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Evaluating the use of intra-articular injections as a treatment for painful hip osteoarthritis: a randomized, double-blind, multicenter, parallel-group study comparing a single 6-mL injection of hylan G-F 20 with saline

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SUMMARY

Objective: Hip osteoarthritis (OA) is difficult to treat. Steroid injections reduce pain with short duration. With widespread adoption of office-based, image-guided injections, hyaluronic acid is a potentially relevant therapy. In the largest clinical trial to-date, we compared safety/efficacy of a single, 6-mL image-guided injection of hylan G-F 20 to saline in painful hip OA.

Method: 357 patients were enrolled in a multicenter, double-blind, randomized saline placebo-controlled trial. Subjects were ≥35 years of age, with painful (Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC]-A1:5.0–8.0; numeric rating scale [NRS]: 0–10) mild-to-moderate hip OA (Kellgren–Lawrence grade II/III) and minimal contralateral hip pain (WOMAC-A1 < 4). Outcome measures included "pain on walking" (WOMAC-A1 and -A), Patient Global Self-Assessment (PTGA), WOMAC-A1 responder rate (+≥2 points on NRS), and adverse events (AEs) over 26 weeks.

Results: 357 patients (hylan G-F 20 single:182; saline:175) were enrolled. Both groups demonstrated significant pain improvement from baseline over 26 weeks ($P < 0.0001$); saline-induced pain reduction was a remarkable 35%. WOMAC-A and PTGA scores also significantly improved ($P < 0.0001$). No statistically significant difference was observed between groups in WOMAC-A1 scores (hylan G-F 20 single: -2.19 ± 0.16; saline: -2.26 ± 0.17) or WOMAC-A1 responders (41–52%). Treatment-related AE rates at target hip were similar (hylan G-F 20 single:23 patients [12.8%]; saline:12 [7.0%]). *Post hoc* analysis found, despite protocol requirements, many patients had psychological (31%) or potential neuropathic pain (27.5%) conditions.

Conclusion: A single 6-mL hylan G-F 20 injection or saline for painful hip OA resulted in similar, statistically significant/clinically relevant pain and function improvements up to 6 months following injection; no differences between hylan G-F 20 and saline placebo were observed.

Introduction

The prevalence of hip osteoarthritis (OA) is estimated to range from 6.7% to 9.2% among adults ≥45 years of age and increases with age[1,2]. In one large general practice study, 24% of patients with OA rated the hip as the most painful joint[3] and about 20% of patients have remaining pain postsurgery[4]. Hip OA is difficult to treat. Intra-articular (IA) corticosteroid injections reduce pain but may be contraindicated when OA is accompanied by osteonecrosis, infection[5] or diabetes[6].

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With need for alternative treatments and widespread adoption of office-based, image-guided injections, viscosupplementation is a potentially relevant therapy for treatment of hip OA. Viscosupplementation has been shown to impact clinical benefit in the treatment of knee OA[7], and a review of nonclinical literature supports several possible mechanistic benefits of hyaluronic acid in knee OA including chondroprotection, analgesia, mechanical, subchondral, and anti-inflammatory effects; and proteoglycan/glycosaminoglycan synthesis[8].

The use of hyaluronic acid for painful hip OA is a more recent phenomenon; robust studies supporting its use in painful hip OA are lacking[9]. Hylan G-F 20, a high-molecular-weight, cross-linked, injectable hyaluronic acid, is approved for treatment of hip OA in Europe[10] and Canada[11] in a dosing regimen of two 2-mL injections. Several studies have described hylan G-F 20 as a safe and effective treatment for hip OA pain[12–15]. However, these have been pilot or open-label (lesser quality, Level II or III) clinical trials focused on safety or proof of concept. One higher quality clinical trial has been reported. This was a large, multicenter, double-blind randomized clinical trial comparing 2 image-guided IA injections of 2 mL hylan G-F 20 with methylprednisolone acetate (MPA + 1 sham injection) in patients with mild-to-moderate hip OA. This study demonstrated that 2 injections of 2 mL hylan G-F 20 were as effective as 1 methylprednisolone injection, each imparting statistically significant and clinically meaningful improvements in pain (Western Ontario McMaster Universities Osteoarthritis Index [WOMAC] A, from baseline over 26 weeks) with no major safety concerns. Patients with more severe OA (KL grade III, not II) responded better to hylan G-F 20, while those with milder disease tended to respond better to MPA. Interpretation of study results was somewhat compromised by a high subject dropout rate. This trial was the first to demonstrate that two injections of hylan G-F 20 could perform as an effective alternative to corticosteroid injection in hip OA, a treatment particularly useful for patients whose medical or orthopedic conditions preclude using corticosteroids, those whom have not responded to past corticosteroids, or those in whom corticosteroid injections are contraindicated because of an upcoming hip replacement[16].

Hylan G-F 20 is also available as a single 6-mL injection, which has been shown to reduce the pain associated with knee OA with the convenience of 1 injection[17]. Therefore, the current study was designed to assess efficacy and safety of this single 6-mL injection of hylan G-F 20 in patients with mild-to-moderate primary OA of the hip.

Subjects and methods

Study design and study participants

This was a multicenter, double-blind, parallel-group, saline placebo-controlled randomized study to compare efficacy and safety of single image-guided, 6-mL injection of hylan G-F 20 to 6-mL saline in subjects with mild-to-moderate primary hip OA (ClinicalTrials.gov, NCT01618708). The study included a screening visit (days −28 to −4, including medication washout period), 2 baseline evaluations, and a 26-week follow-up period. Eligibility criteria included diagnosis of symptomatic hip OA (radiographically confirmed KL grade II or III within 26 weeks of screening) per American College of Rheumatology criteria[18] (hip pain at first baseline plus at least 2 of the following 3 features—erythrocyte sedimentation rate <20 mm/h, radiographic femoral and acetabular osteophytes, or radiographic joint space narrowing [superior, axial, and/or medial]); previous use of analgesics or nonsteroidal anti-inflammatory drugs (NSAIDs) for hip OA pain with completion of pain and OA medication washout period; hip pain as demonstrated by a WOMAC A1 score of 5–8 (on an 11-point numeric rating scale [NRS], with 0 = none to 10 = extreme pain); age ≥35 years; and willingness to receive image-guided injections (including any necessary imaging contrast agent). WOMAC A1 is a single question asking about patients' pain severity when walking on a flat surface. WOMAC A consists of A1 and 4 other questions on pain when going up or down stairs, at night while in bed, while sitting or lying down, and while standing. WOMAC C contains 17 itemized activities to evaluate function. Each item uses a 0–10 scale.

Subjects were excluded if they had WOMAC A1 score of under 5 or 9–10 at screening; symptomatic contralateral hip OA (WOMAC A1 ≥ 4); decrease in WOMAC A1 >1 point from screening to baseline (may indicate “expectancy” of therapeutic effect; for all enrolled subjects, mean of baseline differences from the two recordings was <0.6); presence of comorbidities that may affect the target joint or impact measurement of efficacy (e.g., other types of arthritis, osteonecrosis, active infection at injection site, lower back disorders, symptomatic OA of either knee); surgeries/procedures to the hip/lower extremities within 26 weeks of screening; or IA corticosteroid injection within 12 weeks of screening. The protocol complied with recommendations of the 18th World Health Congress (Helsinki, 1964)[19] and all applicable amendments, and with any applicable country-specific laws, regulations, and guidelines; and was approved by relevant ethics committees and/or institutional review boards. All subjects provided written, informed consent prior to study procedures.

