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CLINICAL SCIENCE

Efficacy and safety of fasinumab in patients with chronic low back pain: a phase II/III randomised clinical trial

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ABSTRACT

Objectives To study the efficacy and safety of fasinumab in moderate-to-severe, chronic low back pain (CLBP).

Methods In this phase II/III, double-blind, placebo-controlled study, patients with CLBP aged ≥35 years with inadequate pain relief/intolerance to acetaminophen, non-steroidal anti-inflammatory drugs and opioids were randomised to fasinumab 6 or 9 mg subcutaneous every 4 weeks (Q4W), 9 mg intravenous every 8 weeks (Q8W) or placebo. Primary endpoint was change from baseline to week 16 in average daily low back pain intensity (LBPI) numeric rating score. Key secondary efficacy variables included Roland-Morris Disability Questionnaire (RMDQ) and Patient Global Assessment (PGA). The results are based on a modified intent-to-treat analysis of 563/800 planned patients when enrolment was stopped early given emerging signals of joint risk in other osteoarthritis (OA) studies at doses being tested here.

Results Significant placebo-adjusted LBPI reductions at week 16 were observed for fasinumab 9 mg Q4W and Q8W (least squares mean (standard error) −0.7 (0.3); both nominal $p<0.05$), but not 6 mg (−0.3 (0.3); $p=0.39$). RMDQ and PGA improvements to week 16 were greatest for fasinumab 9 mg intravenous. Numerically greater efficacy occurred in patients with, versus those without, peripheral OA (pOA) over 16 weeks. Treatment-emergent adverse events (AEs) occurred in 274/418 (65.6%) patients in the combined fasinumab groups and 94/140 (67.1%) placebo patients. Joint AEs, mostly rapid progressive OA type 1, were more frequent in the combined fasinumab groups (19 events in 16 patients (3.8%) vs 1 event in 1 patient (0.7%) for placebo); all except one occurred in pOA patients.

Conclusions Fasinumab highest doses, but not lower dose, improved both CLBP pain and function. Most joint AEs occurred in pOA patients, consistent with earlier findings in symptomatic OA. Further study is needed of patients with CLBP with and without pOA to determine optimal benefit–risk.

Key messages

What is already known about this subject?

- Inadequate relief of chronic pain has a profound effect on an individual's quality of life and is associated with substantial healthcare costs and loss of productivity.

What does this study add?

- There remains an unmet medical need for alternative treatment options that have analgesic efficacy, mitigate the risks associated with current treatment options and provide an acceptable risk/benefit profile.
- Nerve growth factor (NGF) inhibitors have the potential to provide pain relief via a mechanism distinct from that of commonly used analgesic medications such as non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, and thus avoid NSAID or opioid adverse effects such as increased risk of cardiovascular events, gastrointestinal toxicity, drowsiness, respiratory depression, dependence and abuse.
- Treatment with NGF inhibitors has been associated with dose-dependent risk of joint damage including rapidly progressive osteoarthritis (OA), that may be more likely in individuals with peripheral OA (pOA) than in those without pOA, and neurologic symptoms, including paraesthesia.
- Higher doses were required to relieve chronic low back pain (CLBP) than was observed in previous studies in patients with pain due to hip and knee OA.

How might this impact on clinical practice or future developments?

- The results observed in this study support continued evaluation of fasinumab as a possible new treatment option for patients with CLBP with inadequate pain control, or who are intolerant to or have a contraindication for existing therapies.
- For future studies in CLBP, consideration will be given to dose of fasinumab to seek the most favourable risk–benefit profile.

INTRODUCTION

Low back pain (LBP) is a major international health problem.[1] According to the Global Burden of Disease 2017 study, LBP ranked highest among other conditions as measured in disability-adjusted life years.[2] Although most patients are believed to recover quickly from acute episodes, recurrence is common.[3] Chronic LBP (CLBP) is defined as pain persisting for ≥3 months.[4] Guidelines recommend initial treatment with non-pharmacological interventions, including exercise and multidisciplinary rehabilitation.[5–8]

If these interventions are inadequate or if CLBP persists, guidelines recommend non-steroidal anti-inflammatory drugs (NSAIDs) as first-line pharmacological treatments and duloxetine and tramadol as second-line treatments.[7] Stronger opioids are an option only if patients fail the afore-mentioned treatments and if the potential benefits outweigh the risks.[7] However, long-term use of both NSAIDs and opioids is limited by tolerability issues and adverse effects, such as gastrointestinal bleeding, cardiovascular events, and the potential for abuse and dependence.[9]

Neurotrophins are a family of polypeptide growth factors that play a role in the proliferation, differentiation, survival and death of neuronal and non-neuronal cells.[10] Nerve growth factor (NGF) was the first neurotrophin identified.[11] It provokes pain,[12 13] is elevated in the synovial fluid of patients with osteoarthritis (OA)[14 15] and its receptors are upregulated in injured and inflamed tissues.[16 17] NGF produced by peripheral tissues binds neurotrophic receptors (low-affinity p75 and high-affinity tropomyosin-related kinase A) on nociceptive neurons to modulate pain.[18 19] NGF inhibitors might, therefore, provide pain relief via a novel mechanism, potentially avoiding the risks of NSAID or opioids.

Fasinumab is a fully human monoclonal antibody shown to reduce pain in OA.[20 21] This study evaluated the efficacy and safety of fasinumab for moderate-to-severe CLBP in patients with intolerance to, or inadequate pain relief from, acetaminophen, oral NSAIDs and opioids.

METHODS

Patient and public involvement

This phase II/III, randomised, double-blind, double-dummy, placebo-controlled study (NCT02620020) was conducted at 105 sites in the USA, Canada and Europe.

Study population

Eligible patients were ≥35 years old with CLBP and history of inadequate pain relief or intolerance to analgesic therapy, including acetaminophen, at least one oral NSAID and at least one opioid (or unwillingness to take opioids), and a diagnosis of moderate-to-severe CLBP (Quebec Task Force category 1: no radiating pain, or Quebec Task Force category 2: proximal radiation above the knee)[22] for ≥3 months prior to screening. An LBP intensity Numeric Rating Scale (LBPI NRS) score ≥4 at both screening and at randomisation (after withdrawal of previous pain medication(s), without requirement for pain flare), and a Patient Global Assessment (PGA) of LBP of fair, poor or very poor at screening were also required. Presence of OA was not exclusionary (see online supplemental methods for full inclusion and exclusion criteria).

Study design and treatments

The study consisted of a screening period (up to 30 days), a 7-day prerandomisation period during which all pain medication except study-provided rescue medication was discontinued, a 16-week randomised treatment period and a 20-week follow-up period. Patients were randomised (1:1:1:1) according to a computer-generated central randomisation scheme and assigned by interactive voice response system, to either: fasinumab 6 mg subcutaneously (SC) every 4 weeks (Q4W), fasinumab 9 mg SC Q4W, fasinumab 9 mg intravenously (IV) every 8 weeks (Q8W) or placebo SC Q4W or IV Q8W. Patients randomised to fasinumab 6 mg or 9 mg SC received a loading dose (extra nominal dose) on day 1 (total dose of 12 or 18 mg, respectively), followed by nominal doses at weeks 4, 8 and 12 (total of four doses). Patients randomised to fasinumab 9 mg IV Q8W were not loaded, receiving IV fasinumab 9 mg on day 1 and week 8 (total of two doses). To maintain treatment blinding, patients received double-dummy placebo injections (IV or SC) on days of dose administration.

Randomisation was stratified by baseline LBPI NRS score (<7,≥7), duration of CLBP (<5 years, ≥5 years) and maximum Kellgren-Lawrence (K-L) score (≤2, >2) at any knee or hip joint at screening.

The primary efficacy endpoint was the change from baseline to week 16 in the average daily LBPI NRS score on an 11-point

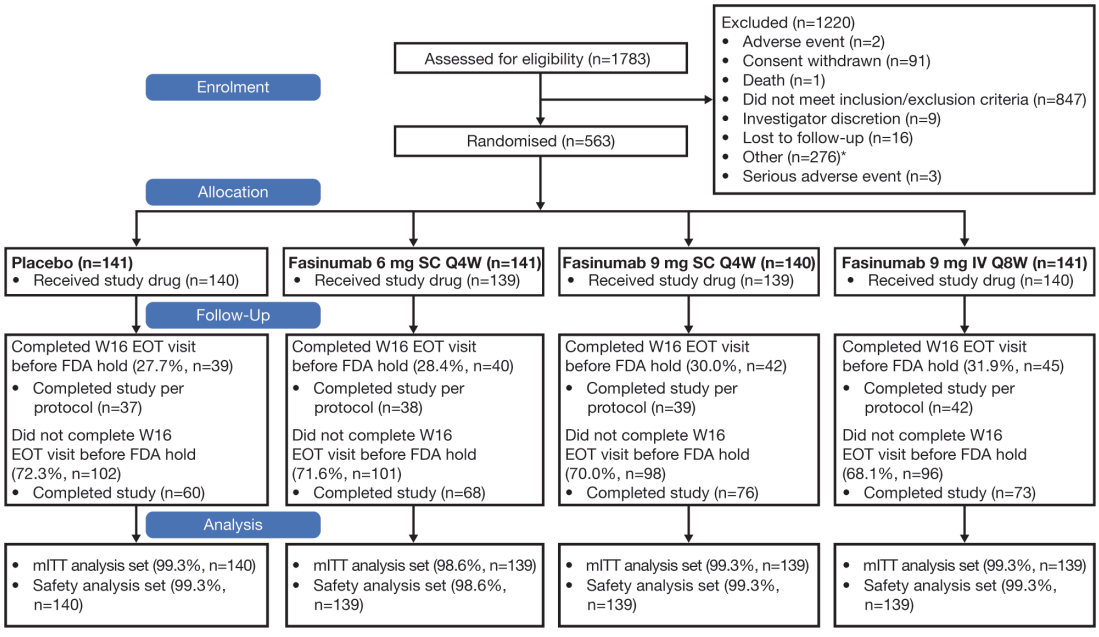

Figure 1 Patient disposition. EOT, end of treatment; FDA, US Food and Drug Administration; IV, intravenous; mITT, modified intent-to-treat; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; W, week. *Includes, among other reasons: out of screening window, study stopped by sponsor; patients could be excluded for >1 reason.

