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Efficacy and safety of fasinumab in an NSAID-controlled study in patients with pain due to osteoarthritis of the knee or hip

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Abstract

Objective Osteoarthritis (OA) causes significant musculoskeletal pain. This study assessed the efficacy and safety of fasinumab, an investigational nerve growth factor inhibitor, in patients with moderate-to-severe OA pain of the knee/hip.

Methods In this Phase 3, randomized, double-blind, placebo- and non-steroidal anti-inflammatory drug (NSAID)-controlled study, patients with OA (Kellgren-Lawrence grade ≥ 2; Western Ontario and McMaster Universities Arthritis Index [WOMAC] pain score ≥ 4) received (2:1:1:1) fasinumab 1 mg every 4 weeks, diclofenac 75 mg twice daily, celecoxib 200 mg daily, or placebo for 24 weeks. Co-primary endpoints were change in WOMAC pain and physical function scores to Week 24 versus placebo. For safety, joints were imaged in all patients at pre-specified times, regardless of symptoms.

Results Of 4531 patients screened, 1650 were randomized. At Week 24, greater improvements were observed for fasinumab versus placebo; least-squares mean difference: −0.63 ($p = 0.0003$) for WOMAC pain and −0.64 ($p = 0.0003$) for physical function. Improvements were numerically greater for fasinumab versus NSAIDs for physical function (−0.64 versus −0.31; nominal $p < 0.05$) and pain (−0.63 versus − 0.39; p = NS). Adjudicated arthropathies occurred in 1.6% of placebo-treated, 1.5% of NSAID-treated, and 5.6% of fasinumab-treated patients; joint replacements occurred in 3.6% of placebo-treated, 4.8% of NSAID-treated, and 3.4% of fasinumab-treated patients.

Conclusion Fasinumab significantly improved WOMAC pain and physical function scores versus placebo in < 24 weeks in difficult-to-treat patients with pain due to OA of the knee/hip. Adjudicated arthropathies were more frequent with fasinumab; there were no differences in the proportions of patients with joint replacements.

Trial registration Clinicaltrials.gov NCT03304379. Date of first registration: October 2, 2017.

Keywords Fasinumab, NGF inhibitor, NSAID, Osteoarthritis, Pain

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Introduction

Osteoarthritis (OA) is a significant cause of chronic musculoskeletal pain, and represents a leading cause of disability, morbidity, reduced quality of life, and societal cost [1–3]. Non-steroidal anti-inflammatory drugs (NSAIDs) are the mainstay of pharmacological treatment for patients with chronic pain due to OA [4–7]. Their use is limited not only by common adverse events (AEs) such as dyspepsia and hypertension, but also by serious, potentially life-threatening AEs such as gastrointestinal bleeding, increased risk of myocardial infarction, congestive heart failure, and renal events [8–13]. Therefore, a patient's particular underlying comorbidities may make NSAIDs a poor choice for treatment of their pain.

Fasinumab and other nerve growth factor (NGF) inhibitors have consistently shown effectiveness in the treatment of OA pain in randomized clinical trials [14–17]; however, they have been associated with joint-related AEs of unclear etiology (referred to as adjudicated arthropathies [AAs]), which have affected their development [16].

This study evaluated the efficacy and safety of fasinumab compared with both placebo and maximally dosed daily oral NSAIDs in patients with OA of the knee or hip. Given that response to placebo in pain trials is highly variable, even when study designs are similar [18, 19], the inclusion of active comparators with well-established efficacy can serve as an important benchmark to assist in gauging the efficacy of treatment.

Patients and methods study design

This was a Phase 3, multi-center, randomized, double-blind, placebo- and NSAID-controlled study conducted in North America, Europe, and South Africa (NCT03304379; date of first registration: October 2, 2017). The study consisted of a screening period of up to 30 days, a 7 − 10-day pre-randomization/washout period (7 days with a + 3-day window), a 24-week treatment period, a 20-week follow-up period, and phone contact 1 year after the last dose of the study drug (Supplementary Fig. 1). Randomized patients were assigned 2:1:1:1 to fasinumab 1 mg subcutaneous (SC) every 4 weeks (Q4W) (Regeneron Pharmaceuticals, Inc.), diclofenac 75 mg oral twice daily (Teva/Actavis), celecoxib 200 mg oral once daily (Teva/Actavis), or placebo. Treatment was blinded using a double dummy design with SC placebo and over-encapsulation of celecoxib, diclofenac, and oral placebo. Further details on randomization and blinding of treatment are provided in the Supplementary Appendix. The study initially included two additional arms of higher fasinumab doses (6 mg every 8 weeks and 3 mg Q4W); however, these arms were terminated in May 2018 due to joint-related AE rates in a separate study [20]. See the Supplementary Appendix **f**or details.

Inclusion and exclusion criteria

Eligible patients (aged ≥ 18 years) had a clinical diagnosis of OA of the knee or hip based on the American College of Rheumatology criteria, radiologic evidence of OA (Kellgren-Lawrence grade [KLG] ≥ 2 at the joint under evaluation [index joint] [21]), an average Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score ≥ 4 in the index joint at both screening and baseline visits [22], and were taking/tolerating standard doses of NSAIDs. See the Supplementary Appendix for exclusion criteria and details regarding failure of prior therapies.

Efficacy evaluation

The co-primary efficacy endpoints were changes in the WOMAC pain and physical function subscale scores from baseline to Week 24 in the index joint of patients treated with fasinumab versus those treated with placebo. We employed the WOMAC 11-point numeric scale, with scoring ranging from 0–10 with the average response to five questions for the pain subscale, and 17 questions for the physical function subscale [22]. Both endpoints were required to be met to consider the results positive for the study population. See the Supplementary Appendix for other efficacy endpoints.

Safety evaluation

Safety assessments included monitoring of treatment-emergent AEs (TEAEs), AEs of special interest (AESIs), vital signs, and radiologic and laboratory tests. See Supplementary Methods for details.

Arthropathies and joint replacements

Radiologic images performed at screening (X-rays of both knees, both hips, and both shoulders, as well as magnetic resonance imaging [MRI] of index, contra-lateral, and KLG ≥ 3 joints) excluded patients who may be at higher risk for arthropathy due to the presence of pre-existing severe articular bone pathology, and served as a baseline to monitor joint safety for all randomized patients.