Eligible subjects were randomized 1:1 to hylan G-F 20 (48 mg in one 6-mL IA injection) or phosphate-buffered saline (one 6-mL IA injection). Randomization was stratified by study site. All injections were performed under fluoroscopy or ultrasound (depending upon clinical site) to ensure accurate IA needle placement. Saline injection mirrored hylan G-F 20 procedures. Subjects were placed in the supine position. The region overlying the targeted hip was prepped and draped in a sterile manner. The skin and local soft tissues (but not into the capsule) were anesthetized with 1% lidocaine. Intermittent fluoroscopy or musculoskeletal ultrasound (with sterile ultrasound gel) was used to place a 3.5-inch spinal needle into the hip joint, targeting the inferior femoral head, at the head–neck junction. A thorough arthrocentesis was performed prior to injection of the study material if synovial fluid presented upon needle entry. If fluoroscopy was used, a small amount of nonionic (Omnipaque [GE Healthcare]) contrast material was injected and limited arthrogram performed to confirm/document IA needle placement. Then, one vial of study agent (hylan G-F 20 as a single 6-mL injection or saline) was injected. The spinal needle was removed and a Band-Aid applied.

Prior and concomitant therapies were identified to the extent possible. Prior medication was defined as any medication received by the patient within 4 weeks of screening, and concomitant medication was defined as received at any time after screening through last visit. Acetaminophen was the only allowable medication for target hip OA pain, and subjects recorded its use on an electronic portable device (ePro) on a daily basis. Short-acting NSAIDs and acetaminophen for pain or for reasons other than pain in the target hip joint (e.g., headache, flu and cold symptoms) were allowed and recorded in the ePro; however these could not be used within 2 days of each study visit.

Assessments

The complete WOMAC NRS 3.1 questionnaire, administered at baseline and weeks 4, 8, 12, 16, 20 and 26, was used as the assessment tool in this study. An 11-point NRS was used to capture the patients' response to each of the questions. Primary endpoint

was mean change from baseline over 26 weeks in subjects' assessment of their walking pain using WOMAC A1. Secondary endpoints included WOMAC A1 responder rate over 26 weeks (defined for each visit as ≥2-point NRS improvement); change from baseline over 26 weeks in pain using WOMAC A and in Patient Global Self-Assessment (PTGA) of target hip OA.

Change in function measured by WOMAC C and changes in use of self-administered rescue medication were also assessed. *Post hoc* analyses were conducted to assess the possible impact of non-articular, neuropathic pain generators (back pain, intervertebral disc disorders, lumbar spinal stenosis, peripheral neuropathy fibromyalgia, sciatica, and/or fibromyalgia).

The incidence of adverse events (AEs), treatment-emergent AEs (TEAEs), and serious adverse events (SAEs) was assessed.

Statistical analysis

A sample size of 350 subjects was determined to provide 80% power to detect a 1-point difference between treatment groups in WOMAC A1 assuming a 2-sided significance level of 5%. Standard deviation was expected to be similar in both groups and an estimate of 3 was used in this calculation. Sample size assumed a dropout rate of 20%.

The Investigator obtained a randomization number through the central randomization service, the interactive voice or web response system, and obtained a kit code corresponding to a blinded patient kit. The patient, site personnel dispensing clinical supply and the masked clinical observer were blinded to the investigative study treatment. The unblinded injector was instructed to not reveal treatment regimens to the masked clinical observer to ensure that blinding remained intact.

Efficacy outcomes were analyzed in these populations: intent-to-treat (ITT) population, including all randomized subjects whether they received any study product or part of the treatment administration (hylan G-F 20, imaging contrast agent, or local anesthesia); modified ITT, including all randomized subjects who received investigational product and had a baseline and ≥1 post-baseline efficacy assessment; and the per-protocol population, including all modified ITT subjects without important protocol deviations (predefined by a blinded project team, prior to database lock). Primary analysis for the primary endpoint of change from baseline over 26 weeks in walking pain using WOMAC A1 was performed on the ITT population. Primary and secondary efficacy analyses were performed on ITT and per-protocol populations, based on a mixed model for repeated measures analysis of covariance assuming "missing at random," with terms for treatment, site (small sites with fewer than 8 randomized patients were grouped), time and time-by-treatment interaction, as well as the baseline score as a covariate and baseline-by-time interaction. Sensitivity analyses for missing data assumptions and for influence of NSAIDs and acetaminophen usage during the trial were performed.

Responder analysis used generalized estimating equations modeling to estimate responder rate (defined for each visit as ≥2-point NRS improvement) over 26 weeks. Each responder (yes/no) endpoint evaluated at multiple postbaseline visits was analyzed using generalized estimating equations for binary outcomes. The model included terms for baseline measure, site, visit, treatment group, and visit-by-treatment-group interaction. Hypothesis testing was performed using least squares means based on the linear predictor of the model.

Usage of NSAIDs and acetaminophen was analyzed using the Wilcoxon rank-sum test. *Post hoc* analyses on observed data were performed on subgroups similar to the efficacy analyses using the mixed model for repeated measures analysis of covariance with additional terms for the subgroup-by-treatment interaction, subgroup-by-time interaction, and subgroup-by-treatment-by-time interaction.

Safety outcomes were analyzed in all randomized subjects who received any study product or part of treatment administration. TEAEs were summarized by treatment group and categorized by severity and relationship to study treatment. Multiple occurrences of the same TEAE in the same subject were counted only once to include the most severe occurrence and most extreme relationship to study procedures. Target hip AEs were summarized separately.

Results

Subject disposition and baseline characteristics

A total of 357 subjects were randomized to hylan G-F 20 single 6-mL injection (n = 182) or saline (n = 175) groups; 352 received treatment (n = 180 for hylan G-F 20 single 6-mL injection; n = 172 for saline); and 267 completed follow-up. Discontinuation rates (hylan G-F 20 single 6-mL injection, 24.2%; saline, 23.4%) were greater than the anticipated 20%. Discontinuations due to AEs, lack of efficacy, and lost to follow-up were similar in each group (Fig. 1).

Baseline characteristics were similar between groups (Table I), with an overall mean age of 60.3 years. The majority of subjects were women. Almost all (99.7%) had radiographically confirmed target hip OA and 26.9% had confirmed contralateral hip OA. Most subjects (62.2%) had moderate disease (a KL grade of III at screening). Some patients reported more than one event of back pain, neuropathic or other musculoskeletal condition (number of patients was n = 51 and n = 47) in the hylan G-F 20 single 6-mL injection and saline groups, respectively; number of events for these two groups was n = 64 and n = 58 respectively. Baseline pain was severe: WOMAC A1 mean ± standard deviation pain scores at baseline were 6.4 ± 0.06 and 6.5 ± 0.07 in hylan G-F 20 single 6-mL injection and saline groups, respectively.