(0–10) NRS. The average daily LBPI NRS score was defined as the average of daily LBPI NRS scores for the 7 days before and including the nominal visit. Secondary endpoints included change from baseline to weeks 2, 4, 8, 12 and 16 in Roland-Morris Disability Questionnaire (RMDQ) total score and PGA score, and change from baseline to weeks 2, 4, 8 and 12 in LBPI NRS score.

In October 2016, the US Food and Drug Administration (FDA) placed the study on partial clinical hold following a single case of rapidly progressive osteoarthritis (RPOA) that occurred in a patient with knee OA (K-L score 3 at screening), prompting review of study entry criteria. Since patients with concomitant OA could have received fasinumab doses that had been eliminated by the sponsor from an ongoing fasinumab phase III OA study (NCT02683239) due to the rate of arthropathy, the FDA required that the protocol be amended to either exclude patients with peripheral OA (pOA) or to lower the doses to be studied. Since 70% of the target sample (563/800 patients) had already been randomised, investigators and relevant health authorities were notified that the sponsor stopped enrolment and any further dosing. The statistical analysis plan was updated prior to database lock and a final analysis was performed on completion of all protocol-described study visits, to allow assessment of safety and efficacy, including subgroup analyses of the primary and secondary endpoints by pOA status.

Safety assessments

The safety and tolerability of fasinumab compared with placebo was assessed by treatment-emergent adverse events (TEAEs) during treatment (including the day from first dose of study drug to 4 weeks after last dose of SC study drug or 8 weeks after last dose of IV study drug, whichever was later) and post-treatment (up to 20 weeks) adverse events (AEs). Joint and general safety were monitored independently (see online supplemental methods) as previously described.[21]

Statistical analysis

The primary efficacy endpoint, change from baseline to week 16 in average daily LBPI NRS score, was analysed using a mixed-effect model repeated measures approach based on the modified intent-to-treat (mITT) analysis set, according to a prespecified analysis established prior to database lock, in response to the early termination of dosing in the study. The mITT analysis set included all randomised patients who received at least one dose of allocated treatment, including all data available up to 5 weeks (4 weeks visit interval + 1 week allowable visit window) after the last dose of study drug. Analyses were deemed exploratory (all p values are nominal). Further details are provided in the online supplemental methods.

The safety analysis set included all randomised patients who received any study drug. Sensitivity analyses for the primary and secondary endpoints used the full analysis set (all randomised

Table 1 Demography and baseline characteristics (full analysis set)

		Fasinumab				
	Placebo (n=141)	6 mg SC Q4W (n=141)	9 mg SC Q4W (n=140)	9 mg IV Q8W (n=141)	Combined (n=422)	Total (N=563)
Age (years), mean (SD)	58.1 (12.5)	58.2 (11.3)	56.6 (11.0)	55.4 (10.5)	56.7 (11.0)	57.1 (11.4)
Age category, n (%)						
<65 years	93 (66.0)	95 (67.4)	109 (77.9)	117 (83.0)	321 (76.1)	414 (73.5)
≥65 years	48 (34.0)	46 (32.6)	31 (22.1)	24 (17.0)	101 (23.9)	149 (26.5)
Sex, n (%)						
Male	58 (41.1)	56 (39.7)	56 (40.0)	60 (42.6)	172 (40.8)	230 (40.9)
Female	83 (58.9)	85 (60.3)	84 (60.0)	81 (57.4)	250 (59.2)	333 (59.1)
Race, n (%)						
White	127 (90.1)	119 (84.4)	118 (84.3)	116 (82.3)	353 (83.6)	480 (85.3)
Black or African American	13 (9.2)	19 (13.5)	19 (13.6)	21 (14.9)	59 (14.0)	72 (12.8)
Asian	1 (0.7)	2 (1.4)	2 (1.4)	1 (0.7)	5 (1.2)	6 (1.1)
American Indian or Alaska Native	0	1 (0.7)	0	1 (0.7)	2 (0.5)	2 (0.4)
Native Hawaiian or other Pacific Islander	0	0	0	1 (0.7)	1 (0.2)	1 (0.2)
Other	0	0	1 (0.7)	1 (0.7)	2 (0.5)	2 (0.4)
Body mass index (kg/m^2), mean (SD); n	29.7 (4.8); 141	29.0 (5.1); 139	29.6 (4.7); 140	30.1 (4.4); 141	29.6 (4.7); 420	29.6 (4.8); 561
Average daily LBPI NRS score, mean (SD); n	6.5 (1.3); 140	6.5 (1.3); 139	6.7 (1.3); 140	6.5 (1.2); 141	6.5 (1.3); 420	6.5 (1.3); 560
Duration of chronic LBP (years), mean (SD); n	11.8 (10.2); 126	13.6 (12.1); 131	13.7 (13.0); 135	12.7 (10.7); 134	13.3 (12.0); 400	13.0 (11.6); 526
Maximum K-L score at any knee or hip joint at screening, n (%)						
0	25 (17.7)	16 (11.3)	35 (25.0)	25 (17.7)	76 (18.0)	101 (17.9)
1	51 (36.2)	49 (34.8)	35 (25.0)	43 (30.5)	127 (30.1)	178 (31.6)
2	40 (28.4)	52 (36.9)	42 (30.0)	50 (35.5)	144 (34.1)	184 (32.7)
3	21 (14.9)	21 (14.9)	23 (16.4)	18 (12.8)	62 (14.7)	83 (14.7)
4	4 (2.8)	3 (2.1)	5 (3.6)	5 (3.5)	13 (3.1)	17 (3.0)
pOA, n (%)						
Yes	82 (58.2)	94 (66.7)	68 (48.6)	78 (55.3)	240 (56.9)	322 (57.2)
No	59 (41.8)	47 (33.3)	72 (51.4)	63 (44.7)	182 (43.1)	241 (42.8)

Baseline average daily LBPI NRS score was defined as the average of the non-missing daily LBPI NRS scores for 5 days prior to randomisation (from day −4 to day 1). pOA defined by medical history and/or K-L score ≥2 in hip or ≥3 in knee.
IV, intravenous
; K-L, Kellgren-Lawrence; LBP, lower back pain; LBPI NRS, Lower Back Pain Intensity Numeric Rating Scale; pOA, peripheral osteoarthritis; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous.

Table 2 Change from baseline to week 8 and week 16 in the average daily LBPI NRS, RMDQ and PGA of LBP scores (mITT analysis set)