An independent, blinded adjudication committee, composed of musculoskeletal radiologists, adjudicated radiographic images for arthropathies. Radiographs were obtained prospectively of shoulders, hips, and knees at regularly scheduled times (16, 24, and 44 weeks) during both the dosing and follow-up periods, regardless of whether the patient had joint pain. All images were then evaluated by independent central readers; any findings suspicious for arthropathy (e.g. excessive joint space narrowing [JSN] or deterioration in the articular surface)

were escalated to the adjudication committee for review. The following images were evaluated by the adjudication committee (which typically requested an MRI for comparison with baseline images): routine scheduled images escalated by the central readers, unscheduled images prompted by joint symptoms, and preoperative images from patients undergoing joint replacement (JR).

All study treatment was temporarily withheld from the patient while awaiting the outcome of arthropathy adjudication. Adjudications were based purely on radiologic findings, without any consideration of clinical circumstances. Definitions for adjudicated events have been previously defined [14]; in brief, the following were comprised under the umbrella term of AA: 1) rapidly progressive OA type 1 (RPOA-1), defined as JSN on X-ray associated with cartilage thinning or loss on MRI (if an MRI could not be obtained, determination was based on X-ray alone); 2) rapidly progressive OA type 2 (RPOA-2), defined as limited/focal articular collapse primarily observed on MRI, and not necessarily on radiography; 3) primary osteonecrosis; and 4) subchondral insufficiency fracture. More than one subtype could have been adjudicated within the same joint simultaneously or with sequential imaging. If the adjudication committee determined the findings to be suggestive of AA, the study drug was discontinued permanently and, per protocol, patients were referred to an orthopedist.

AA events were also evaluated to determine whether they met the criteria for destructive arthropathy (DA). DAs were defined as abnormal bone fragmentation, destruction, or fracture over a short period of time, including near-total or total collapse of an articular surface and evident unequivocally on X-ray. This category was included to highlight the most severe events akin to those described at the US Food and Drug Administration 2012 Arthritis Advisory Committee [23].

See the Supplementary Appendix for details of post hoc MRI whole organ analysis, which was conducted to evaluate articular cartilage in RPOA-1 cases.

Pharmacokinetics and immunogenicity analyses

See the Supplementary Appendix for details.

Statistical analyses

Baseline demographics, clinical characteristics, and analgesic history of the full analysis set (FAS; all randomized patients, based on the treatment allocated 'as randomized') were described as summary statistics. The co-primary endpoints were assessed in the FAS and modified full analysis set (mFAS; which excluded 219 patients from four sites with suspected or established good clinical practice violations) populations. Other efficacy-related endpoints were assessed for the FAS. For analysis of categorical variables in secondary endpoints (e.g. proportions of patients with ≥ 30% improvement in WOMAC pain subscale scores at Week 24), the Cochran-Mantel–Haenszel approach stratified by the randomization strata was used, with missing data considered as non-response.

A sequential rejective multiple-test procedure was applied to control the overall type I error of the study at 0.05 [24] for the co-primary and key secondary endpoints.

The incidence rates for AAs and corresponding two-sided 95% confidence intervals (CIs) were estimated. On-study AEs, serious AEs (SAEs), AESIs, TEAEs, AEs by system organ class and preferred term, and AEs of fracture (other than subchondral insufficiency fractures [SIFs] and tooth fractures) of the safety analysis set (SAF; i.e. all randomized patients from the FAS who received any study drug) were described by summary statistics.

Please see the Supplementary Appendix for further details on the statistical analysis of this study.

Results

Patient disposition

The study was conducted from October 2017 to November 2020. During this period, 4531 patients were screened and 1650 were randomized to the study (Supplementary Fig. 2). Of the patients randomized, 308 were allocated to the placebo group, 612 to the combined NSAIDs group (diclofenac or celecoxib), and 612 to the fasinumab 1 mg Q4W group.

Demographic and clinical characteristics

The demographic and clinical characteristics of the FAS population were generally similar across the treatment groups (Table 1), and were consistent with an advanced, difficult-to-treat population with OA [25, 26]. Overall, most participants were female (70.2%) and White (65.6%), with a mean (standard deviation [SD]) age of 62.2 (9.3) years and a mean (SD) body mass index of 31.1 (4.7) kg/m^2. Most patients (90.3%) had a knee as the index joint and 22.0% had a baseline KLG of 4, indicating end-stage, bone-on-bone disease. The mean (SD) duration of existing OA prior to enrollment was 9.0 (8.1) years and the mean (SD) WOMAC pain subscale score at baseline for the index joint was 6.4 (1.3), indicating moderate-to-severe pain. Analgesic history was also consistent across the treatment groups: almost all patients had previously taken acetaminophen (99.9%) or an NSAID (100%), and 75.0% had reported previous and/or current use of opioids for OA pain.

Table 1 Baseline demographic and disease characteristics (FAS)

	Placebo (*n* = 308)	NSAIDs (*n* = 612)	Fasinumab 1 mg Q4W (*n* = 612)	Total (*N* = 1532)
Age, years, mean (SD)	62 (9.3)	62 (9.4)	62 (9.1)	62.2 (9.3)
Age group, years, n (%)				
18–64	196 (63.6)	371 (60.6)	367 (60.0)	934 (61.0)
65–74	79 (25.6)	181 (29.6)	193 (31.5)	453 (29.6)
≥ 75	33 (10.7)	60 (9.8)	52 (8.5)	145 (9.5)
Sex, n (%)				
Male	86 (27.9)	194 (31.7)	176 (28.8)	456 (29.8)
Female	222 (72.1)	418 (68.3)	436 (71.2)	1076 (70.2)
Body mass index, kg/m^2, mean (SD)	31.1 (4.8)	31.1 (4.8)	31.2 (4.7)	31.1 (4.7)
Index joint in EDC, n (%)				
Knee	276 (89.6)	553 (90.4)	554 (90.5)	1383 (90.3)
Hip	32 (10.4)	59 (9.6)	58 (9.5)	149 (9.7)
KLG for index joint in EDC, n (%)				
0	1 (0.3)	0	0	1 (< 0.1)
1	0	1 (0.2)	0	1 (< 0.1)
2	111 (36.0)	212 (34.6)	198 (32.4)	521 (34.0)
3	127 (41.2)	267 (43.6)	278 (45.4)	672 (43.9)
4	69 (22.4)	132 (21.6)	136 (22.2)	337 (22.0)
WOMAC pain subscale score of index joint, mean (SD)	6.4 (1.4)	6.4 (1.3)	6.5 (1.3)	6.4 (1.3)
Duration of OA at baseline, years, mean (SD)	9.9 (8.3)	8.8 (8.1)	8.7 (8.0)	9.0 (8.1)
Analgesic history, n (%)				
NSAID				
Ever taken for OA	308 (100)	612 (100)	612 (100)	1532 (100)
Currently taking at screening for OA	308 (100)	612 (100)	612 (100)	1532 (100)
Acetaminophen				
Ever taken acetaminophen for pain due to OA of the knee or hip	308 (100)	611 (99.8)	612 (100)	1531 (99.9)
Opioid or tramadol				
Ever/current use of opioids for OA	222 (72.1)	468 (76.5)	459 (75.0)	1149 (75.0)