Walking pain

In both groups, WOMAC A1 scores significantly improved from baseline over 26 weeks and at every time point ($P < 0.0001$ vs baseline for hylan G-F 20 single 6-mL injection and saline); however, no statistically significant differences were observed between groups [Table II; Fig. 2(A)]. There were also no significant differences between groups when compared by imaging method (fluoroscopy or ultrasound) or by unilateral or bilateral hip OA.

Age, weight, and radiographic stage of arthritis also had no effect on response to treatment with a single 6-mL injection of hylan G-F 20 or saline as measured by change from baseline in WOMAC A1 over 26 weeks.

About half the subjects responded to injections, demonstrating clinically important reduction in pain (40.7–51.7% in the hylan G-F 20 single 6-mL injection group; 41.7–50.3% in the saline group) over 26 weeks [Fig. 2(B)], with no statistically significant differences between groups.

Hip pain, function, and subject global assessment of hip OA

WOMAC A, WOMAC C, and PTGA [Table II; Fig. 3(A)–(C)] also were significantly improved from baseline over 26 weeks and at every time point in both groups ($P < 0.0001$), with no significant differences between treatments. WOMAC A and PTGA, similar to WOMAC A1, showed no significant differences between groups when compared by imaging method or presence of unilateral or bilateral hip OA.

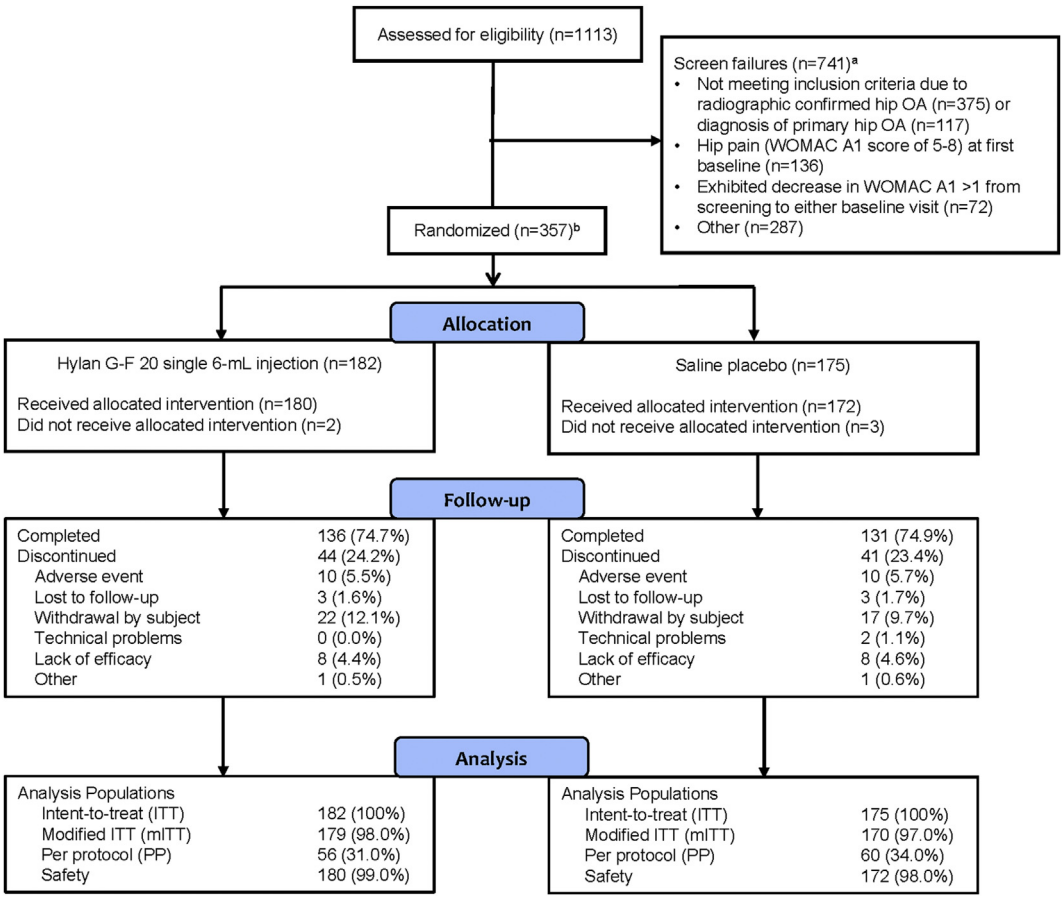

Fig. 1. Patient disposition. [a]Patient could have met more than one criterion. Most common reasons listed. [b]Five patients were screen failures and randomized by error. No treatment kit was dispensed.

Use of rescue medication

Rescue medication use was largely comparable between groups throughout the study; however, there was a statistically significant greater intake of acetaminophen in the hylan G-F 20 single 6-mL injection group vs saline at week 4 ($P = 0.0133$; Table III), corresponding with a greater number of days of rescue medication taken at the same time point ($P = 0.0078$; Table III). After Week 4, the amounts taken were not significantly different between groups. In addition, number of subjects taking NSAIDs since last visit was significantly greater in the saline group at week 16 vs hylan G-F 20 single 6-mL injection ($P = 0.0421$ [observed data without multiplicity adjustment]; Table III), but differences between groups were not significant at most time points after Week 4.

Post hoc analyses

Post hoc analyses on WOMAC A1, WOMAC A, and PTGA scores were performed in subgroups of subjects with or without potential neuropathic pain comorbidities [Fig. 4(A)–(F), n = number of patients] that might mask treatment effects. No statistically significant differences were found between hylan G-F 20 single 6-mL injection and saline-treated subjects on WOMAC A1, WOMAC A, and PTGA for any comparison in these subgroups at any time point.

Saline effect in WOMAC A1, WOMAC A, and PTGA (Fig. 4) was numerically greater in subjects with potential neuropathic pain comorbidities than without at weeks 8–20, whereas hylan G-F 20 single 6-mL injection effect was not much affected, regardless of presence of potential neuropathic pain comorbidities.

Safety and tolerability

Occurrence of TEAEs was similar in hylan G-F 20 single 6-mL injection and saline groups (Table IV). Most TEAEs were mild-to-moderate in severity. The event counts of target hip TEAEs and injection site reactions occurred in a greater percentage although not a statistically significant greater number of subjects treated with a single 6-mL injection of hylan G-F 20 vs saline. Arthralgia was the most common TEAE at the target hip. SAEs occurred in a greater percentage of subjects treated with saline vs hylan G-F 20 single 6-mL injection (15/172 [8.7%] and 10/182 [5.6%]) with only 1 of these (saline group; arthralgia) considered treatment-related.