		Fasinumab		
	Placebo (n=140)	6 mg SC Q4W (n=139)	9 mg SC Q4W (n=139)	9 mg IV Q8W (n=140)
	LBPI NRS			
Baseline average daily LBPI NRS score, mean (SD); n	6.5 (1.3); 139	6.5 (1.3); 137	6.7 (1.3); 139	6.4 (1.2); 140
Week 8				
Average daily LBPI NRS score, mean (SD); n	5.3 (2.1); 96	4.7 (2.0); 99	4.3 (2.4); 105	4.1 (2.3); 103
Change from baseline to week 8, mean (SD); n	−1.3 (1.8); 95	−1.9 (1.9); 98	−2.4 (2.2); 105	−2.3 (2.2); 103
LS mean (SE)	−1.2 (0.2)	−1.8 (0.2)	−2.3 (0.2)	−2.2 (0.2)
95% CI	−1.6 to −0.8	−2.2 to −1.4	−2.7 to −1.9	−2.6 to −1.8
Difference versus placebo, LS mean (SE)		−0.5 (0.3)	−1.1 (0.3)	−1.0 (0.3)
95% CI		−1.06 to −0.03	−1.57 to −0.55	−1.48 to −0.47
P value versus placebo		0.04	<0.01	<0.01
Week 16				
Average daily LBPI NRS score, mean (SD); n	4.7 (2.0); 50	4.3 (1.9); 48	4.2 (2.3); 55	3.9 (2.4); 56
Change from baseline to week 16, mean (SD); n	−1.9 (2.1); 49	−2.1 (1.9); 48	−2.6 (2.0); 55	−2.5 (2.2); 56
LS mean (SE)	−1.7 (0.2)	−2.0 (0.2)	−2.5 (0.2)	−2.4 (0.2)
95% CI	−2.19 to −1.29	−2.46 to −1.56	−2.90 to −2.03	−2.83 to −1.97
Difference versus placebo, LS mean (SE)		−0.3 (0.3)	−0.7 (0.3)	−0.7 (0.3)
95% CI		−0.88 to 0.34	−1.32 to −0.12	−1.26 to −0.07
P value versus placebo		0.39	0.02	0.03
	RMDQ			
Baseline RMDQ total score, mean (SD); n	10.9 (5.3); 132	10.8 (5.2); 135	10.7 (5.7); 136	11.7 (5.3): 136
Week 8				
RMDQ total score, mean (SD); n	7.9 (5.6); 100	5.7 (5.2); 101	5.9 (5.6); 105	5.6 (5.4); 104
Change from baseline to week 8, mean (SD); n	−3.2 (4.9); 92	−5.4 (5.3); 97	−4.7 (4.9); 102	−6.2 (5.4); 101
LS mean (SE)	−3.1 (0.5)	−5.3 (0.5)	−5.0 (0.5)	−5.9 (0.5)
95% CI	−3.99 to −2.17	−6.18 to −4.40	−5.86 to −4.10	−6.77 to −5.01
Difference versus placebo, LS mean (SE)		−2.2 (0.6)	−1.9 (0.6)	−2.8 (0.6)
95% CI		−3.42 to −1.01	−3.10 to −0.70	−4.01 to −1.61
P value versus placebo		<0.01	<0.01	<0.01
Week 16				
RMDQ total score, mean (SD); n	6.6 (5.6); 50	5.1 (4.9); 48	4.8 (4.6); 55	5.0 (5.2); 57
Change from baseline to week 16, mean (SD); n	−3.8 (4.5); 46	−6.0 (5.7); 46	−6.2 (4.7); 55	−6.6 (5.6); 55
LS mean (SE)	−3.8 (0.5)	−6.0 (0.5)	−5.8 (0.5)	−6.3 (0.5)
95% CI	−4.88 to −2.76	−7.09 to −4.97	−6.78 to −4.76	−7.30 to −5.28
Difference versus placebo, LS mean (SE)		−2.2 (0.7)	−2.0 (0.7)	−2.5 (0.7)
95% CI		−3.65 to −0.77	−3.36 to −0.54	−3.88 to −1.06
P value versus placebo		<0.01	<0.01	<0.01
	PGA of LBP			
Baseline PGA, mean (SD); n	3.5 (0.7); 140	3.5 (0.7); 139	3.4 (0.8); 139	3.4 (0.7); 140
Week 8				
PGA, mean (SD); n	3.0 (0.8); 100	2.7 (0.8); 101	2.6 (0.9); 105	2.5 (1.0); 104
Change from baseline to week 8, mean (SD); n	−0.5 (0.8); 100	−0.8 (0.9); 101	−0.8 (0.9); 105	−0.9 (1.0); 104
LS mean (SE)	−0.5 (0.1)	−0.8 (0.1)	−0.8 (0.1)	−0.9 (0.1)
95% CI	(−0.65 to −0.33)	(−0.94 to −0.62)	(−0.95 to −0.64)	(−1.05 to −0.74)
Difference versus placebo, LS mean (SE)		−0.3 (0.1)	−0.3 (0.1)	−0.4 (0.1)
95% CI		−0.51 to −0.08	−0.52 to −0.09	−0.62 to −0.19
P value versus placebo		0.01	0.01	<0.01
Week 16				
PGA, mean (SD); n	2.8 (0.8); 50	2.5 (0.9); 48	2.5 (0.9); 55	2.3 (1.0); 57
Change from baseline to week 16, mean (SD); n	−0.7 (0.8); 50	−0.9 (1.1); 48	−0.8 (1.0); 55	−1.0 (0.9); 57
LS mean (SE)	−0.7 (0.1)	−0.9 (0.1)	−0.8 (0.1)	−1.0 (0.1)
95% CI	−0.88 to −0.49	−1.08 to −0.69	−1.03 to −0.65	−1.20 to −0.83
Difference versus placebo, LS Mean (SE)		−0.2 (0.1)	−0.1 (0.1)	−0.3 (0.1)
95% CI		−0.46 to 0.07	−0.41 to 0.11	−0.59 to −0.07
P value versus placebo		0.15	0.26	0.01

Analyses are based on MMRM model with baseline randomisation strata, baseline score, treatment, visit and treatment-by-visit interaction. P values are nominal. Average daily LBPI NRS score was defined as the average of the non-missing daily LBPI NRS scores for the 7 days before and including the nominal visit. The daily LBPI NRS score for the week 16 nominal visit day was missing for all patients because the daily LBPI NRS score was entered each day starting at 18:00 and clinic visits typically occurred during the day with diaries returned at the end of the visit. Therefore, the average LBPI NRS score at week 16 was based on 6 days.
IV, intravenous; LS, least squares; mITT, modified intent-to-treat; MMRM, mixed effect model repeated measures; LBP NRS, Lower Back Pain Numeric Rating Scale; PGA, Patient Global Assessment; Q4W, every 4 weeks; Q8W, every 8 weeks; RMDQ, Roland-Morris Disability Questionnaire; SC, subcutaneous.

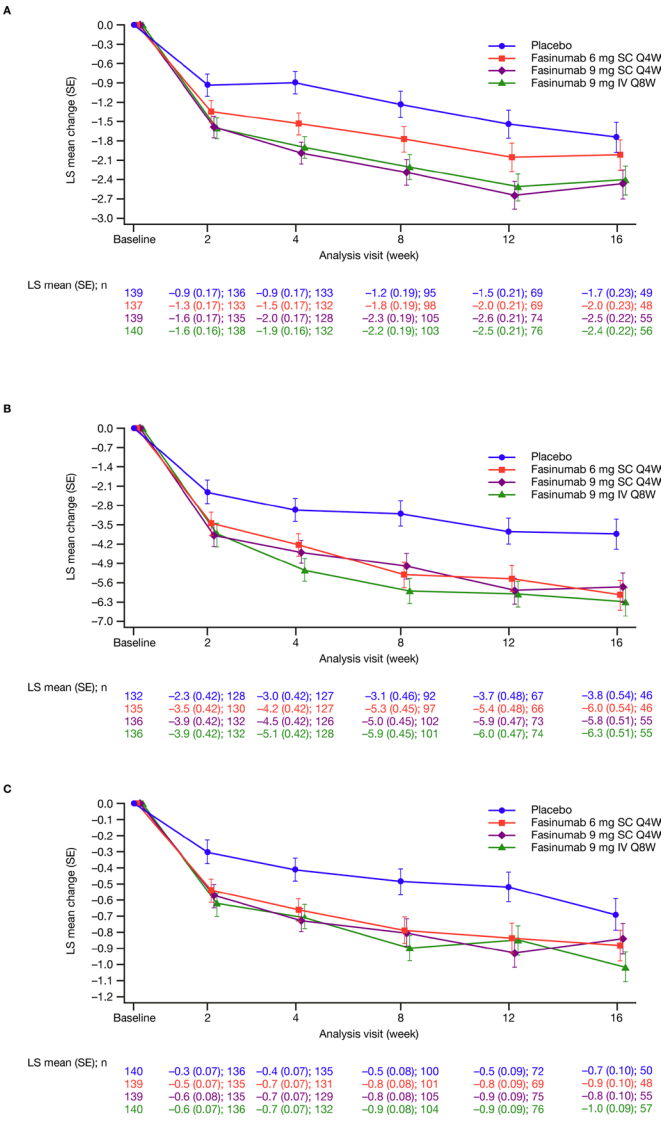

Figure 2 Least squares mean change from baseline in (A) average daily Lower Back Pain Intensity Numeric Rating Scale score (B) Roland-Morris Disability Questionnaire total score (C) Patient Global Assessment of lower back pain score by study visit (modified intent-to-treat analysis set). Analyses are based on mixed effect model repeated measures with baseline randomisation strata, baseline, treatment, visit and treatment-by-visit interaction. IV, intravenous; LS, least squares; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous.

patients). Assuming a significance level of 0.05 and a 20% dropout rate by week 16, an enrolment of 200 patients per treatment group would provide at least 91% power to detect a treatment difference of 0.9 between fasinumab 9 mg SC Q4W and placebo for the primary efficacy endpoint with a common SD of 2.4.

To assess potential differences in efficacy and safety between those with and without pOA at baseline, subgroup analyses were performed on the primary and secondary efficacy endpoints, using medical history and/or radiographic evidence of OA (K-L score ≥2 at the hip or K-L score ≥3 at the knee based on screening radiographs), in line with key components of the American College of Rheumatology OA criteria.[23] Subgroup analyses for the primary efficacy endpoint were also conducted for randomisation strata (baseline LBPI NRS score (<7, ≥7), duration of chronic LBP (≥5 years, <5 years) and maximum K-L score in any knee or hip joint (≤2,>2)).

RESULTS

Overall, 1783 patients were screened; 563 patients were randomised (figure 1). Patient demographic and baseline characteristics were generally balanced across groups (table 1). Most patients (82.2%) had a maximum K-L score at any knee or hip joint of ≤2 at screening; 14.7% and 3.0% of patients had scores of 3 and 4, respectively, (table 1). Of 558 patients who received at least one dose of study drug (safety analysis set), 35.3% to 42.4% of the fasinumab SC groups and 36.4% of the placebo SC group received all planned doses through week 16; corresponding values for IV groups were 54.3% (fasinumab 9 mg Q8W) and 51.4% (placebo) (online supplemental table 1).