EDC Electronic data capture, *FAS* Full analysis set, *KLG* Kellgren-Lawrence grade, *NSAID* Non-steroidal anti-inflammatory drug, *OA* Osteoarthritis, *Q4W* Every 4 weeks, *SD* Standard deviation, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

Efficacy

WOMAC pain and physical function subscale scores: fasinumab versus placebo

Baseline WOMAC pain and physical function subscale scores in the index joints were similar across treatment groups for both the FAS and mFAS populations (Table 2). The results described below are in the FAS population unless otherwise specified.

At Week 24, a statistically significant treatment effect was observed in the fasinumab 1 mg Q4W group compared with placebo for both WOMAC pain and physical function subscale scores of the index joint: the least-squares (LS) mean difference versus placebo was −0.63 ($p = 0.0003$, 95% CI: −0.97, −0.29) for WOMAC pain and −0.64 ($p = 0.0003$, 95% CI: −0.98, −0.29) for physical function.

The co-primary endpoint was also analyzed using the mFAS population. Once again, at Week 24, a greater change from baseline was observed in the fasinumab 1 mg Q4W group compared with placebo for both WOMAC pain and physical function subscale scores: the LS mean difference versus placebo was −0.77 (nominal $p \leq 0.0001$, 95% CI: −1.15, −0.38; standardized effect size 0.37) for pain and −0.82 (nominal $p < 0.0001$, 95% CI: −1.20, −0.44; standardized effect size 0.39) for physical function.

A greater proportion of patients showed a clinically meaningful benefit of treatment with fasinumab at Week 24 compared with placebo, as indicated by a ≥ 30% improvement in the WOMAC pain subscale score of the index joint (59.8% versus 48.7%; odds ratio versus placebo 1.581; $p = 0.0013$) (Fig. 1A). A higher proportion of patients in the fasinumab 1 mg Q4W group compared with placebo also had ≥ 50% (nominal $p = 0.0061$) and ≥ 70% (nominal $p = 0.0018$) reductions from baseline to Week 24 in the WOMAC pain subscale.

Table 2 Change from baseline to Week 24 in the WOMAC pain and physical function subscale scores versus placebo and NSAIDs

	FAS			mFAS		
	Placebo (*n* = 308)	**NSAIDs (*n* = 612)**	**Fasinumab 1 mg Q4W (*n* = 612)**	**Placebo (*n* = 264)**	**NSAIDs (*n* = 525)**	**Fasinumab 1 mg Q4W (*n* = 524)**
WOMAC pain subscale						
Baseline score						
Patients, n	308	611	612	264	524	524
Mean (SD)	6.42 (1.39)	6.38 (1.34)	6.46 (1.32)	6.38 (1.48)	6.38 (1.41)	6.47 (1.39)
Median (range)	6.40 (1.2, 10.0)	6.40 (1.4, 10.0)	6.40 (1.0, 10.0)	6.20 (1.2, 10.0)	6.40 (1.4, 10.0)	6.40 (1.0, 10.0)
Week 24 score						
Patients, n	208	427	439	173	364	372
Mean (SD)	3.74 (2.22)	3.25 (2.17)	3.00 (2.10)	3.95 (2.22)	3.40 (2.19)	3.12 (2.12)
Median (range)	3.40 (0.0, 9.6)	3.20 (0.0, 9.6)	2.80 (0.0, 9.2)	3.80 (0.0, 9.6)	3.20 (0.0, 9.6)	2.90 (0.0, 9.2)
Change from baseline						
Patients, n	208	426	439	173	363	372
Mean (SD)	−2.63 (2.13)	−3.12 (2.21)	−3.47 (2.10)	−2.39 (2.08)	−2.97 (2.22)	−3.36 (2.12)
Median (range)	−2.60 (−8.4, 3.6)	−3.10 (−8.6, 2.8)	−3.60 (−10.0, 2.4)	−2.40 (−8.4, 3.6)	−3.00 (−8.6, 2.8)	−3.40 (−10.0, 2.4)
LS mean (SE)	−2.21 (0.17)	−2.60 (0.13)	−2.84 (0.13)	−2.01 (0.18)	−2.48 (0.14)	−2.78 (0.14)
95% CI	−2.53, −1.89	−2.85, −2.35	−3.09, −2.59	−2.36, −1.65	−2.75, −2.21	−3.05, −2.50
Difference versus placebo						
LS mean (SE)	-	−0.39 (0.18)	−0.63 (0.18)	-	−0.47 (0.19)	−0.77 (0.20)
95% CI	-	−0.74, −0.05	−0.97, −0.29	-	−0.85, −0.09	−1.15, −0.38
p-value*	-	0.0239	0.0003†	-	0.0152	< 0.0001
Difference versus NSAIDs						
LS mean (SE)	-	-	−0.23 (0.14)	-	-	−0.30 (0.15)
95% CI	-	-	−0.51, 0.05	-	-	−0.60, 0.004
p-value*	-	-	0.1004	-	-	0.0530
WOMAC physical function subscale						
Baseline score						
Patients, n	304	609	610	260	523	522
Mean (SD)	6.40 (1.50)	6.32 (1.42)	6.39 (1.46)	6.40 (1.56)	6.39 (1.45)	6.43 (1.50)
Median (range)	6.40 (1.4, 10.0)	6.30 (1.9, 10.0)	6.40 (0.6, 10.0)	6.35 (1.4, 10.0)	6.40 (1.9, 10.0)	6.50 (0.6, 10.0)
Week 24 score						
Patients, n	208	427	439	173	364	372
Mean (SD)	3.90 (2.22)	3.46 (2.18)	3.08 (2.11)	4.12 (2.21)	3.61 (2.19)	3.21 (2.14)
Median (range)	3.70 (0.0, 9.6)	3.40 (0.0, 9.7)	2.90 (0.0, 9.0)	3.80 (0.0, 9.6)	3.50 (0.0, 9.7)	3.00 (0.0, 9.0)
Change from baseline						
Patients, n	207	426	439	172	363	372
Mean (SD)	−2.53 (2.17)	−2.79 (2.13)	−3.25 (2.08)	−2.31 (2.10)	−2.70 (2.10)	−3.19 (2.11)
Median (range)	−2.50 (−8.7, 3.1)	−2.80 (−8.7, 2.6)	−3.30 (−10.0, 2.7)	−2.30 (−8.7, 3.1)	−2.70 (−8.7, 2.3)	−3.20 (−10.0, 2.7)
LS mean (SE)	−2.02 (0.16)	−2.33 (0.13)	−2.65 (0.13)	−1.80 (0.18)	−2.26 (0.14)	−2.62 (0.14)
95% CI	−2.34, −1.70	−2.58, −2.08	−2.90, −2.41	−2.16, −1.45	−2.53, −1.98	−2.90, −2.35
Difference versus placebo						
LS mean (SE)	-	−0.31 (0.17)	−0.64 (0.18)	-	−0.45 (0.18)	−0.82 (0.19)
95% CI	-	−0.65, 0.03	−0.98, −0.29	-	−0.82, −0.09	−1.20, −0.44
p-value*	-	0.0738	0.0003†	-	0.0159	< 0.0001
Difference versus NSAIDs						
LS mean (SE)	-	-	−0.32 (0.14)	-	-	−0.37 (0.15)
95% CI	-	-	−0.59, −0.06	-	-	−0.67, −0.07
p-value†	-	-	0.0176	-	-	0.0163

