogue scale.

in VAS) also demonstrated an early and sustained better treatment response with Hylan G-F 20 compared with placebo. A patient in each treatment group experienced an AE, but no sequelae occurred, and no special treatment was required for either patient. Overall, these findings show that IA injection of Hylan G-F 20 yields effective relief of pain and is well-tolerated in patients with KOA with its benefits lasting up to 26 weeks. This study adds to the abundance of clinical trial literature on the use of HA in KOA and can help address the ongoing controversy surrounding the efficacy and safety of HA. More specifically, this trial provides further supporting evidence on the use of Hylan G-F 20 in this patient population, which can help with the objective of more definitively concluding the therapeutic value of HA products and their place in therapy.

The findings of this trial are generally consistent with previously published evidence on Hylan G-F 20. Early research demonstrated that a regimen of three once-weekly injections of IA Hylan G-F is an effective and safe treatment relative to placebo and conventional OA therapies such as NSAIDs.^{31,35–38} The study by Wobig et al. was the pivotal Hylan G-F 20 trial, which also showed early and sustained tolerability and symptomatic relief over 26 weeks compared with placebo.³¹ Another trial by Chevalier et al. had similar results with the single-injection formulation of Hylan G-F 20.²⁹ This study confirms the findings from these prior trials, revealing that the therapeutic effects of Hylan G-F 20 can last up to 6 months post-injection, though it has also been suggested that its benefits may be evident for even longer, which was

confirmed in a recent meta-analysis that examined the 1-year efficacy and safety of Hylan G-F 20.^{16,30,39}

Historically, there has been conflicting evidence on the use of viscosupplementation with HA in OA, which has resulted in uncertainty and inconsistency in clinical practice and recommendations.⁵¹⁶ This is likely driven by variability in the molecular characteristics (e.g. crosslinking, molecular weight) between the different HA products available on the market.^{5,40} A number of early HA studies have demonstrated unimpressive results, not always showing significantly more favourable outcomes compared with placebo.⁴¹⁻⁴³ However, recent publications, also evaluating the newer, crosslinked, higher-molecular-weight HA formulations, have assessed the clinical impact of different HA characteristics on patient-reported outcomes, with the higher-molecular-weight and crosslinked products showing greater efficacy.^{1,27,28,44-46} Hylan G-F 20 has also demonstrated substantial reductions in opioid and corticosteroid use several months after the initial injection in real-world practice.¹⁴¹⁵ In a retrospective analysis on adults with KOA, Khangulov et al. found that Hylan G-F 20 significantly reduced the mean number of days on opioids from 13.5 to 5.0 days ($p=0.007$) and the mean total amount of opioids from 493.7 morphine milligram equivalents (MME) to 165.4 MME ($p=0.013$) in the 6 months after compared with the 6 months before injection.¹⁴ The number of injections of IA corticosteroids was also significantly lower 6 months after treatment with Hylan G-F 20 in this study, from a mean of 1.39 to 0.56 ($p<0.0001$). Langworthy et al. conducted a similar analysis evaluating opioids and IA corticosteroids 6 months after Hylan G-F 20 in patients with KOA and found that patients had significant decreases in total MME, MME per day and opioid prescription days of 14.0%, 14.2% and 12.6%, respectively (all $p<0.01$).¹⁵ Additionally, half of the patients prescribed opioids before Hylan G-F 20 were also prescribed opioids after Hylan G-F 20. There was also a significant decrease in the number of IA corticosteroids following Hylan G-F 20 (56.1% decrease; $p<0.01$).

The coexistence of other chronic conditions in patients with KOA can also influence treatment decisions. For example, a considerable proportion of patients with KOA also have type 2 diabetes mellitus.⁴⁷⁻⁵⁰ In this subgroup of patients with KOA, evidence has shown AEs with acetaminophen, NSAIDs and IA corticosteroids, whilst IA HA may be administered to these patients with limited safety concerns.⁵⁰ Additionally, corticosteroid therapy can lead to hyperglycaemia; therefore, it should be used with caution for those who are at risk for diabetes (i.e. pre-diabetic individuals) or already have the disease.^{51,52}