Efficacy

Baseline LBPI scores were comparable across treatment groups (table 2). Significant reductions versus placebo in LBPI scores from baseline to week 16 were observed in the fasinumab 9 mg SC Q4W and 9 mg IV Q8W groups (least squares mean (standard error) −0.7 (0.3), nominal p=0.02; and −0.7 (0.3), nominal p=0.03, respectively), but not for the 6 mg SC Q4W group (–0.3 (0.3); nominal p=0.39) (table 2). Pain scores improved as early as week 2 (figure 2A). At week 8, all fasinumab doses provided reductions in LBPI scores versus placebo (least squares mean (standard error) 6 mg SC –0.5 (0.3), nominal p=0.04; 9 mg SC Q4W –1.1 (0.3), nominal p<0.01; 9 mg IV Q8W –1.0 (0.3), nominal p<0.01) (table 2). Mean baseline RMDQ (10.7 to 11.7) and PGA (3.4 to 3.5) scores were comparable across groups. RMDQ reductions were observed as early as week 2 in all fasinumab groups versus placebo and maintained to week 16, with the greatest reductions in the 9 mg IV group (table 2 and figure 2B,C). Placebo-adjusted changes in RMDQ at week 16 were –2.2 to –2.5 across fasinumab groups (all nominal p<0.01). Placebo-adjusted changes in PGA at week 16 (–0.1 to –0.3) reached significance only for fasinumab 9 mg IV (nominal p=0.01).

Subgroup analyses

In patients with (57.2%) and without (42.8%) pOA, placebo-adjusted improvements in LBPI scores were greatest in the 9 mg dose groups from week 2 through week 16 (online supplemental table 2 and online supplemental figure 1). Improvement versus placebo was generally numerically greatest in patients with, versus those without, pOA over the 16 week treatment period, with greater separation seen between the pOA subgroups at earlier time points when more patient data were available. A similar pattern was observed for RMDQ and PGA scores (online supplemental table 2 and online supplemental figures 2 and 3). Placebo-adjusted LBPI scores from baseline to week 16 were consistent across randomisation strata (data not shown).

Safety

On treatment, the percentages of patients with ≥1 TEAE were similar between placebo (67.1%; n=94) and combined fasinumab groups (65.6%; n=274), and across the fasinumab dose groups (online supplemental table 3). The system organ class (SOC) with the highest incidence of TEAEs while on treatment was musculoskeletal and connective tissue disorders (16.0% for combined fasinumab groups and 22.1% for placebo) (table 3). Arthralgia was the only TEAE reported in >10% of patients in any treatment group, with a similar incidence in the placebo and

Table 3 TEAEs with >3% incidence by system organ class and preferred term during the on-treatment period (safety analysis set)

Primary system organ class preferred term	Placebo (n=140)	Fasinumab 6 mg SC Q4W (n=139)	Fasinumab 9 mg SC Q4W (n=139)	Fasinumab 9 mg IV Q8W (n=140)	Fasinumab Combined (N=418)
TEAEs, n	90	79	115	85	279
Patients with at least one TEAE, n (%)	52 (37.1)	41 (29.5)	63 (45.3)	56 (40.0)	160 (38.3)
Musculoskeletal and connective tissue disorders, n (%)	31 (22.1)	15 (10.8)	25 (18.0)	27 (19.3)	67 (16.0)
Arthralgia	17 (12.1)	15 (10.8)	16 (11.5)	21 (15.0)	52 (12.4)
Pain in extremity	12 (8.6)	3 (2.2)	5 (3.6)	4 (2.9)	12 (2.9)
Back pain	7 (5.0)	0	4 (2.9)	5 (3.6)	9 (2.2)
Nervous system disorders, n (%)	18 (12.9)	17 (12.2)	26 (18.7)	18 (12.9)	61 (14.6)
Headache	9 (6.4)	9 (6.5)	9 (6.5)	9 (6.4)	27 (6.5)
Paraesthesia	4 (2.9)	6 (4.3)	9 (6.5)	9 (6.4)	24 (5.7)
Dizziness	4 (2.9)	5 (3.6)	6 (4.3)	3 (2.1)	14 (3.3)
Hypoaesthesia	4 (2.9)	4 (2.9)	7 (5.0)	3 (2.1)	14 (3.3)
Infections and infestations, n (%)	12 (8.6)	15 (10.8)	18 (12.9)	14 (10.0)	47 (11.2)
Nasopharyngitis	8 (5.7)	9 (6.5)	8 (5.8)	10 (7.1)	27 (6.5)
Urinary tract infection	0	4 (2.9)	5 (3.6)	2 (1.4)	11 (2.6)
Upper respiratory tract infection	4 (2.9)	2 (1.4)	5 (3.6)	2 (1.4)	9 (2.2)
Gastrointestinal disorders, n (%)	6 (4.3)	7 (5.0)	11 (7.9)	4 (2.9)	22 (5.3)
Diarrhoea	4 (2.9)	4 (2.9)	5 (3.6)	3 (2.1)	12 (2.9)
Nausea	2 (1.4)	4 (2.9)	7 (5.0)	1 (0.7)	12 (2.9)
General disorders and administration site conditions, n (%)	0	1 (0.7)	6 (4.3)	2 (1.4)	9 (2.2)
Oedema peripheral	0	1 (0.7)	6 (4.3)	2 (1.4)	9 (2.2)

TEAEs included any AEs reported during the on-treatment period (the day from first dose of study drug to 4 weeks after the last dose of SC study drug or 8 weeks after the last dose of IV study drug).
MedDRA (V.18.0) coding applied.
A patient who reported two or more TEAEs with the same preferred term is counted only once for that term.
A patient who reported two or more TEAEs with different preferred terms within the same system organ class is counted only once in that system organ class.
For system organ classes, the table is sorted by decreasing frequency in combined fasinumab group. Within each system organ class, preferred terms are sorted by decreasing frequency count in combined fasinumab group.
IV, intravenous; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; TEAE, treatment-emergent adverse event.

combined fasinumab groups (12.1% and 12.4%, respectively). TEAEs of paraesthesia were more frequent for the combined fasinumab groups than for placebo (5.7% vs 2.9%); most of these events were of mild-to-moderate severity. During the post-treatment follow-up period, the overall incidence of AEs in the combined fasinumab groups (29.9%) was similar to that for placebo (27.9%) (online supplemental table 4).

In total, 16 serious AEs (SAEs) occurred in 14 patients (placebo, n=4 (2.9%); combined fasinumab groups (n=10 (2.4%)) during the on-treatment period (online supplemental tables 3 and 5). Three SAEs were considered related to study drug, two of which were in the fasinumab 9 mg groups (haemorrhagic stroke and meniscus injury). In total, 35 SAEs occurred in 31 patients in the post-treatment follow-up period (online supplemental table 6); most were in the SOC of musculoskeletal and connective tissue disorders, all of which occurred in the fasinumab groups (5 patients, 3.6%, in the 9 mg IV group, and 3 patients, 2.2%, in each SC group; 11 total patients, 2.6%). Within this SOC, the most frequent SAE was RPOA. One patient (fasinumab 6 mg) with a history of smoking died of small cell lung cancer during the post-treatment follow-up period (considered unrelated to study drug).

AEs of special interest included sympathetic nervous system dysfunction and adjudicated arthropathies (AAs). No confirmed cases of the former were observed. There were 20 joints with AAs in 17 patients (table 4). All except one AA were detected outside of the prespecified on-treatment period (online supplemental figure 5), and all but one occurred in the fasinumab groups. Of the 20 joints with AAs, 19 were in patients in the pOA subgroup (table 4), and most (15/20) occurred in joints with screening K-L scores of ≥2 at the knee or hip (online supplemental table 7); in 3 knee joints, the screening K-L score was 0 or 1; in 2 shoulder joints, K-L score was not assessed but screening radiographs documented 1 with moderate OA and 1 with severe OA). Adjudicators could report more than one AA category per joint. Most AAs were categorised as RPOA (ie, RPOA type 1 or 2) and among these, 14 joints had RPOA1 (X-ray joint space narrowing; cartilage loss by MRI) solely; 2 joints in two patients (6 mg SC and 9 mg IV) had an RPOA2 (bone fragmentation or destruction; one with RPOA1); 1 joint had subchondral insufficiency fracture (SIF) as the sole finding (9 mg IV); and three joints had SIFs in conjunction with RPOA1. Only two AAs (one RPOA1; (9 mg SC), and one RPOA2; (9 mg IV)) were detected on imaging prompted by symptoms; others were detected on scheduled images. No primary osteonecrosis was observed.

Four joint replacements (knee) were performed in four patients. Two of these occurred following detection of an AA (9 mg SC, RPOA1; 9 mg IV, RPOA2). For the remaining two, preoperative imaging did not detect AA. In one case (9 mg SC), joint replacement was pursued to address functional consequences of pre-existing OA; in the other case (placebo), it was based on need for revision surgery related to historical hemiarthroplasty.