Analyses are based on a multiple imputation approach using a mixed-effect model for repeated measures with baseline randomization strata, baseline, treatment, visit, and treatment by-visit interaction

CI Confidence interval, *FAS* Full analysis set, *LS* Least squares, *mFAS* Modified full analysis set, *NSAID* Non-steroidal anti-inflammatory drug, *Q4W* Every 4 weeks, *SD* Standard deviation, *SE* Standard error, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

* The *p*-value is presented for descriptive purposes only unless otherwise specified

† Indicates the *p*-value is statistically significant

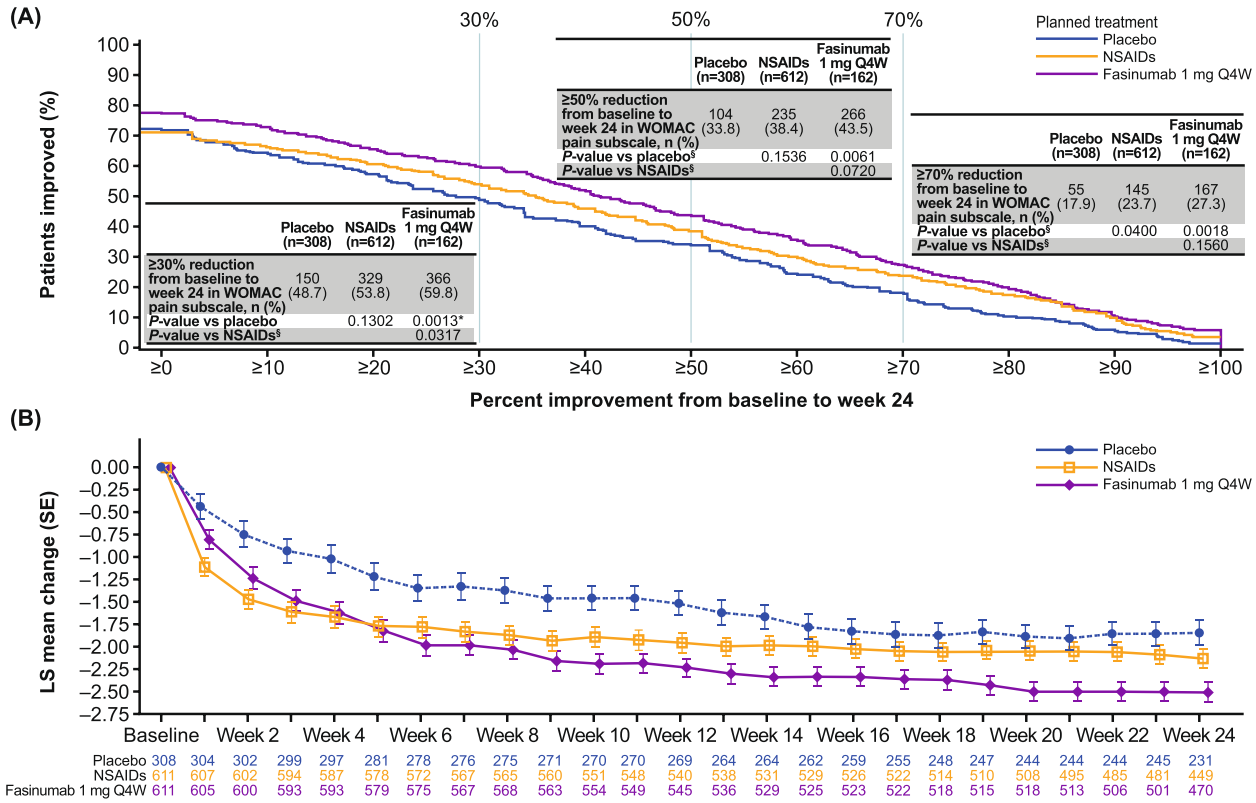

Fig. 1 Change from baseline to Week 24 in (**A**) the percentage of patients achieving various levels of pain relief as measured by the WOMAC pain subscale score,[†] and (**B**) the average weekly walking index joint pain score using NRS pain assessment by week[‡] (FAS). *Indicates *p*-value is statistically significant. [†]Patients with missing data are considered as a non-response. [‡]Analyses are based on mixed model with repeated measures, with baseline randomization strata, baseline, treatment, visit, and treatment by-visit interaction. [§]The *p*-value is presented for descriptive purposes only. *FAS* Full analysis set, *LS* Least squares, *NRS* Numeric rating scale, *NSAID* Non-steroidal anti-inflammatory drug, *Q4W* Every 4 weeks, *SE* Standard error, *WOMAC* Western Ontario and McMaster Universities Osteoarthritis Index

Despite advanced structural damage, pain in joints with a KLG of 4 also responded well to treatment with fasinumab. At Week 24, point estimates for change from baseline in WOMAC pain score versus placebo was –0.83 for joints with a KLG of 4 versus –0.62 for those with a KLG of 2–3. Additional subgroup analyses by index joint (knee/hip), geographic region, age, sex, weight, and body mass index were consistent except for hip index joint and the geographic region that largely included participants from sites excluded in the mFAS (Supplementary Fig. 3). The small number of patients with hip index joints confounds the ability to interpret the data.