Discussion

The current study demonstrated that both a single, 6-mL injection of hylan G-F 20 and a single 6-mL injection of saline significantly improved walking pain, hip pain, subject self-assessment of hip OA, and function at intervals up to 6 months after injection. About half the subjects in each treatment group responded to the injections, demonstrating clinically significant improvement. However, we were unable to identify any significant differences in any of the primary or secondary endpoints between the two treatments over 26 weeks or at any interval. Thus, this negative trial failed to show any significant difference between a single 6-mL injection of hylan G-F 20 and saline placebo on reducing pain or improving function in patients with painful, mild-to-moderate hip OA. Through a limited *post hoc* analysis, we were unable to identify any significant patient-specific factors that predicted response to either treatment. The

Table I
Patient demographics and baseline characteristics

Characteristic	Hylan G-F 20 single 6-mL injection (n = 182)	Saline (n = 175)	Total (N = 357)
Age, years*	60.8 ± 10.0	59.8 ± 8.8	60.3 ± 9.4
Male, n (%)	76 (41.8)	70 (40.0)	146 (40.9)
Race, n (%)			
White	166 (91.2)	164 (93.7)	330 (92.4)
Black or African American	14 (7.7)	10 (5.7)	24 (6.7)
Unknown	1 (0.5)	1 (0.6)	2 (0.6)
Not reported	1 (0.5)	0 (0)	1 (0.3)
Body mass index, kg/m^2*	30.9 ± 14.2	29.1 ± 7.6	30.0 ± 11.5
Prior medications	123 (67.6)	110 (62.9)	233 (65.3)
Kellgren–Lawrence grade at target hip, n (%)			
Grade 0	0 (0)	1 (0.6)†	1 (0.3)
Grade 1	0 (0)	0 (0)	0 (0)
Grade 2	71 (39.0)	63 (36.0)	134 (37.5)
Grade 3	111 (61.0)	111 (63.4)	222 (62.2)
Grade 4	0 (0)	0 (0)	0 (0)
Radiographically confirmed OA at contralateral hip, n (%)	51 (28.0)	45 (25.7)	96 (26.9)
If radiographically confirmed OA, then Kellgren–Lawrence grade at contralateral hip, n (%)			
Grade 0	7 (3.8)	7 (4.0)	14 (3.9)
Grade 1	22 (12.1)	12 (6.9)	34 (9.5)
Grade 2	15 (8.2)	17 (9.7)	32 (9.0)
Grade 3	5 (2.7)	9 (5.1)	14 (3.9)
Grade 4	1 (0.5)	0 (0)	1 (0.3)
Missing	1 (0.5)	0 (0)	1 (0.3)
Total number of patients reporting ≥1 term	51 (28.0)	47 (26.9)	98 (27.5)
Patients reporting each‡:			
Back pain, neuropathic or other musculoskeletal condition§, n (%)			
Fibromyalgia	3 (1.6)	2 (1.1)	5 (1.4)
Back pain	35 (19.2)	28 (16.0)	63 (17.6)
Intervertebral disc degeneration	9 (4.9)	8 (4.6)	17 (4.8)
Intervertebral disc disorder	0 (0)	2 (1.1)	2 (0.6)
Intervertebral disc protrusion	9 (4.9)	10 (5.7)	19 (5.3)
Lumbar spinal stenosis	4 (2.2)	2 (1.1)	6 (1.7)
Neuropathy peripheral	3 (1.6)	3 (1.7)	6 (1.7)
Sciatica	1 (0.5)	3 (1.7)	4 (1.1)
Arthrocentesis‖, n (%)	9 (5.0)	7 (4.1)	16 (4.5)
Image-guided needle placement‖, n (%)			
Fluoroscopy	159 (88.3)	152 (88.4)	311 (88.4)
Ultrasound	21 (11.7)	20 (11.6)	41 (11.6)

* Data are presented as mean ± standard deviation.
† Patient was randomized and included in the ITT population but was a protocol deviation. According to the Statistical Analysis Plan agreed upon with FDA, the patient could not be dropped from ITT analysis, but was dropped from per-protocol analysis and made no difference in the results.
‡ Some patients reported more than one condition.
§ Collectively refers to "potential neuropathic pain comorbidities" in the context.
‖ Data are based on the safety population; hylan G-F 20 single 6-mL injection (n = 180) and placebo (n = 172).

single injection of 6 mL of hylan G-F 20 was well tolerated: there were no differences in treatment-related AEs between groups. These findings are comparable to the open label trials, case reports, and a double-blind randomized clinical trial describing improvement in pain and function in hip OA with hylan G-F 20[12–16].

Painful hip OA is frustrating to treat. Many patients have pain and functional limitations but are not yet appropriate for surgery. Arthritis pain waxes and wanes, making clinical assessment difficult and confounding research efforts. Despite the many analgesic options, most drugs offer only modest benefit, and their use must be weighed against the very real risk of adverse effects[20–24].

In light of the limited efficacy and tolerability of currently available medications, and in the context of widespread adoption of office-based image-guided procedures, IA corticosteroid injections have recently become a standard recommendation for treating hip OA[20]. Clinical experience and published studies suggest IA steroids reliably reduce pain and improve function for 1–3 weeks[20]. There are some concerns about risk of deleterious effects on articular cartilage and peri-articular soft tissues[25]. Recent studies[26,27] also suggest a correlation between repeat hip steroid injections and arthroplasty infections.

Patient-specific issues may have confounded this study's results. Despite exclusion criteria, nearly a quarter of enrolled patients had a history of back pain, intervertebral disc disorders, sciatica, fibromyalgia and spinal stenosis, conditions that can be associated with hip pain of radicular or neurogenic etiology. Interestingly, saline injection reduced pain more in patients with these potentially "neurogenic" comorbidities than without. This observation is consistent with that reported in a trial using onabotulinumtoxinA and saline IA injection for knee OA, in which subjects with neuropathic pain responded much better in the saline vs onabotulinumtoxinA group[28]. Recently published Osteoarthritis Research Society International (OARSI) recommendations on design and conduct of clinical trials in patients with OA suggest trials be very explicit about restricting confounding comorbidities, and that pain outcome tools to characterize baseline pain subphenotype (such as neuropathic or nociceptive) may be useful to limit enrollment of placebo responders[29,30].

Although the treatment effects observed in both groups could be entirely placebo-mediated, the surprising robust reduction in pain following IA hip saline injection suggests saline performed as a treatment. Saline injections have demonstrated clinical efficacy in other OA models[31–33]. Moreover, placebo alone has shown efficacy in OA treatment studies. A large meta-analysis described placebo as an effective OA treatment, most effective for subjective outcomes such as pain scores and superior to non-treatment,

Table II
Change from baseline over 26 weeks and at analysis visits for WOMAC A1 and responder, WOMAC A, WOMAC C, and PGTA.