An increase in mean alkaline phosphatase (ALP) occurred over time in all three fasinumab groups (figure 3). The extent of the increase was similar across groups and small compared with baseline values. A small number of patients had increases in ALP above the upper limit of normal (ULN; 150 U/L): placebo (n=3), fasinumab 6 mg (n=2), 9 mg SC (n=4) and 9 mg IV (n=3), none

Table 4 Summary of AAs across the treatment period and post-treatment follow-up period (safety analysis set)

		Fasinumab			
	Placebo	6 mg SC Q4W	9 mg SC Q4W	9 mg IV Q8W	Combined
All patients, n	140	139	139	140	418
Patients with positive adjudications, n (%)	1 (0.7)	5 (3.6)	4 (2.9)	7 (5.0)	16 (3.8)
Total number of adjudications	46	80	89	110	279
Number of joints with positive adjudications, n (% of total adjudications) and JR outcome	1 (2.2)	7 (8.8)	4 (4.5)	8 (7.3)	19 (6.8)
RPOA1	1	5	3	6	14*
RPOA1, RPOA2†	0	1	0	0	1
RPOA1, SIF†	0	2	1	0	3
RPOA1 → JR	0	0	1	0	1
RPOA2 → JR	0	0	0	1	1
SIF	0	0	0	1	1
Patients with pOA, n	82	92	68	78	238
Patients with positive adjudications, n (%)‡	1 (1.2)	5 (5.4)	4 (5.9)	6 (7.7)	15 (6.3)
Total number of adjudications	41	60	56	88	204
Number of joints with positive adjudications (% of total adjudications) and JR outcome	1 (2.4)	7 (11.7)	4 (7.1)	7 (8.0)	18 (8.8)
RPOA1	1	5	3	5	13#
RPOA1, RPOA2†	0	1	0	0	1
RPOA1, SIF†	0	2	1	0	3
RPOA1 → JR*	0	0	1	0	1
RPOA2 → JR	0	0	0	1	1
SIF	0	0	0	1	1
Patients without pOA, n	58	47	71	62	180
Patients with positive adjudications, n (%)‡	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)	1 (0.6)
Total number of adjudications	5	20	33	22	75
Number of joints with positive adjudications (% of total adjudications)	0	0	0	1 (4.5)	1 (1.3)
RPOA1	0	0	0	1	1

pOA defined by medical history and/or K-L score ≥2 in hip or ≥3 in knee.
*Two RPOA1 events (6 and 9 mg Q4W groups; both in patients with pOA) were reported two times (as a sole finding and as RPOA1, SIF).
†More than one adjudicated arthropathy category could have been reported simultaneously in a single joint.
‡Per cent values calculated using the number of patients in each subgroup as denominator.
IV, intravenous; JR, total joint replacement; K-L, Kellgren-Lawrence; pOA, peripheral osteoarthritis; Q4W, every 4 weeks; Q8W, every 8 weeks; RPOA1, rapid progressive OA type 1; RPOA2, rapid progressive OA type 2; SC, subcutaneous; SIF, subchondral insufficiency fracture.

of which met the prespecified definition for potential clinical significance (≥1.5×ULN). During the 20-week post-treatment follow-up period, mean ALP values returned towards baseline (figure 3). A similar pattern was observed for patients with and without pOA (online supplemental figure 4).

Treatment-emergent antidrug antibody (ADA) responses occurred in five patients (1.3%) on fasinumab and one patient (0.8%) on placebo. All ADA-positive patients exhibited low titre responses, and none was neutralising. A positive ADA response did not affect concentrations of fasinumab.

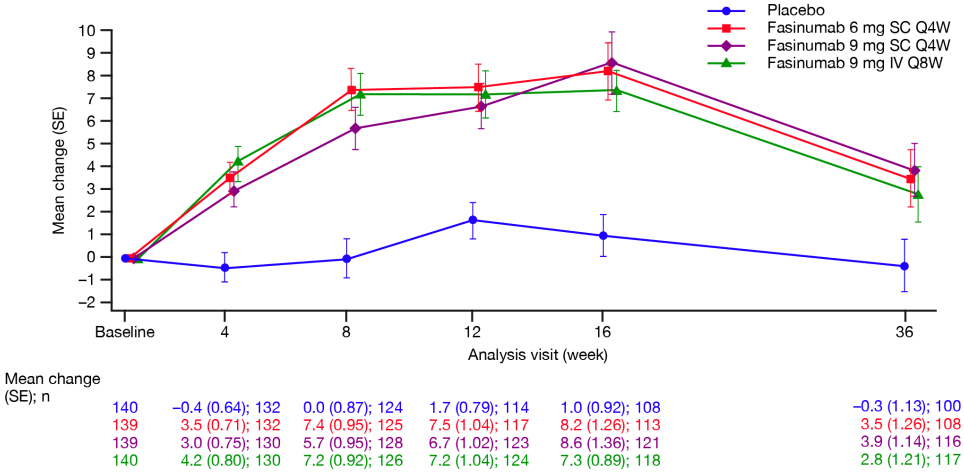

Figure 3 Mean change from baseline in alkaline phosphatase (U/L) (safety analysis set). IV, intravenous; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous.

DISCUSSION

In this study, fasinumab provided improvements in CLBP, function and overall patient assessment of benefit. Although these outcome measures were focused on assessment at the end of the 16-week treatment period (primary endpoint), improvements were noted across most parameters and dose regimens as early as week 2. A key limitation of the study is that because of the FDA hold and early termination of dosing, results are based on an incomplete cohort (35%–56% receiving all planned doses of study drug); data for fewer patients than originally planned were available for efficacy and safety analyses, and p values were considered nominal. Exposure data are limited because of the relatively short treatment duration (16 weeks) and because not all subjects received all planned doses. Moreover, the pOA subgroup analyses were exploratory (a formal diagnosis of OA per American College of Rheumatology (ACR) criteria was not required at study entry and patients were not stratified for OA), but provided an opportunity to address emerging concerns about AA risk in pOA patients as the development programme matured. The use of loading doses in the fasinumab SC groups should also be considered when interpreting the efficacy and safety results. Although the loading dose may have influenced SC treatment effect at earlier time points, it did not seem to impact differences in effect noted across the 9 mg SC and IV dose groups, though this possibility cannot be excluded for the 6 mg SC group.

Although cross-study comparisons are imprecise, the placebo-adjusted treatment effect of fasinumab at endpoint, which ranged from –0.3 for fasinumab 6 mg SC Q4W to –0.7 for 9 mg SC Q4W and IV Q8W, is broadly consistent with studies in patients with CLBP of another NGF inhibitor, IV or SC tanezumab, which reported week-16 placebo-adjusted treatment effects of –0.3 for 5 mg and –0.4 to –0.8 for 10 mg.[24 25] The efficacy of fasinumab in the current study also appears comparable or slightly better than most potent opioids (placebo-adjusted treatment effect of –0.4 was reported in a systematic review and meta-analysis),[26] and maximal doses of NSAIDs (treatment effect of –0.4 for naproxen was reported in the IV tanezumab trial).[25]

CLBP can be caused by various aetiologies including chronic muscular pain, discogenic pain and facet joint OA. However, prior studies have been unable to deconvolute the various components that might contribute to pain in different patients. Our study provided an opportunity to evaluate responses across subgroups without and with pOA, known to be associated with facet joint OA.[27] Since studies focused on OA had suggested a dose-related risk of arthropathy,[20] analysis by pOA status was also an opportunity to uncover differential safety patterns in the treatment of CLBP. Patients with pOA generally experienced greater placebo-adjusted improvement in pain and function than those without, in part driven by greater resolution of pain in the placebo group of the non-pOA subgroup, and was particularly evident at earlier timepoints (4 and 8 weeks), when more patient data were available for assessment. These findings might reflect differential components of pain in these two subgroups. For example, a greater proportion of patients without pOA may have had CLBP caused by factors other than OA of the spine, such as proximal radiculopathy (ie, included in Quebec Task Force category 2). NGF inhibitor therapy has shown no benefit in patients with pain caused by radiculopathy (ie, sciatica).[28]

The incidence of TEAEs was similar between placebo and fasinumab. However, patients treated with fasinumab had higher rates of AAs across all doses studied. All but one AA occurred in patients with concomitant pOA, suggesting that pOA patients may be more predisposed than those without to risk of arthropathy at the high fasinumab doses used in this CLBP study. These findings are consistent with studies that reported higher rates of arthropathy at the highest doses of fasinumab and tanezumab, beyond those producing maximal treatment benefit in OA pain.[20 25 29–31] Across a higher dose range studied in CLBP here, there was no clear difference across doses in the frequency of AA events, even when focusing only on the pOA subgroup.

Elevations in ALP with fasinumab treatment were observed in a phase IIb/III study in patients with OA of the knee or hip.[20] In the current study, mean ALP elevations (peak at week 16) were lower than observed in the previous OA study, even in the pOA subgroup. ALP levels returned towards normal during the post-treatment follow-up, as has been previously reported.[20] It is unclear whether these small changes in ALP associated with treatment represent bone turnover or a more independent effect on enzyme production or enzymatic activity.

Despite dosing being prematurely terminated, all fasinumab doses provided improvements versus placebo in measures of pain (average daily LBPI NRS score), function (RMDQ) and overall patient assessment (PGA) over the first 8 weeks of the study. Significant pain improvement was maintained over 16 weeks for both fasinumab 9 mg groups, but not for 6 mg. Further studies will be needed to determine whether the robust efficacy shown at week 8 is sustained for longer durations at lower doses. Although the treatment benefit in this study was numerically greater in the pOA subgroup, the rates of AA in these patients were substantially higher. This study, therefore, validated concerns about the use of fasinumab in CLBP subjects with concomitant OA, whose benefit–risk at the highest doses was unacceptable. For patients without pOA, low rates of AA were observed at these high doses, though treatment effect was more modest. In these patients, since their back pain may be dominated by mechanisms other than OA, fasinumab may be less likely to provide benefit. Hypothetically these patients may also need even higher doses, and joint AEs would need to be carefully balanced against treatment benefits. Further studies with longer treatment and follow-up are needed to inform benefit–risk.