Patient global assessment: fasinumab versus placebo

Patient global assessment (PGA) was performed throughout the trial treatment period. Baseline PGA scores were similar across the treatment groups in the FAS population (mean: 3.4 for each group). At Week 24, there was a statistically significant change from baseline in the fasinumab 1 mg Q4W group compared with placebo: LS mean difference versus placebo was –0.14 ($p=0.0365$, 95% CI: –0.28, –0.01).

WOMAC pain and physical function subscale scores: fasinumab versus NSAIDs

The placebo-adjusted treatment response for WOMAC physical function in the FAS population treated with fasinumab 1 mg Q4W was twice that for maximally dosed, daily NSAIDs (–0.64 versus –0.31; nominal $p<0.05$) (Table 2). For WOMAC pain, the magnitude of change from baseline was also greater for fasinumab than for NSAIDs (–0.63 versus –0.39), but the difference was not significant.

Similarly, in the mFAS population, the placebo-adjusted differences in change from baseline in WOMAC pain were –0.77 for fasinumab and – 0.47 for NSAIDs narrowly missing statistical significance (nominal $p=0.053$). For change from baseline in WOMAC physical function, the differences were –0.82 for fasinumab and – 0.45 for NSAIDs (nominal $p=0.016$).

A greater proportion of patients showed a clinically meaningful benefit when treated with fasinumab compared with NSAIDs, as indicated by a ≥ 30% improvement in the WOMAC pain subscale score at the time of the primary endpoint (nominal $p < 0.05$; Fig. 1A).

Numerical rating scale walking index joint pain score: fasinumab versus placebo and NSAIDs

There were greater reductions in the weekly average walking index joint pain score as measured by numerical rating scale from baseline to Week 24 for the fasinumab 1 mg Q4W group compared to both the placebo (Week 1 through Week 24; nominal $p \leq 0.05$) and NSAIDs groups (Week 10 through Week 24; nominal $p \leq 0.05$) (Fig. 1B).

Safety

Safety data are presented for the patients who received fasinumab 1 mg Q4W, NSAIDs, and placebo.

Adverse events

Most on-study AEs (i.e. AEs that occurred at any time during the study after the first dose of the study drug, including both the on-treatment and post-treatment periods, but not the 1-year follow-up for JRs) were mild or moderate in severity, and the proportions of patients with severe AEs were comparable across the three treatment groups (Table 3).

There were four deaths reported in the study: three in the NSAIDs group and one in the fasinumab group. Two deaths in the NSAID group and one in the fasinumab group were considered by the investigators to be not related to the study drug. The third death in the NSAID group, an 82-year-old male with cardiac failure, was considered by the investigator to be related to the study drug. The patient had a history of hypertension and diabetes.

Adjudicated arthropathies

In the SAF population, there were 48 patients with an AA reported in at least one joint: five joints in five patients (1.6%) in the placebo group, ten joints in nine patients (1.5%) in the NSAIDs group, and 39 joints in 34 patients (5.6%) in the fasinumab 1 mg Q4W group (Table 4). Knees were the most prevalent location.

Across all treatment groups, the majority (82.1–100%) of AAs were classified as RPOA-1 (i.e. JSN associated with cartilage thinning or loss). AA joints with RPOA-2 (i.e. limited/focal articular collapse) were seen in a small number of patients in the fasinumab 1 mg Q4W group; one patient had RPOA-2 in two joints. There were two patients (0.3%) with AA in the fasinumab 1 mg Q4W group who also met the criteria for DA. See Supplementary Fig. 4 for example images.

Only one patient in the fasinumab 1 mg Q4W group had an AA (RPOA-1) detected on imaging, which was triggered due to worsening symptoms. The remainder (including all treatment groups) were detected on routine imaging. The median time to first AA event was 202 days in the placebo group, 124 days in the NSAIDs group, and 187 days in the fasinumab 1 mg Q4W group.

To better understand the pathology of the RPOA-1 AAs, a post hoc analysis was performed to assess the status of articular cartilage at baseline and the time of the event across treatment groups using whole-organ MRI scoring (see Supplementary Methods; Table 5). Twenty-seven knees with RPOA-1 (placebo, $n = 4$; NSAIDs, $n = 5$; fasinumab 1 mg Q4W, $n = 18$) had available MRIs at both baseline and the time of the event, and so could be evaluated for changes in articular cartilage. Fourteen of 27 joints overall, including 9/18 (50%) joints in the fasinumab group, showed regions of full-thickness articular cartilage loss at baseline. None of the joints that began the study with normal cartilage subsequently progressed to full-thickness loss; however, one joint in a patient from the placebo group began the study with focal partial thickness that progressed to a full-thickness defect. Four joints (one in the placebo group, one in the NSAIDs group, and two in the fasinumab group) had diffuse partial thickness defects at baseline that progressed to full-thickness defects during the study. In the fasinumab group, of the nine patients who started the study with full-thickness cartilage defects, five had no change and four had worsening.

Joint replacements

Including the extended follow-up period for JRs (up to 72 weeks), similar rates of JR surgical procedures were observed across the three treatment groups: 11 patients (3.6%) in the placebo group, 29 (4.8%) in the NSAIDs group, and 21 (3.4%) in the fasinumab 1 mg Q4W group (Table 4). The most frequent joint undergoing a JR was the knee (68.2–76.7%), and most joints that ultimately had JR surgery were index joints (72.7–91.7%) and/or had clear evidence of pre-existing OA at baseline (KLG of 2–4). One joint in the placebo group and four joints in the fasinumab group had AA prior to JR surgery. The median time to first event of JR surgery in affected patients was 251 days in the placebo group, 324 days in the NSAIDs group, and 333.5 days in the fasinumab 1 mg Q4W group.