Characteristic	Hylan G-F 20 single 6-mL injection (n = 182)	Saline (n = 175)	Difference
WOMAC* A1			
Baseline			
Mean (S.E.M.)	6.42 (0.06)	6.48 (0.07)	
Change from baseline over 26 weeks			
LS mean (S.E.M.)	−2.19 (0.16)	−2.26 (0.17)	0.07 (0.23)
95% CI	(−2.51, −1.86)	(−2.59, −1.93)	(−0.38, 0.52)
p-value for the difference between groups			0.7462
P-value for the within-treatment comparison	<0.0001	<0.0001	
Change from baseline at week 4			
LS mean (S.E.M.)	−1.77 (0.16)	−1.95 (0.17)	0.19 (0.23)
95% CI	(−2.09, −1.44)	(−2.29, −1.62)	(−0.27, 0.64)
P-value for the difference between groups			0.4211
P-value for the within-treatment comparison	<0.0001	<0.0001	
Change from baseline at week 8			
LS mean (S.E.M.)	−2.27 (0.19)	−2.38 (0.19)	0.10 (0.27)
95% CI	(−2.65, −1.90)	(−2.76, −2.00)	(−0.42, 0.63)
P-value for the difference between groups			0.6985
P-value for the within-treatment comparison	<0.0001	<0.0001	
Change from baseline at week 12			
LS mean (S.E.M.)	−2.11 (0.19)	−2.37 (0.20)	0.26 (0.27)
95% CI	(−2.49, −1.73)	(−2.76, −1.98)	(−0.27, 0.80)
P-value for the difference between groups			0.3358
P-value for the within-treatment comparison	<0.0001	<0.0001	
Change from baseline at week 16			
LS mean (S.E.M.)	−2.47 (0.21)	−2.28 (0.21)	−0.19 (0.29)
95% CI	(−2.87, −2.06)	(−2.69, −1.87)	(−0.75, 0.38)
P-value for the difference between groups			0.5158
P-value for the within-treatment comparison	<0.0001	<0.0001	
Change from baseline at week 20			
LS mean (S.E.M.)	−2.29 (0.20)	−2.16 (0.20)	−0.13 (0.28)
95% CI	(−2.68, −1.90)	(−2.56, −1.77)	(−0.68, 0.41)
P-value for the difference between groups			0.6357
P-value for the within-treatment comparison	<0.0001	<0.0001	
Change from baseline at week 26			
LS mean (S.E.M.)	−2.21 (0.22)	−2.42 (0.23)	0.21 (0.31)
95% CI	(−2.65, −1.78)	(−2.87, −1.98)	(−0.40, 0.82)
P-value for the difference between groups			0.4997
P-value for the within-treatment comparison	<0.0001	<0.0001	
WOMAC* A1 responder†			
Over 26 weeks			
Responder	82 (45.05)	80 (45.71)	
Non-responder	65 (35.71)	63 (36.00)	
Estimate of common odds ratio			0.95
95% CI for odds ratio			(0.67, 1.34)
P-value			0.7708
At week 4			
Responder	75 (41.21)	80 (45.71)	
Non-responder	92 (50.55)	77 (44.00)	
Odds ratio			0.74
95% CI for odds ratio			(0.47, 1.17)
P-value			0.2031
At week 8			
Responder	94 (51.65)	85 (48.57)	
Non-responder	70 (38.46)	71 (40.57)	
Odds ratio			1.15
95% CI for odds ratio			(0.73, 1.81)
P-value			0.5554
At week 12			
Responder	85 (46.70)	88 (50.29)	
Non-responder	63 (34.62)	57 (32.57)	
Odds ratio			0.78
95% CI for odds ratio			(0.49, 1.23)
P-value			0.2854
At week 16			
Responder	86 (47.25)	80 (45.71)	
Non-responder	58 (31.87)	65 (37.14)	
Odds ratio			1.10
95% CI for odds ratio			(0.69, 1.76)
P-value			0.6815
At week 20			
Responder	81 (44.51)	73 (41.71)	
Non-responder	51 (28.02)	57 (32.57)	

Table II (*continued*)

Characteristic	Hylan G-F 20 single 6-mL injection (n = 182)	Saline (n = 175)	Difference
Odds ratio			1.24
95% CI for odds ratio			(0.77, 2.01)
P-value			0.3799
At week 26			
Responder	74 (40.66)	74 (42.29)	
Non-responder	59 (32.42)	53 (30.29)	
Odds ratio			0.81
95% CI for odds ratio			(0.49, 1.33)
P-value			0.4045
WOMAC A			
Baseline			
Mean (S.E.M.)	6.35 (0.07)	6.39 (0.08)	
Change from baseline over 26 weeks			
LS mean (S.E.M.)	−2.19 (0.16)	−2.26 (0.16)	0.07 (0.22)
95% CI	(−2.51, −1.88)	(−2.58, −1.94)	(−0.37, 0.51)
P-value for the difference between groups			0.7551
P-value for the within-treatment comparison	<0.0001	<0.0001	
Change from baseline at week 4			
LS mean (S.E.M.)	−1.83 (0.15)	−1.95 (0.16)	0.12 (0.22)
95% CI	(−2.14, −1.53)	(−2.27, −1.64)	(−0.30, 0.54)
P-value for the difference between groups			0.5753
P-value for the within-treatment comparison	<0.0001	<0.0001	
Change from baseline at week 8			
LS mean (S.E.M.)	−2.27 (0.19)	−2.36 (0.19)	0.09 (0.26)
95% CI	(−2.63, −1.90)	(−2.73, −1.98)	(−0.43, 0.61)
P-value for the difference between groups			0.7344
P-value for the within-treatment comparison	<0.0001	<0.0001	
Change from baseline at week 12			
LS mean (S.E.M.)	−2.12 (0.18)	−2.44 (0.19)	0.32 (0.26)
95% CI	(−2.48, −1.76)	(−2.81, −2.07)	(−0.19, 0.83)
P-value for the difference between groups			0.2140
P-value for the within-treatment comparison	<0.0001	<0.0001	
Change from baseline at week 16			
LS mean (S.E.M.)	−2.42 (0.20)	−2.32 (0.20)	−0.10 (0.27)
95% CI	(−2.80, −2.03)	(−2.71, −1.93)	(−0.64, 0.44)
P-value for the difference between groups			0.7180
P-value for the within-treatment comparison	<0.0001	<0.0001	
Change from baseline at week 20			
LS mean (S.E.M.)	−2.28 (0.19)	−2.20 (0.19)	−0.07 (0.27)
95% CI	(−2.65, −1.90)	(−2.58, −1.82)	(−0.60, 0.45)
P-value for the difference between groups			0.7817
P-value for the within-treatment comparison	<0.0001	<0.0001	
Change from baseline at week 26			
LS mean (S.E.M.)	−2.23 (0.21)	−2.30 (0.22)	0.06 (0.30)
95% CI	(−2.65, −1.82)	(−2.72, −1.87)	(−0.52, 0.65)
P-value for the difference between groups			0.8352
P-value for the within-treatment comparison	<0.0001	<0.0001	
WOMAC C*			
Baseline			
Mean (S.E.M.)	6.33 (0.09)	6.44 (0.08)	
Change from baseline over 26 weeks			
LS mean (S.E.M.)	−2.05 (0.16)	−2.11 (0.16)	0.06 (0.22)
95% CI	(−2.37, −1.73)	(−2.43, −1.78)	(−0.38, 0.50)
P-value for the difference between groups			0.7894
P-value for the within-treatment comparison	<0.0001	<0.0001	
Change from baseline at week 4			
LS mean (S.E.M.)	−1.81 (0.16)	−1.83 (0.16)	0.02 (0.22)
95% CI	(−2.12, −1.49)	(−2.15, −1.50)	(−0.42, 0.46)
P-value for the difference between groups			0.9304
P-value for the within-treatment comparison	<0.0001	<0.0001	
Change from baseline at week 8			
LS mean (S.E.M.)	−2.14 (0.18)	−2.23 (0.19)	0.09 (0.26)
95% CI	(−2.50, −1.78)	(−2.60, −1.86)	(−0.42, 0.60)
P-value for the difference between groups			0.7226
P-value for the within-treatment comparison	<0.0001	<0.0001	
Change from baseline at week 12			
LS mean (S.E.M.)	−1.94 (0.19)	−2.28 (0.19)	0.34 (0.26)
95% CI	(−2.30, −1.57)	(−2.65, −1.90)	(−0.17, 0.85)
P-value for the difference between groups			0.1916
P-value for the within-treatment comparison	<0.0001	<0.0001	
Change from baseline at week 16			
LS mean (S.E.M.)	−2.27 (0.20)	−2.17 (0.20)	−0.09 (0.27)