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Competing interests PD, SJD, CAE, HG, GPG, NS, DMW and GDY are employees of Regeneron Pharmaceuticals. JG reports consulting fees from Pfizer and participation in other activities with Regeneron Pharmaceuticals outside the submitted work. AJK reports participation in other activities with Altoona Center for Clinical Research, PC, during the conduct of the study; and other activities from AbbVie, Celgene, Horizon, Janssen, Merck, Novartis, Pfizer, UCB, Genzyme, Sanofi, Regeneron Pharmaceuticals, SUN Pharma Advanced Research, Boehringer Ingelheim, Flexion, Amgen and Gilead, outside the submitted work. NS reports grants from Regeneron Pharmaceuticals during the conduct of this study; and personal fees from Regeneron Pharmaceuticals and Orthofix, outside the submitted work.

Patient consent for publication Not required.

Ethics approval The protocol was approved by local institutional review boards and/or ethics committees (see online supplemental methods) and conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, consistent with Good Clinical Practices and applicable regulatory requirements. Informed consent was obtained from each patient.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymized participant data will be considered for sharing once the product and indication has been approved by major health authorities (e.g., FDA, EMA, PMDA, etc), if there is legal authority to share the data and there is not a reasonable likelihood of participant re-identification. Submit requests to https://vivli.org/

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Supplementary Materials

Efficacy and safety of fasinumab in patients with chronic low back pain: a phase II/III randomized clinical trial

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Supplementary Methods

Inclusion criteria

A patient must have met all of the following criteria to be eligible for inclusion in the study:

1. Male or female ≥35 years of age at the screening visit
2. Provided signed informed consent
3. Body mass index ≤39 kg/m^2
4. Clinical diagnosis of chronic moderate-to-severe LBP for ≥3 months (prior to the screening visit)
    a. Quebec taskforce category 1 (pain without radiation) or category 2 (pain with proximal radiation above the knee)
    b. Primary pain location between 12th thoracic vertebra and lower gluteal fold
    c. At both the screening and the randomization visit, an LBPI NRS score of ≥4 over the previous 24 hours
    d. During the pre-randomization period, mean daily LBPI score of ≥4
    e. At the screening visit, PGA of LBP of fair, poor, or very poor
5. History of regular analgesic medication, such as NSAIDs, COX-2 inhibitors, opioids, paracetamol/acetaminophen, or a combination thereof
    a. Taking medication >4 days per week in the month prior to screening

   b. Willing to discontinue current opioid pain medications starting at pre-randomization visit through the week 16 study visit

   c. Willing to discontinue current NSAID pain medications (oral or topical) starting at pre-randomization visit through 16 weeks after last dose of study drug

6. A history of inadequate pain relief or intolerance to analgesics used for chronic LBP as defined by:

   a. Intolerance or inadequate pain relief from paracetamol/acetaminophen, and

   b. Intolerance or inadequate pain relief from at least 1 oral NSAID, and

   c. Intolerance or inadequate pain relief from at least 1 opioid, unwillingness to take opioid therapy, or lack of access to opioid therapy

7. Willing to consider TJR surgery, if necessary
   NOTE: This inclusion criterion was added in protocol amendment 2

8. Willing and able to comply with clinic visits and study-related procedures

9. Able to understand and complete study-related questionnaires

Exclusion criteria

A patient who met any of the following criteria was excluded from the study:

1. Four or more consecutive LBPI NRS data entries missed during the pre-randomization period.

2. History of Quebec taskforce category >2 (pain with proximal radiation above the knee) lumbosacral radiculopathy within the past 2 years prior to the screening visit

3. Patient was not a candidate for MRI

4. Evidence on baseline lumbar spine MRI (or lumbar spine X-ray, if requested) of severe spinal stenosis, disc herniation with substantial neural encroachment, recent vertebral fracture, an active destructive process, or marked segmental instability (as indicated by bone marrow oedema or Modic type I change, respectively)

5. History of major trauma, or back surgery in the past 6 months prior to the screening visit.

6. History or presence of pyriformis syndrome

7. History or presence at the screening visit of non-OA inflammatory joint disease (e.g. rheumatoid arthritis, lupus erythematosus, psoriatic arthritis, pseudogout, joint infections), multiple sclerosis, seronegative spondyloarthropathy, Paget's disease of the spine, pelvis, or femur, fibromyalgia, or tumours or infections of the spinal cord

8. Use of extended-release opioids or long-acting opioids such as oxycodone controlled-release, oxymorphone extended release, hydromorphone, transdermal fentanyl, or methadone within 3 months prior to the screening visit

9. Use of a monoamine reuptake inhibitor, tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors for treatment of pain within 4 weeks prior to the screening visit
10. Systemic (i.e. oral or intramuscular) corticosteroids or intra-articular corticosteroid injections within 30 days prior to the screening visit
11. Epidural steroid injections within 3 months prior to the screening visit
12. Botox injections for LBP within 6 months prior to the screening visit
13. History or presence on imaging of arthropathy (osteonecrosis, subchondral insufficiency fracture, rapidly progressing OA type 1 or type 2), stress or recent fracture, neuropathic joint arthropathy, hip dislocation (prosthetic hip dislocation is eligible), knee dislocation (patella dislocation is eligible), congenital hip dysplasia with degenerative joint disease, extensive subchondral cysts, evidence of bone fragmentation or collapse, or primary metastatic tumour with the exception of chondromas or pathological fractures during the screening period
14. Was scheduled for a joint replacement surgery during the study period
15. Signs and symptoms of carpal tunnel syndrome within 6 months of screening
16. History or presence at the screening visit of autonomic neuropathy, diabetic neuropathy, or other peripheral neuropathy including reflex sympathetic dystrophy
17. Evidence of autonomic neuropathy at the screening visit, as defined in the Survey of Autonomic Symptoms

18. History or diagnosis of chronic autonomic failure syndrome including pure autonomic failure and multiple system atrophy (Shy-Drager syndrome)

19. Poorly controlled diabetes (Haemoglobin A1c [HbA1c] >9.0%) at the screening visit

20. Confirmed elevated screening alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5x upper limit of normal (ULN)
    NOTE: This inclusion criterion was added in protocol amendment 1

21. Resting heart rate of <50 beats per minute (bpm) at the screening, pre-randomization, or randomization visits

22. History or presence of 2nd or 3rd degree heart block, 1st degree heart block with abnormal QRS, or bifascicular block by ECG at the screening visit

23. History or presence of orthostatic hypotension at the screening, pre-randomization, or baseline visits

24. Poorly controlled hypertension

    - Systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg at the screening visit

    - Systolic blood pressure of 160 mm Hg to 179 mm Hg or diastolic blood pressure of 100 mm Hg to 109 mm Hg at the screening visit, AND a history of end-organ damage (including history of left ventricular hypertrophy, heart failure, angina, myocardial infarction, stroke, transient ischemic attack (TIA), peripheral arterial disease, and moderate to advanced retinopathy [haemorrhages or exudates, papilledema])

25. Congestive heart failure with NY Heart Classification of stage 3 or 4

26. TIA or cerebrovascular accident within the past 12 months prior to the screening visit, or myocardial infarction or acute coronary syndromes within the past 6 months prior to the screening visit

27. Significant concomitant illness including, but not limited to, psychiatric, cardiac, renal, hepatic, neurological, endocrinological, metabolic, or lymphatic disease that, in the opinion of the investigator, would adversely affect the patient's participation in the study

28. New major illness diagnosed within 2 months prior to the screening visit

29. Known history of ocular herpes simplex virus, herpes simplex virus pneumonia, or herpes simplex virus encephalitis

30. Known history of human immunodeficiency virus infection

31. Known history of infection with hepatitis B virus. Patients with a history of hepatitis B are eligible if there is documentation of a negative test for hepatitis B surface antigen and a positive test for antibodies to the hepatitis B virus surface antigen

32. Known history of infection with hepatitis C virus. Patients with a history of hepatitis C are eligible if there is documentation of a negative hepatitis C virus RNA test

33. History or presence of malignancy within the last 5 years prior to screening, except patients who have been treated successfully with no recurrence for >1

year of basal cell or squamous cell carcinoma of the skin or in-situ cervical cancer

34. Known allergy or sensitivity to doxycycline or related compounds, or monoclonal antibodies

35. History of (within 5 years prior to the screening visit) current alcoholism, alcohol abuse, substance abuse, or abuse of prescription pain medication

36. History of cannabis use for the treatment of pain within the past 6 months prior to the screening visit

37. History of hospital admission for depression or suicide attempt within 5 years or active, severe major depression at screening

38. Current or pending worker's compensation, litigation, disability, or any other monetary settlement related to LBP

39. Ongoing participation in a clinical research study evaluating another investigational drug or having received another investigational product within 30 days or 5 half-lives, whichever is longer

40. Exposure to an anti-NGF antibody within 6 months prior to the screening visit or known sensitivity or intolerance to anti-NGF antibodies

41. Pregnant or breast-feeding women

42. Women of childbearing potential who had a positive pregnancy test result or did not have their pregnancy test result at baseline

43. Women of childbearing potential who were unwilling to use acceptable contraceptive methods during the study and for 20 weeks after the last dose of study drug. Acceptable methods of contraception included combined (oestrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal); progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable); intrauterine device; intra-uterine hormone-releasing system; bilateral tubal occlusion; vasectomized partner; sexual abstinence; or condom in combination with either cap, diaphragm, or sponge with spermicide (double-barrier contraception).

Safety monitoring

An independent data monitoring committee (DMC), consisting of statistical and medical experts, met periodically to review unblinded data as the study progressed. The DMC assessed the safety of fasinumab, with a focus on joint-related adverse events, sympathetic nervous system dysfunction, and neurosensory disturbances. The DMC made recommendations to the sponsor based on the conduct of the study, however no action was requested during the study period.