Table 3 Summary of on-study[a] AEs, on-study AEs by system organ class and preferred term (≥ 2% in any group), and on-study AEs of fracture (SAF population)

	Placebo (*n* = 309)	**NSAIDs (*n* = 609)**	**Fasinumab 1 mg Q4W (*n* = 609)**
Overview of on-study AEs			
Total AEs, n	657	1356	1382
Total SAEs, n	21	52	34
Total severe AEs, n	19	41	37
Total AESIs, n	7	29	48
Patients with any AE, n (%)	201 (65.0)	439 (72.1)	437 (71.8)
Patients with any SAE, n (%)	19 (6.1)	39 (6.4)	29 (4.8)
Patients with any severe AE, n (%)	17 (5.5)	36 (5.9)	31 (5.1)
Patients with any AESI, n (%)	7 (2.3)	26 (4.3)	39 (6.4)
Patients with any AE leading to death, n (%)	0	2 (0.3)	0
Patients with any AE leading to withdrawal from the study, n (%)	4 (1.3)	23 (3.8)	16 (2.6)
Patients with any AE leading to study treatment discontinuation, n (%)	15 (4.9)	57 (9.4)	51 (8.4)
System organ class preferred term,[b] n (%)	Summary of on-study AEs by preferred term (≥ 2% in any group)		
Musculoskeletal and connective tissue disorders	77 (24.9)	185 (30.4)	201 (33.0)
Arthralgia	36 (11.7)	78 (12.8)	80 (13.1)
Back pain	17 (5.5)	44 (7.2)	46 (7.6)
Rapidly progressive OA	3 (1.0)	8 (1.3)	21 (3.4)
Joint swelling	0	6 (1.0)	17 (2.8)
Pain in extremity	4 (1.3)	10 (1.6)	16 (2.6)
Muscle spasms	6 (1.9)	10 (1.6)	13 (2.1)
OA	11 (3.6)	18 (3.0)	12 (2.0)
Infections and infestations	91 (29.4)	161 (26.4)	179 (29.4)
Urinary tract infection	25 (8.1)	34 (5.6)	49 (8.0)
Upper respiratory tract infection	15 (4.9)	30 (4.9)	30 (4.9)
Nasopharyngitis	22 (7.1)	38 (6.2)	29 (4.8)
Bronchitis	8 (2.6)	7 (1.1)	13 (2.1)
Influenza	9 (2.9)	12 (2.0)	10 (1.6)
Nervous system disorders	64 (20.7)	161 (26.4)	160 (26.3)
Headache	48 (15.5)	107 (17.6)	95 (15.6)
Dizziness	6 (1.9)	14 (2.3)	22 (3.6)
Paresthesia	3 (1.0)	11 (1.8)	16 (2.6)
Gastrointestinal disorders	51 (16.5)	97 (15.9)	88 (14.4)
Diarrhea	11 (3.6)	15 (2.5)	20 (3.3)
Nausea	7 (2.3)	8 (1.3)	13 (2.1)
Dyspepsia	3 (1.0)	12 (2.0)	9 (1.5)
Toothache	5 (1.6)	13 (2.1)	7 (1.1)
Constipation	9 (2.9)	8 (1.3)	6 (1.0)
Injury, poisoning, and procedural complications	19 (6.1)	51 (8.4)	57 (9.4)
Fall	4 (1.3)	13 (2.1)	13 (2.1)
Vascular disorders	17 (5.5)	41 (6.7)	26 (4.3)
Hypertension	9 (2.9)	27 (4.4)	16 (2.6)
Summary of on-study AEs of fracture[c]			
Fracture AEs, n	3	13	4
Patients with at least one fracture AE, n (%)	3 (1.0)	10 (1.6)	4 (0.7)

AE Adverse event, *AESI* AE of special interest, *NSAID* Non-steroidal anti-inflammatory drug, *OA* Osteoarthritis, *Q4W* Every 4 weeks, *SAE* Serious AE, *SAF* Safety analysis set

[a] On-study includes the on-treatment and post-treatment periods

[b] Medical Dictionary for Regulatory Activities (Version 23.1) coding dictionary applied. A patient who reported two or more AEs with different preferred terms within the same system organ class is counted only once in that system organ class. A patient who reported two or more AEs with the same preferred term is counted only once for that term

[c] Fractures other than subchondral insufficiency fractures and tooth fractures are displayed

Table 4 Summaries of AAs and all JRs (SAF population)

	Placebo (*n* = 309)	NSAIDs (*n* = 609)	Fasinumab 1 mg Q4W (*n* = 609)
Model adjusted rates for AAs			
Adjusted incidence rate per 100 patient-years (95% CI)	1.42 (0.58, 3.49)	1.30 (0.65, 2.58)	4.96 (3.35, 7.34)
Incidence rate difference per 100 patient-years (95% CI)	-	−0.12 (−1.63, 1.38)	3.54 (1.35, 5.74)
Summary of AAs, n (%)			
Patients with negative adjudication	4 (1.3)	16 (2.6)	27 (4.4)
Patients with AAs	5 (1.6)	9 (1.5)	34 (5.6)
Patients with AAs in more than 1 joint	0	1 (0.2)	5 (0.8)
RPOA-1	5 (1.6)	8 (1.3)	29 (4.8)
RPOA-1 + SIF[a]	0	1 (0.2)	2 (0.3)
RPOA-1/RPOA-2[b]	0	0	2 (0.3)
RPOA-2	0	0	2 (0.3)
Patients with AAs meeting the DA criteria[c]	0	0	2 (0.3)
AA joints, n	5 (100)	10 (100)	39 (100)
RPOA-1	5 (100)	9 (90.0)	32 (82.1)
RPOA-1 + SIF[a]	0	1 (10.0)	2 (5.1)
RPOA-1/RPOA-2[b]	0	0	2 (5.1)
RPOA-2	0	0	3 (7.7)
Knee	5 (100)	7 (70.0)	25 (64.1)
Hip	0	1 (10.0)	5 (12.8)
Shoulder	0	2 (20.0)	9 (23.1)
AA on index joint[d]	0	4 (40.0)	14 (35.9)
AAs on non-index joint[d]	5 (100)	6 (60.0)	25 (64.1)
Baseline KLG			
0	0	0	2 (5.1)
1	0	1 (10.0)	2 (5.1)
2	2 (40.0)	3 (30.0)	14 (35.9)
3	1 (20.0)	4 (40.0)	11 (28.2)
4	2 (40.0)	0	1 (2.6)
Summary of all JRs, n (%)			
Patients with JR surgery	11 (3.6)	29 (4.8)	21 (3.4)
Joints with completed JR surgery, n	12	30	22
Knee	9/12 (75.0)	23/30 (76.7)	15/22 (68.2)
Hip	3/12 (25.0)	6/30 (20.0)	5/22 (22.7)
Shoulder	0/12	1/30 (3.3)	1/22 (4.5)
JR on an index joint	11/12 (91.7)	24/30 (80.0)	16/22 (72.7)
JR on a non-index joint	1/12 (8.3)	6/30 (20.0)	6/22 (27.3)
Joints with AA prior to a completed JR surgery, n[c]	1	0	4
Baseline KLG			
2	2/12 (16.7)	0/30	3/22 (13.6)
3	5/12 (41.7)	12/30 (40.0)	5/22 (22.7)
4	5/12 (41.7)	17/30 (56.7)	12/22 (54.5)