(*continued on next page*)

Table II (*continued*)

Characteristic	Hylan G-F 20 single 6-mL injection (n = 182)	Saline (n = 175)	Difference
95% CI	(−2.65, −1.88)	(−2.57, −1.78)	(−0.63, 0.45)
P-value for the difference between groups			0.7394
P-value for the within-treatment comparison	<0.0001	<0.0001	
Change from baseline at week 20			
LS mean (S.E.M.)	−2.05 (0.19)	−2.01 (0.20)	−0.05 (0.27)
95% CI	(−2.43, −1.67)	(−2.40, −1.62)	(−0.58, 0.49)
P-value for the difference between groups			0.8658
P-value for the within-treatment comparison	<0.0001	<0.0001	
Change from baseline at week 26			
LS mean (S.E.M.)	−2.09 (0.21)	−2.13 (0.21)	0.05 (0.29)
95% CI	(−2.50, −1.68)	(−2.55, −1.71)	(−0.53, 0.63)
P-value for the difference between groups			0.8753
P-value for the within-treatment comparison	<0.0001	<0.0001	
PTGA[‡]			
Baseline			
Mean (S.E.M.)	6.45 (0.08)	6.52 (0.09)	NA (NA)
Change from baseline over 26 weeks			
LS mean (S.E.M.)	−2.00 (0.16)	−2.06 (0.17)	0.06 (0.23)
95% CI	(−2.32, −1.68)	(−2.38, −1.73)	(−0.39, 0.50)
P-value for the difference between groups			0.7977
P-value for the within-treatment comparison	<0.0001	<0.0001	
Change from baseline at week 4			
LS mean (S.E.M.)	−1.68 (0.16)	−1.89 (0.17)	0.21 (0.23)
95% CI	(−2.00, −1.36)	(−2.22, −1.56)	(−0.24, 0.66)
P-value for the difference between groups			0.3664
P-value for the within-treatment comparison	<0.0001	<0.0001	
Change from baseline at week 8			
LS mean (S.E.M.)	−2.16 (0.19)	−2.31 (0.20)	0.15 (0.27)
95% CI	(−2.54, −1.79)	(−2.69, −1.92)	(−0.38, 0.67)
P-value for the difference between groups			0.5852
P-value for the within-treatment comparison	<0.0001	<0.0001	
Change from baseline at week 12			
LS mean (S.E.M.)	−1.84 (0.19)	−2.19 (0.19)	0.34 (0.27)
95% CI	(−2.22, −1.47)	(−2.57, −1.81)	(−0.18, 0.86)
P-value for the difference between groups			0.1944
P-value for the within-treatment comparison	<0.0001	<0.0001	
Change from baseline at week 16			
LS mean (S.E.M.)	−2.28 (0.20)	−2.09 (0.21)	0.19 (0.28)
95% CI	(−2.68, −1.88)	(−2.49, −1.68)	(−0.75, 0.37)
P-value for the difference between groups			0.5013
P-value for the within-treatment comparison	<0.0001	<0.0001	
Change from baseline at week 20			
LS mean (S.E.M.)	−1.97 (0.21)	−1.78 (0.21)	−0.19 (0.29)
95% CI	(−2.38, −1.56)	(−2.19, −1.36)	(−0.76, 0.38)
P-value for the difference between groups			0.5143
P-value for the within-treatment comparison	<0.0001	<0.0001	
Change from baseline at week 26			
LS mean (S.E.M.)	−2.07 (0.22)	−2.11 (0.23)	0.03 (0.32)
95% CI	(−2.52, −1.63)	(−2.55, −1.66)	(−0.59, 0.65)
P-value for the difference between groups			0.9193
P-value for the within-treatment comparison	<0.0001	<0.0001	

CI = confidence interval; LS = least-squares; NA = not applicable; NRS = Numeric Rating Scale; PGTA = Patient Global Self-Assessment; SE = standard error; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

[*] WOMAC NRS 3.1 questionnaire (11-point NRS). The analysis is based on a mixed model repeated measures approach with treatment group, pooled study site, analysis visit week (4, 8, 12, 16, 20, 26), treatment-by-analysis visit week interaction as factors and baseline score and baseline-by-analysis visit week interaction as covariates.

[†] ≥2-point improvement on NRS. The analysis is based on a generalized estimating equations (GEE) model for binary outcomes [the WOMAC A1 responder status = Yes/No for each patient at each analysis visit] using the SAS procedure PROC GENMOD with treatment group, pooled study site, analysis visit week (4, 8, 12, 16, 20, 26), and treatment-by-analysis visit week interaction as factors and baseline WOMAC A1 score as covariate. The odds ratio estimates and 95% CIs for the odds ratios are obtained from the analysis.

[‡] 11-point NRS.

with major placebo effect determinants as active treatment thought to be baseline severity, route of delivery, and sample size[34].

The intra-articular injection method used in this study may also explain the robust results in both the treatment and placebo groups. Recent network meta-analyses of knee OA trials compared effectiveness of alternative types of placebo delivery[35] and placebo vs other pharmacologic treatments[36]. IA and topical placebo showed significantly greater effect sizes than oral placebo[35]. IA placebo also produced an effect size appreciably greater than acetaminophen[35] and no oral NSAIDs analyzed had an effect size significantly greater than IA placebo[36]. Our study may be interpreted as showing no difference between two IA treatments, yet because of delivery system both imparted robust results.