An independent blinded adjudication committee composed of musculoskeletal radiologists reviewed images for joint AEs, pre-operative images in patients undergoing joint replacements, and routine study scheduled images of suspicious findings by the central reader, for AAs. Positive adjudications met the definition for one or more of the following categories: rapidly progressive osteoarthritis (RPOA) type 1 (RPOA1), RPOA type 2 (RPOA2), subchondral insufficiency fracture (SIF), or primary osteonecrosis. RPOA1 was defined as joint space narrowing exceeding pre-

specified thresholds. For knee joints with a baseline joint space width (JSW) ≥2 mm, reduction had to be ≥2 mm or 50% from baseline at any time point during the study, whichever was greater. For knee joints with baseline JSW <2 mm, a reduction of JSW to 0 mm qualified as RPOA1. For hip joints; if JSW was >1.5 mm at baseline, a reduction of >1.5 mm from baseline qualified as RPOA1. If JSW was <1.5 mm at baseline, then a reduction in JSW to 0 mm also qualified as RPOA1. RPOA2 was defined as changes in bone structure on plain film or magnetic resonance imaging (MRI), atypical of advanced OA. Subchondral insufficiency fracture was defined as subchondral radiolucency, which could have a possible sclerotic linear component and articular surface flattening, confirmed by MRI. Primary osteonecrosis was defined as a focal circumscribed or extended region of mottled radiolucency without evidence of subchondral collapse or bone fragmentation, confirmed by MRI. Because the categories are not always considered mutually exclusive, particularly when reviewing MRIs, the adjudication process across the fasinumab program was updated during the conduct of the study such that the adjudication committee had the option to select more than one category simultaneously in a single joint. All patients received x-rays of the knees, hips, and shoulders at screening as well as MRI of any knee or hip with K-L score ≥3.

Analysis sets

The safety analysis set included all randomized patients who received any study drug. The full analysis set included all randomized patients and was based on the treatment allocated (as randomized). The full analysis set was used to perform sensitivity analysis for the primary and selected secondary endpoints.

A modified intent-to-treat set (mITT) was specified in the final SAP, before database lock, in response to the unplanned early termination of dosing in the study. This set included all randomized patients who received at least one dose of study drug based on the treatment allocated (as randomized) including data up to 5 weeks after the last dose of study drug. Originally, the efficacy data in the study was to be analyzed based on data collected up to week 16, which was 4 weeks after the last planned dose of study therapy for patients receiving fasinumab Q4W. However, with the early cessation of dosing, many patients at week 16 would have discontinued dosing more than 5 weeks before the week 16 visit and thus would not be expected to continue to derive efficacy from the study drug. Thus, this modification to the treatment set was implemented.

Statistical analysis

The primary efficacy endpoint, change from baseline to week 16 in LBPI NRS score, was analysed using a mixed-effect model repeated measures approach based on the mITT analysis set. The model included the randomization strata, baseline LBPI score, treatment, study week, and treatment-by-week interaction. Denominator degrees of freedom were estimated using Kenward-Roger's approximation. Data from all patients, including data collected after discontinuing treatment up to the earlier of withdrawal of consent, week 16, or 5 weeks after the last dose of study drug, were used in the primary efficacy analyses according to the intent-to-treat principle using the MMRM approach with no imputation for missing data. Additional sensitivity analysis was performed using the full analysis set, which included all randomized patients, for the primary and secondary endpoints.

Supplementary Results

Patient disposition

Approximately 30% (166 patients) of the 563 randomized patients completed the week 16 end of treatment visit before the study was placed on partial clinical hold. Of these patients, six discontinued treatment early due to an AE (three patients), physician decision (two patients), or withdrawal by patient (one patient). The remaining 70% (397 patients) did not complete dosing through the end of the treatment period (week 16 visit) before the study was placed on partial clinical hold. Across the treatment groups, 42% to 54% of these patients were followed for safety and completed their remaining visits to week 36 following the partial clinical hold.

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Supplementary Table 1. Study drug administration (safety analysis set)

		Fasinumab			
	Placebo (n=140)	**6 mg SC Q4W (n=139)**	**9 mg SC Q4W (n=139)**	**9 mg IV Q8W (n=140)**	**Total (N=558)**
SC study drug injection*					
Compliance (%), mean (SD)	94.3 (15.0)	95.1 (14.1)	97.5 (11.6)	95.0 (14.4)	95.5 (13.9)
Number of SC injections (% of patients)					
1	33 (23.6%)	32 (23.0%)	33 (23.7%)	34 (24.3%)	132 (23.7%)
2	33 (23.6%)	32 (23.0%)	28 (20.1%)	28 (20.0%)	121 (21.7%)
3	23 (16.4%)	26 (18.7%)	19 (13.7%)	22 (15.7%)	90 (16.1%)
4	51 (36.4%)	49 (35.3%)	59 (42.4%)	56 (40.0%)	215 (38.5%)
IV study drug infusion					
Compliance (%), mean (SD)	95.7 (14.1)	95.3 (15.8)	98.9 (7.3)	97.5 (10.9)	96.9 (12.5)
Number of IV injections (% of patients)					
1	68 (48.6%)	67 (48.2%)	61 (43.9%)	64 (45.7%)	260 (46.6%)
2	72 (51.4%)	71 (51.1%)	78 (56.1%)	76 (54.3%)	297 (53.2%)
Missing	0	1	0	0	1
Mean total fasinumab dose/patient, mg	N/A	22.0	33.7	13.9	N/A

*SC treatment included loading dose as well as nominal dose on day of first study drug treatment

Compliance = (Number of actual injections or infusions of study drug during exposure period)/(Number of planned injections or infusions of study drug during exposure period on or before the time that the patient discontinued from the study) x 100%.

IV, intravenous; N/A, not applicable; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; SD, standard deviation.

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Supplementary Table 2. Change from baseline to week 16 in the average daily LBPI NRS, RMDQ, and PGA of LBP scores in patients with and without OA of the peripheral joints (mITT analysis set)

		Fasinumab		
	Placebo	**6 mg SC Q4W**	**9 mg SC Q4W**	**9 mg IV Q8W**
		LBPI NRS		
Patients with OA of the peripheral joints, n	82	92	68	78
Baseline average daily LBPI NRS score, mean (SD); n	6.4 (1.2); 81	6.6 (1.3); 90	6.7 (1.4); 68	6.2 (1.1); 78
Week 8				
Average daily LBPI NRS score, mean (SD); n	5.6 (2.1); 55	4.8 (2.1); 62	3.9 (2.3); 51	4.0 (2.2); 59
Change from baseline to week 8, mean (SD); n	–1.0 (2.0)	–1.9 (2.1)	–2.7 (1.9)	–2.2 (2.0)
LS mean (SE)	–0.9 (0.3)	–1.8 (0.2)	–2.6 (0.3)	–2.2 (0.3)
95% CI	(–1.39, –0.40)	(–2.24, –1.31)	(–3.11, –2.08)	(–2.67, –1.70)
Difference vs placebo, LS mean (SE)		–0.9 (0.3)	–1.7 (0.4)	–1.3 (0.3)
95% CI		(–1.53, –0.22)	(–2.40, –1.00)	(–1.96, –0.62)
Week 16				
Average daily LBPI NRS score, mean (SD); n	4.5 (2.4); 32	4.2 (2.1); 32	3.6 (2.2); 26	4.0 (2.5); 34
Change from baseline to week 16, mean (SD); n	–2.1 (2.4); 31	–2.5 (2.0); 32	– 2.9 (1.8); 26	–2.2 (2.0); 34
LS mean (SE)	–1.7 (0.3)	–2.0 (0.3)	–2.6 (0.3)	–2.3 (0.3)
95% CI	(–2.26, –1.09)	(–2. 56, –1.43)	(–3.20, –1.94)	(–2.84, –1.70)

Difference vs placebo, LS mean (SE)		–0.3 (0.4)	–0.9 (0.4)	–0.6 (0.4)
95% CI		(–1.11, 0.48)	(–1.73, –0.04)	(–1.39, 0.21)
Patients without OA of the peripheral joints, n	58	47	71	62
Baseline average daily LBPI NRS score, mean (SD); n	6.6 (1.4); 58	6.3 (1.3); 47	6.7 (1.2); 71	6.7 (1.2); 62
Week 8				
Average daily LBPI NRS score, mean (SD); n	4.9 (2.0); 41	4.5 (1.7); 37	4.6 (2.5); 54	4.3 (2.6); 44
Change from baseline to week 8, mean (SD); n	–1.7 (1.4); 41	–1.8 (1.5); 37	–2.1 (2.4); 54	–2.3 (2.6); 44
LS mean (SE)	–1.6 (0.3)	–1.6 (0.4)	–1.9 (0.3)	–2.2 (0.3)
95% CI	(–2.26, –0.94)	(–2.37, –0.90)	(–2.58, –1.26)	(–2.82, –1.49)
Difference vs placebo, LS mean (SE)		–0.0 (0.4)	–0.3 (0.4)	–0.6 (0.40)
95% CI		(–0.87, 0.80)	(–1.08, 0.44)	(–1.34, 0.23)
Week 16				
Average daily LBPI NRS score, mean (SD); n	4.9 (1.2); 18	4.6 (1.4); 16	4.7 (2.2); 29	3.8 (2.4); 22
Change from baseline to week 16, mean (SD); n	–1.4 (1.5); 18	–1.5 (1.5); 16	–2.4 (2.1); 29	–2.9 (2.5); 22
LS mean (SE)	–1.7 (0.4)	–1.9 (0.4)	–2.2 (0.4)	–2.6 (0.4)
95% CI	(–2.47, –1.01)	(–2.66, –1.06)	(–2.91, –1.53)	(–3.29, –1.84)
Difference vs placebo, LS mean (SE)		–0.1 (0.5)	–0.5 (0.4)	–0.8 (0.5)
95% CI		(–1.08, 0.84)	(–1.34, 0.38)	(–1.73, 0.07)