AA Adjudicated arthropathy, *CI* Confidence interval, *DA* Destructive arthropathy, *JR* Joint replacement, *KLG* Kellgren-Lawrence grade, *NSAID* Non-steroidal anti-inflammatory drug, *OA* Osteoarthritis, *Q4W* Every 4 weeks, *RPOA-1* Rapidly progressive OA type 1, *RPOA-2* Rapidly progressive OA type 2, *SAF* Safety analysis set, *SIF* Subchondral insufficiency fracture

[a] Patients had RPOA-1 and SIF

[b] Patients had RPOA-1 and RPOA-2

[c] All AAs leading to JR were RPOA-1

[d] Percentage is calculated using the denominator of joints with any positive AA

Table 5 Status of articular cartilage at baseline and the time of the event for RPOA-1 cases

Group	Articular cartilage status at baseline[a]		Change in articular cartilage at time of RPOA-1 detection				
			No change	Focal thinning	Diffuse thinning	New full-thickness loss	Worsening full-thickness loss
Placebo (*n* = 4)	Normal	0	0	0	0	0	0
	Focal thinning	1 (25)	0	0	0	1	0
	Diffuse thinning	1 (25)	0	0	0	1	0
	Full-thickness loss	2 (50)	1	0	0	0	1
NSAIDs (*n* = 5)	Normal	0	0	0	0	0	0
	Focal thinning	1 (20)	1	0	0	0	0
	Diffuse thinning	1 (20)	0	0	0	1	0
	Full-thickness loss	3 (60)	1	0	0	0	2
Fasinumab 1 mg Q4W (*n* = 18)	Normal	6 (33)	0	2	4	0	0
	Focal thinning	1 (6)	1	0	0	0	0
	Diffuse thinning	2 (11)	0	0	0	2	0
	Full-thickness loss	9 (50)	5	0	0	0	4

NSAID Non-steroidal anti-inflammatory drug, *Q4W* Every 4 weeks, *RPOA-1* Rapidly progressive osteoarthritis type 1, *WORMS* Whole organ magnetic resonance imaging

[a] Articular cartilage status is equivalent to the following WORMS score: Normal = WORMS 0, focal thinning = WORMS 2–3, diffuse thinning = WORMS 4, full-thickness loss = WORMS 2.5, 5, 6. The weight-bearing region of the knee showing joint space narrowing was evaluated including both the tibia and the femur; the worst score for the region is presented

Peripheral sensory and sympathetic nervous system AEs

Twenty-seven patients had an on-study peripheral sensory AESI: two (0.6%) in the placebo group, ten (1.6%) in the NSAIDs group, and 15 (2.5%) in the fasinumab 1 mg Q4W group. The most frequently reported events (≥ 2% of patients in any treatment group) included paresthesia, hypoesthesia, carpal tunnel syndrome, and sciatica. None of the events were reported as SAEs and all were considered by the investigator to be not related to the study drug. All events were reported as mild or moderate, except for two cases of severe sciatica in the fasinumab 1 mg Q4W group, one of which resolved and one of which was ongoing at end of follow-up.

There were no AESIs of sympathetic nervous system (SNS) dysfunction reported during the study. To further evaluate for the potential of SNS dysfunction, patients were evaluated for orthostatic vital sign changes at regular study visits. The rate of orthostatic changes was similar across treatment groups (2.4% in the placebo group, 1.5% in the NSAIDs group, and 1.2% in the fasinumab 1 mg Q4W group).

Pharmacokinetics

In the pharmacokinetic analysis set, mean functional fasinumab 1 mg Q4W trough concentrations (C_{trough}) in serum increased incrementally from 0.0469 mg/L to 0.0644 mg/L after the first and second doses. Mean C_{trough} following the fourth (Week 16) and sixth (Week 24) doses were 0.0738 and 0.0713 mg/L, respectively, suggesting steady-state was reached following the fourth dose (Week 16) (Supplementary Fig. 5).

Immunogenicity

The overall incidence of treatment-emergent anti-drug antibodies (ADAs) was low in all treatment groups, and all positive ADA responses were of low titer. The incidence of treatment-emergent ADAs for fasinumab 1 mg Q4W (0.7%) was similar to that for placebo (1.0%). Furthermore, treatment-emergent ADAs alone did not appear to impact fasinumab concentrations in serum.

Discussion

This study was designed to select patients from a difficult-to-treat population with moderate-to-severe pain due to OA of the knee or hip who had not responded to other therapies, a patient group with a clinically significant unmet medical need. Indeed, nearly 75% of patients in this study had previously received or were intolerant to opioids, higher than previously reported rates in the general population with OA (~ 25%) and even in those with severe disease (~ 40%) [27].

In this difficult-to-treat population, fasinumab 1 mg Q4W SC showed greater improvements in the co-primary endpoints of WOMAC pain and physical function subscale scores than placebo up to 24 weeks, and resulted in a numerically greater improvement in WOMAC pain scores and a nominally statistically significant greater improvement in WOMAC physical function scores than NSAIDs. This study established direct and meaningful benefit on important clinical outcomes for the 1 mg dose of fasinumab administered Q4W. The efficacy analyses included data showing better pain control compared with NSAIDs administered at the maximum labeled dose in a consistent

manner, for a longer time than typically prescribed in routine clinical practice. Therefore, not only was fasinumab 1 mg Q4W shown to be effective, but it also showed numerically greater improvements than NSAIDs used at their maximal dosing regimens. Furthermore, fasinumab efficacy was maintained in joints with advanced structural damage at baseline (KLG of 4).