Finally, in light of the discussion above, further consideration may be required regarding outcome measures in clinical trials of OA treatments. The current study used subjective measures of pain, function, and OA severity, making results subject to placebo effects and other effects inherent with subjective measures. Including a more objective outcome measure, such as the 6-min walk test[37],

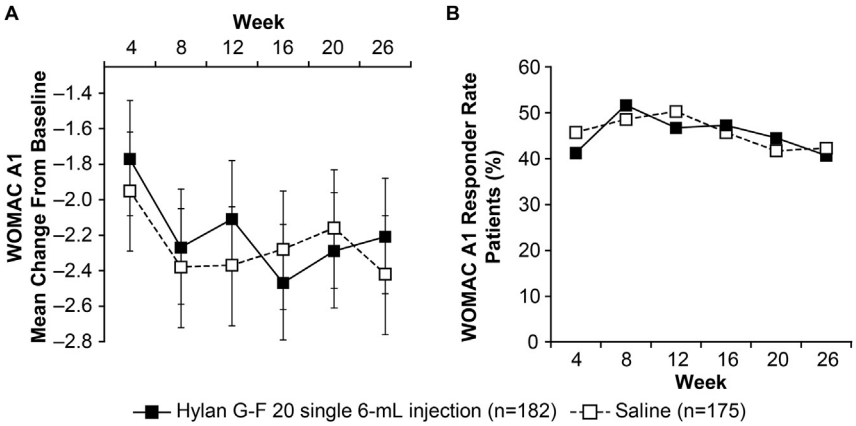

Fig. 2. WOMAC A1. (A) Mean change from baseline, and (B) responder rates over 26 weeks. Data are presented as least squares means ± 95% confidence intervals. Responder rate defined as ≥ 2 point change in WOMAC A1 numeric rating scale [NRS]. $P < 0.0001$ vs baseline in WOMAC A1 over 26 weeks and for all time points in both groups. WOMAC = Western Ontario and McMaster Universities Index.

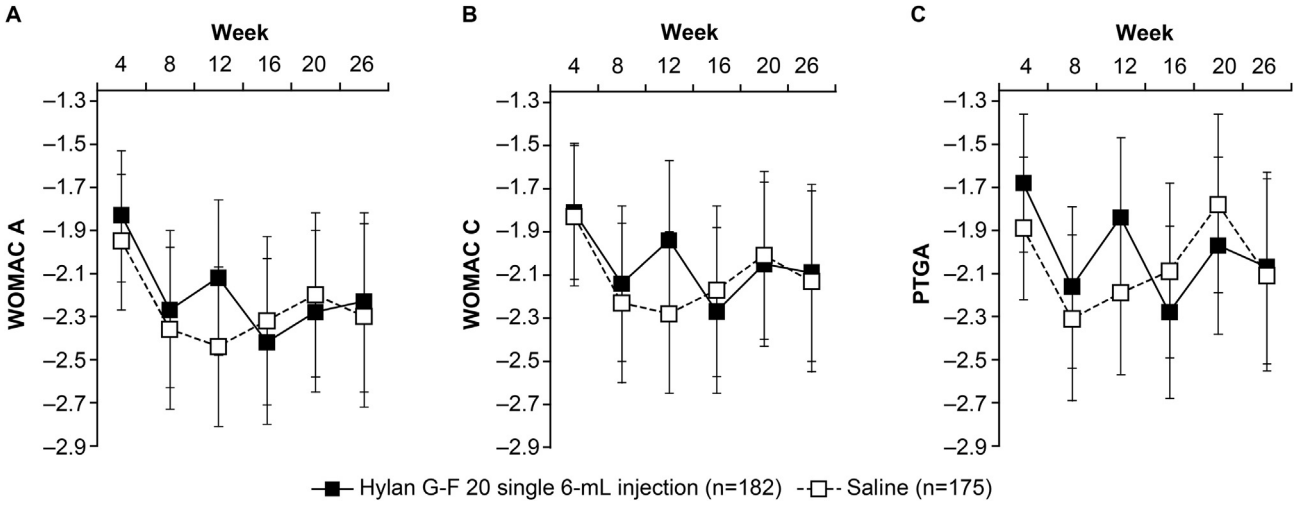

Fig. 3. Mean change from baseline over 26 weeks in (A) WOMAC A, (B) WOMAC C, and (C) PTGA scores. Data are presented as least squares means ± 95% confidence intervals. $P < 0.0001$ vs baseline in WOMAC A, PTGA, and WOMAC C for all time points in both groups. PTGA = Patient Global Self-Assessment; WOMAC = Western Ontario and McMaster Universities Index.

which has been found to be a reliable measure of functional performance in patients following total-hip arthroplasty[38], may also better capture treatment effects in future studies.

The advent of Internet- and mobile-based applications in health care has generated recent interest in real-time assessment and feedback to patients to improve health outcomes, which may supplement or, in some cases, supplant more subjective assessments. For example, a seminal study in the use of mHealth technology (i.e., the use of a mobile app for health care) to monitor physical activity in real time and improve outcomes for knee OA

Table III
NSAID and rescue medication use

Week	Acetaminophen use Milligrams, mean (SD)		Acetaminophen use Days, mean (SD)		NSAID use Since Last Visit n (%)	
	Hylan G-F 20 single 6-mL injection	Saline	Hylan G-F 20 single 6-mL injection	Saline	Hylan G-F 20 single 6-mL injection	Saline
4	7543.1 (13393.8)*	5171.3 (12263.2)	5.5 (7.2)†	3.7 (6.3)	50 (27.5)	40 (22.9)
8	7091.5 (14399.5)	6588.8 (18264.9)	4.9 (7.4)	4.0 (7.6)	43 (23.6)	35 (20.0)
12	6269.4 (17336.6)	5048.8 (12770.6)	4.0 (7.1)	3.4 (6.1)	37 (20.3)	34 (19.4)
16	5788.1 (15320.7)	4057.5 (9681.3)	4.0 (7.5)	3.2 (6.0)	23 (12.6)‡	38 (21.7)
20	4582.9 (11793.2)	3730.1 (9774.4)	3.1 (5.6)	2.9 (6.1)	28 (15.4)	26 (14.9)
26	7426.3 (26202.3)	4836.5 (12306.7)	4.1 (8.8)	3.9 (8.1)	33 (18.1)	37 (21.1)

NSAID = non-steroidal anti-inflammatory drugs; SD = standard deviation.
* $P = 0.0133$.
† $P = 0.0078$.
‡ $P = 0.0421$ vs placebo.