A key consideration for interpreting the results of this trial was that it was conducted over 30 years ago. Clinical trial design and practice has evolved since 1989, and

some characteristics of this trial should be analysed with respect to their effect on the generalizability of the results to modern day practice. In terms of clinical trial endpoints, older trials such as this one have commonly used the VAS to measure efficacy of treatments in reducing pain in KOA. In contrast, more recent trials have popularized the use of other efficacy outcomes such as the Knee Injury and Osteoarthritis Outcome Score, Western Ontario and McMaster Universities Index for pain, stiffness and function, and Average Daily Pain. Knee Injury and Osteoarthritis Outcome Score and Western Ontario and McMaster Universities Index both represent valid, reliable and responsive outcome measures in KOA.⁵³ As such, these tools may be considered more accurate for assessing subsequent IA assessment strategies. However, Average Daily Pain may not be as reliable a measurement as this outcome has confounded data even when comparing short-acting *versus* long-acting steroids.⁵⁴ Additionally, there has since been a growing body of research on the inflammatory mediators found in the synovial fluid and the role they can play in the evaluation of therapies for OA.⁵⁵⁻⁵⁹ Furthermore, the types of comparators used within clinical trials have changed in the last few decades. It has become increasingly common for trials to use active comparators (e.g. corticosteroids, platelet-rich plasma and other HA products), which may be considered as conventional treatments in current practice, and more relevant comparators considering the importance of mitigating the IA placebo effect.⁶⁰ Despite these differences in design, some characteristics of this trial have withstood the test of the time such as the use of HA to treat KOA and the standard administration procedures of the IA injections. Additionally, the trial was conducted largely in accordance with OARSI recommendations for the design, conduct and reporting of clinical trials for KOA.⁶¹ This is particularly important in light of a recent targeted literature review of KOA trials investigating IA interventions, which found that a median of 19 out of 24 (range, 9-24) OARSI recommendations were adhered to amongst 139 trials.⁶² If clinical trials are conducted with high quality and rigour, even dated findings may be considered relevant and informative for current clinical practice.

This study had several strengths. First, it was a patient-blinded and evaluator-blinded, randomized controlled trial. In clinical trials, blinding minimizes bias during assessment of subjective outcomes.^{63,64} Second, this trial included a washout period implemented to avoid any carryover of effects from previous therapies into the study period. This is particularly important considering the trial did not exclude patients who received injectables prior to the start of the study. Third, efficacy was evaluated in this trial using the VAS. This frequently used tool is considered valid and reliable in measuring pain within clinical trials.⁶⁵⁻⁶⁷ Fourth, the results of both

patient-assessed and evaluator-assessed outcomes were consistent with each other. Finally, results were analysed using an ITT approach, which minimized the risk of attrition bias.

A limitation of this study was the lack of blinding of the treating physician. Despite this, it should be noted that measures of pain were patient-reported, and safety outcomes were assessed by another investigator who was unaware of which group each patient was assigned to, thereby minimizing the possibility of assessor bias. Additionally, sex differences between groups at baseline were observed (73% versus 53% men in the Hylan G-F 20 and placebo groups, respectively), as well as a slightly higher number of patients with Larsen grade IV disease in the placebo group (7% versus 20%). The higher proportion of women and those with grade IV disease in the placebo group were attributed to sampling bias considering the relatively small sample size (30 patients total). Furthermore, the trial applied no restrictions on baseline pain in terms of patient inclusion or exclusion criteria. Rather, patients could enter the trial so long as they experienced knee pain of any severity every day at work. It is common for modern trials to include an acceptable baseline range of pain as part of their inclusion criteria. However, it should be noted that there were no significant differences between groups for pain at baseline in any measure (Appendix Tables 2 and 3). Another limitation was that the trial was conducted over 30 years ago; however, this study is still relevant as it adds to the literature on Hylan G-F 20 versus placebo and is consistent with the previously published evidence on the topic. Additionally, this trial was conducted at a single centre in Germany. Given that this trial is older and is only representative of patients at a single site, there is added uncertainty on the generalizability of these results to patients with KOA seen in current clinical practice and to

patients with KOA in other geographical locations. Even with these limitations, it is important to note that clinical trial evidence will always continue to inform clinical practice, and all research, regardless of their results and when and where they were conducted, should be available in the published literature. Another limitation was that this trial followed patients for up to 26 weeks, and it cannot support the longer-term (i.e. 1 year) effects of Hylan G-F 20. Finally, there is no CONSORT patient flow diagram presented in this study. The CONSORT statement (2010) outlines the current customary procedure for performing and reporting a randomized clinical trial.⁶⁸ However, the CONSORT flow diagram is not presented in this document due to the trial's age. The initial CONSORT statement was released in 1994, 5 years after this study was completed.⁶⁹

Conclusions

Three, once-weekly injections of Hylan G-F 20 are both well-tolerated and efficacious relative to placebo in patients with chronic idiopathic KOA.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request. Qualified researchers may request access to patient-level data and related study documents, including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of the trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: <https://www.vivli.org>.

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