These results are in line with results from phase 3 studies of tanezumab, another NGF inhibitor, versus NSAIDs in patients with OA of the hip or knee [28, 29]. Improvements in WOMAC pain and physical function scores were seen with both tanezumab and NSAIDs; however, the improvements were numerically greater with tanezumab.

An increased risk of AAs was observed in the fasinumab group compared with the NSAIDs and placebo groups. Similar findings for joint-related AEs have been reported for tanezumab [28, 29]. RPOA-1 (JSN) accounted for most AAs. Notably, there were no differences between the treatment groups with respect to the incidence of JRs over time. The design of the study incorporated follow-up for up to 72 weeks, approximately 1 year after the last treatment dose. During this time the rates of JR across the treatment groups remained similar, despite the difference in AA rates observed in the fasinumab group.

Characterizing the changes in articular cartilage based on MRI enabled a better understanding of the pathology classified as RPOA-1. Our post hoc analysis findings suggest there are two major categories of articular cartilage change among patients with confirmed RPOA-1 identified in this study: (1) new or worsening partial thickness articular cartilage defects; and (2) worsening in knees with pre-existing full-thickness articular cartilage defects (50% of RPOA-1 knees in all treatment groups).

Partial thickness articular cartilage defects detected on MRI are a common finding in athletes [30] and older adults without OA [31]. In OA patients, partial thickness defects appear to be associated with radiographic progression [32, 33] but are only weakly correlated with pain [34], which is the main reason patients opt for JR.

In contrast, the presence of full-thickness cartilage defects has been shown to be an independent predictor of JR, regardless of KLG [35, 36]. The observation that approximately half of RPOA-1 cases had regions of full-thickness cartilage defects at baseline is surprising because the classification was expected to identify joints beginning with ample cartilage that lost substantial volume over the course of the trial. The finding implies that many RPOA-1 cases were already at higher risk for pain progression and JR at study start. The explanation for these findings is unclear; however, joint space width measurements on X-ray are the main trigger for adjudication, and X-rays are known to be a poor reflection of articular cartilage status at a given point in time [37].

Key limitations of this study include the exploratory nature of some of the analyses, the termination of the higher fasinumab dose groups impacting the final number of participants with planned doses of study drug, and limited exposure data. However, the study has several strengths, including the global participation of sites, the well-defined prespecified endpoints, recruitment of a population with a high unmet need, and use of two relevant active comparators.

Conclusion

In this difficult-to-treat population of patients with moderate-to-severe pain due to OA of the knee or hip, fasinumab 1 mg Q4W for 24 weeks resulted in statistically significant greater improvements in WOMAC pain and physical function subscale scores than placebo, and numerically greater improvements in WOMAC pain scores and nominally statistically significant greater improvement in WOMAC physical function scores than NSAIDs. The safety profile was consistent with that previously reported for fasinumab and the class of anti-NGF compounds in general. An increased risk of AAs was observed in the fasinumab group compared with the NSAIDs and placebo groups. Post hoc MRI analyses to characterize RPOA-1 cases showed that approximately half had pre-existing regions of full-thickness defects, suggesting that many RPOA-1 cases were already at high risk for pain progression and JR at study start.

Abbreviations

AA	Adjudicated arthropathy
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
CI	Confidence interval
DA	Destructive arthropathy
FAS	Full analysis set
JR	Joint replacement
JSN	Joint space narrowing
KLG	Kellgren-Lawrence grade
LS	Least squares
mFAS	Modified full analysis set
MRI	Magnetic resonance imaging
NGF	Nerve growth factor
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
PGA	Patient global assessment
Q4W	Every 4 weeks
RPOA-1	Rapidly progressive osteoarthritis type 1
RPOA-2	Rapidly progressive osteoarthritis type 2
SAE	Serious adverse event
SAF	Safety analysis set
SC	Subcutaneous
SD	Standard deviation
SIF	Subchondral insufficiency fracture
TEAE	Treatment-emergent adverse event
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
All authors contributed to the interpretation of results, critical review of the manuscript for important intellectual content, and final approval of submission of the manuscript for publication. SD, HG, GV, CE, SZ, JC, LB, NT, GG, and PD contributed to collection of the data.

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Data availability
Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, and statistical analysis plan) that support the methods and findings reported in this manuscript. Submit requests to https://vivli.org/.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines and applicable International Council for Harmonisation Good Clinical Practice Guidelines. The institutional review board or independent ethics committee at each study center reviewed and approved the protocol, protocol amendments, informed consent form, and any other relevant documents (see the Supplementary Appendix for details). All participants provided written informed consent to participate in the study. During routine blinded monitoring, prior to database lock, the sponsor suspected and identified non-compliance with good clinical practice at four sites comprising 219 patients. Patients from these sites were subsequently excluded from the modified full analysis set, as prespecified in the statistical analysis plan (see the Supplementary Appendix for details).

Consent for publication
Not applicable.

Competing interests
SJD, HG, GPG, and PD are all employees of and shareholders in Regeneron Pharmaceuticals, Inc. who report having three patents pending with Regeneron Pharmaceuticals, Inc. SE, CE, TH, HEH, KCT, JC, YP, LB, NT, GM, and NB are all employees of and shareholders in Regeneron Pharmaceuticals, Inc. GV has served as a consultant for AbbVie, Celgene, GSK, Janssen, Lilly, Merck, Novartis, Pfizer, Sanofi/Regeneron, and UCB; and as an Investigator for AbbVie, Image Analysis, Bristol Myers Squibb, Janssen, Lilly, Merck, MLKCDT, Novartis, Pfizer, and Sanofi/Regeneron. TF owns equity in Clario, Inc, and has received grants or contracts from various pharmaceutical and biotechnology companies developing new drugs to treat osteoarthritis. JDD is an employee of and shareholder in Regeneron Pharmaceuticals, Inc. who reports having two patents pending with Regeneron Pharmaceuticals, Inc. SZ has no conflict of interest to disclose. MF is an employee of Teva Pharmaceuticals; has been funded by Teva Pharmaceuticals for travel and attendance at investigator meetings; and has received and holds stocks or stock options.

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