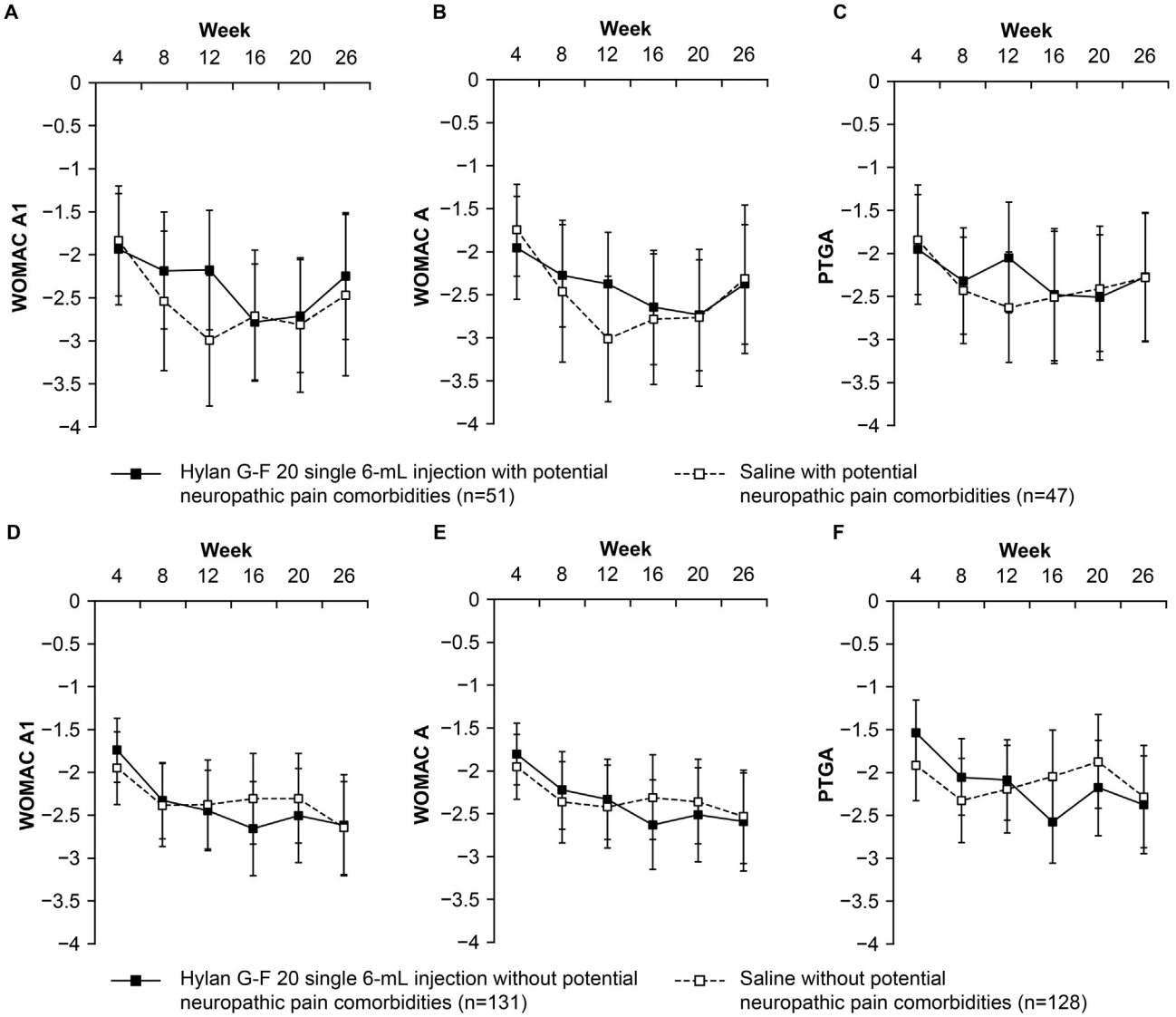

Fig. 4. Mean change from baseline in (A, D) WOMAC A1, (B, E) WOMAC A, and (C, F) PTGA in patients with potential neuropathic comorbidities (A–C) or without (D–F). Data are presented as means of observed cases from the intent-to-treat population ±95% confidence intervals where n = number of patients. PTGA = Patient Global Self-Assessment; WOMAC = Western Ontario and McMaster Universities Index.

Table IV
Patient counts with treatment-emergent adverse events (TEAEs)

n (%)	Hylan G-F 20 single 6-mL injection (n = 180)	Saline (n = 172)	*P*-value
Patients with TEAEs	98 (54.4)	87 (50.6)	0.536
Treatment-related AEs	25 (13.9)	15 (8.7)	0.174
Treatment-related AEs at the target hip	23 (12.8)	12 (7.0)	0.101
Injection site reactions[*]	13 (7.2)	4 (2.3)	0.058
Patients discontinuing due to AEs	10 (5.5)	10 (5.7)	
Treatment-emergent adverse events >2% at the target hip[†]			
Arthralgia	22 (12.2)	21 (12.2)	0.999
Injection site joint pain	8 (4.4)	3 (1.7)	0.251
Osteoarthritis[‡]	5 (2.8)	5 (2.9)	0.999
Injection site pain	4 (2.2)	1 (0.6)	0.395
Groin pain	4 (2.2)	0	0.143

TEAE = treatment-emergent adverse event; adverse event reported during or following administration of hylan G-F 20 single 6-mL injection or saline.
Multiple occurrences of the same TEAE in the same patient were counted only once for calculating patient frequency of AEs.
P-values are from *post hoc* comparisons of frequencies using the Chi-square test, with no multiplicity adjustment.

[*] Number of patients reporting injection site reactions at the target hip includes: injection site joint pain – 6 hylan G-F 20 single 6-mL injection, 3 saline; injection site pain – 2 hylan G-F 20 single 6-mL injection, 1 saline; neuralgia – 1 saline; erythema – 1 hylan G-F 20 single 6-mL injection; arthralgia, musculoskeletal stiffness, and myalagia – 1 each for hylan G-F 20 single 6-mL injection. In other than the target hip; neuralgia – 1 hylan G-F 20 single 6-mL injection.

[†] Safety set.

[‡] 9 of 10 reported TEAEs of osteoarthritis were judged not related to treatment; 1 TEAE of osteoarthritis in the hylan G-F 20 single 6-mL injection group judged related to treatment was a self-limited transient post-injection flare.

patients treated with hylan G-F 20 showed a positive impact on increasing mobility parameters of steps per day and pain[39].

Hyaluronic acid injections appear to be safe and effective alternatives to steroid injections, particularly in knee OA. For example, approximately 14 million patients have received hylan G-F 20 (data on file). More limited evidence exists showing hylan G-F 20 given as 2-mL injections is also safe, well-tolerated, and effective for hip OA[12,15,16]. In our study, which used a single 6-mL injection of hylan G-F 20, statistically and clinically relevant improvements in pain and function at intervals up to 6 months were seen; however, there was no discernible difference compared with saline placebo.

Author contributions

All authors contributed to the acquisition, analysis, or interpretation of data and the drafting and/or critical revision of the manuscript. VB and AV conceived and designed the study. VB, NS, and RJP provided study materials and patients. RJP and G-LJ provided technical and/or administrative/logistical support. BA provided statistical expertise. AV served as the study director, engaged study sites, provided oversight of study execution through completion of enrollment and served as the medical monitor for the study.

Victoria Brander (vabrander@gmail.com), Guang-Liang Jiang (Leon.Jiang@sanofi.com), and Anna Vardanyan (Anna.Vardanyan@sanofi.com) take responsibility for the integrity of the work as a whole from inception to finished article.

Competing interest statement

Victoria Brander has served as an investigator and as a lecturer for Sanofi; Nebojsa Skrepnik has been a consultant for Sanofi and Orthofix; Robert J. Petrella served as an investigator for Sanofi; Guang-Liang Jiang, Beverly Accomando, and Anna Vardanyan are employees of Sanofi.

Role of the funding source

Sanofi Biosurgery, LLC funded the study. Sanofi authors were involved in the study design, collection, analysis and interpretation of data, and in the writing and decision to submit the manuscript for publication.

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