RMDQ

Patients with OA of the peripheral joints, n	82	92	68	78
Baseline RMDQ total score, mean (SD); n	11.1 (4.8); 74	11.4 (5.1); 90	10.3 (5.0); 67	11.7 (5.4); 75
Week 8				
RMDQ total score, mean (SD); n	8.7 (5.5); 58	6.2 (5.4); 63	4.8 (4.9); 51	5.5 (5.0); 60
Change from baseline to week 8, mean (SD); n	–2.6 (4.1); 50	–5.5 (5.7); 61	–5.3 (5.1): 50	–7.0 (5.4); 57
LS mean (SE)	–2.4 (0.6)	–5.1 (0.5)	–6.0 (0.6)	–6.1 (0.6)
95% CI	(–3.60, –1.27)	(–6.16, –4.05)	(–7.22, –4.85)	(–7.27, –5.02)
Difference vs placebo, LS mean (SE)		–2.7 (0.8)	–3.6 (0.8)	–3.7 (0.8)
95% CI		(–4.19, –1.15)	(–5.23, –1.98)	(–5.28, –2.14)
Week 16				
RMDQ total score, mean (SD); n	6.5 (5.8); 32	4.6 (4.4); 33	3.5 (3.0); 26	4.9 (4.9); 34
Change from baseline to week 16, mean (SD); n	–3.9 (4.5); 28	–7.2 (6.0); 31	–6.8 (4.5); 26	–6.6 (5.7); 32
LS mean (SE)	–3.3 (0.7)	-6.4 (0.6)	–6.6 (0.7)	–6.5 (0.7)
95% CI	(–4.64, –1.92)	(–7.69, –5.16)	(–7.99, –5.19)	(–7.82, –5.23)
Difference vs placebo, LS mean (SE)		–3.1 (0.9)	–3.3 (1.0)	–3.2 (0.9)
95% CI		(–4.96, –1.33)	(–5.24, –1.39)	(–5.08, –1.42)
Patients without OA of the peripheral joints	58	47	71	62
Baseline RMDQ total score, mean (SD); n	10.6 (5.9); 58	9.7 (5.1); 45	11.1 (6.3); 69	11.6 (5.1); 61
Week 8				
RMDQ total score, mean (SD); n	6.7 (5.6); 42	5.0 (4.8); 38	6.9 (6.1); 54	5. 9 (6.0); 44

Change from baseline to week 8, mean (SD); n	–3.8 (5.6); 42	–5.2 (4.6); 36	–4.2 (4.6); 52	–5.1 (5.3)
LS mean (SE)	–4.5 (0.8)	–6.3 (0.9)	–5.0 (0.7)	–6.4 (0.8)
95% CI	(–6.04, –3.05)	(–8.02, –4.62)	(–6.57, –3.52)	(–7.90, –4.83)
Difference vs placebo, LS mean (SE)		–1.8 (1.0)	–0.5 (0.9)	–1.8 (0.9)
95% CI		(–3.69, 0.13)	(–2.23, 1.23)	(–3.61, –0.04)
Week 16				
RMDQ total score, mean (SD); n	6.7 (5.4); 18	6.2 (5.9); 15	6.0 (5.4); 29	5.2 (5.9); 23
Change from baseline to week 16, mean (SD); n	–3.7 (4.6); 18	–3.7 (4.4); 15	–5.7 (5.0); 29	–6.7 (5.6); 23
LS mean (SE)	–5.1 (0.9)	–5.8 (1.0)	–6.1 (0.8)	–6.7 (0.9)
95% CI	(–6.82, –3.37)	(–7.74, –3.85)	(–7.71, –4.44)	(–8.38, –4.98)
Difference vs placebo, LS mean (SE)		–0.7 (1.2)	–1.0 (1.0)	–1.6 (1.1)
95% CI		(–3.02, 1.63)	(–3.03, 1.07)	(–3.71, 0.54)
		PGA of LBP		
Patients with OA of the peripheral joints, n	82	92	68	78
Baseline PGA, mean (SD); n	3.5 (0.7); 82	3.5 (0.7); 92	3.3 (0.9); 68	3.4 (0.6); 78
Week 8				
PGA, mean (SD); n	3.1 (0.8); 58	2.7 (0.9); 63	2.4 (0.9); 51	2.6 (0.9); 60
Change from baseline to week 8, mean (SD); n	–0.5 (0.8); 58	–0.8 (1.0); 63	–0.9 (1.1); 51	–0.9 (0.9); 60
LS mean (SE)	–0.5 (0.1)	–0.8 (0.1)	–1.0 (0.1)	–0.8 (0.1)
95% CI	(–0.67, –0.25)	(–1.00, –0.60)	(–1.19, –0.74)	(–1.05, –0.63)
Difference vs placebo, LS mean (SE)		–0.3 (0.1)	–0.5 (0.2)	–0.4 (0.2)

95% CI		(–0.61, –0.05)	(–0.80, –0.20)	(–0.66, –0.08)
Week 16				
PGA, mean (SD); n	2.7 (0.8); 32	2.4 (0.9); 33	2.3 (0.9); 26	2.3 (1.0); 34
LS mean (SE)	–0.7 (0.1)	–0.9 (0.1)	–1.0 (0.2)	–1.0 (0.1)
95% CI	(–0.98, –0.45)	(–1.16, –0.64)	(–1.26, –0.68)	(–1.25, –0.73)
Difference vs placebo, LS mean (SE)		–0.2 (0.2)	–0.3 (0.2)	–0.3 (0.2)
95% CI		(–0.55, 0.18)	(–0.65, 0.13)	(–-0.64, 0.09)
Patients without OA of the peripheral joints, n	58	47	71	62
Baseline PGA, mean (SD); n	3.6 (0.7); 58	3.4 (0.7); 47	3.4 (0.7); 71	3.4 (0.8); 62
Week 8				
PGA, mean (SD); n	3.0 (0.7); 42	2.7 (0.8); 38	2.7 (0.9); 54	2.5 (1.1); 44
Change from baseline to week 8, mean (SD); n	–0.6 (0.9); 42	–0.8 (0.8); 38	–0.7 (0.8); 54	–0.9 (1.0); 44
LS mean (SE)	–0.6 (0.1)	–0.8 (0.2)	–0.7 (0.1)	–1.0 (0.1)
95% CI	(–0.84, –0.31)	(–1.08, –0.50)	(–0.97, –0.44)	(–1.28, –0.74)
Difference vs placebo, LS mean (SE)		–0.2 (0.2)	–0.1 (0.2)	–0.4 (0.2)
95% CI		(–0.55, 0.13)	(–0.43, 0.19)	(–0.76, –0.12)
Week 16				
PGA, mean (SD); n	3.0 (0.6); 18	2.7 (1.0); 15	2.7 (1.0); 29	2.4 (0.9); 23
Change from baseline to week 16, mean (SD); n	–0.6 (0.6); 18	–0.5 (1.1); 15	–0.8 (0.8); 29	–1.0 (0.9); 23
LS mean (SE)	–0.7 (0.2)	–0.9 (0.2)	–0.8 (0.1)	–1.1 (0.2)
95% CI	(–0.99, –0.39)	(–1.20, –0.54)	(–1.06, –0.51)	(–1.39, –0.81)

Difference vs placebo, LS mean (SE)	–0.2 (0.2)	–0.1 (0.2)	–0.4 (0.2)
95% CI	(–0.58, 0.22)	(–0.45, 0.25)	(–0.78, –0.05)

Analyses are based on MMRM model with baseline randomization strata, baseline score, treatment, visit, and treatment-by-visit interaction.

CI, confidence interval; IV, intravenous; LBPI NRS, low back pain intensity numeric rating scale; LS, least squares; OA, osteoarthritis; PGA, patient global assessment; Q4W, every 4 weeks; Q8W, every 8 weeks; RMDQ, Roland-Morris Disability Questionnaire; SD, standard deviation; SE, standard error; SC, subcutaneous; TEAE, treatment-emergent adverse event.

Supplementary Table 3. Summary of TEAEs during the on-treatment period (safety analysis set)

		Fasinumab			
	Placebo (n=140)	**6 mg SC Q4W (n=139)**	**9 mg SC Q4W (n=139)**	**9 mg IV Q8W (n=140)**	**Combined (N=418)**
Patients with any TEAE, n (%)	94 (67.1%)	85 (61.2%)	95 (68.3%)	94 (67.1%)	274 (65.6%)
Patients with any serious TEAE, n (%)	4 (2.9%)	2 (1.4%)	3 (2.2%)	5 (3.6%)	10 (2.4%)
Patients with any severe TEAE, n (%)	5 (3.6%)	4 (2.9%)	2 (1.4%)	3 (2.1%)	9 (2.2%)
Patients with any TEAE leading to study drug discontinuation, n (%)	9 (6.4%)	5 (3.6%)	5 (3.6%)	5 (3.6%)	15 (3.6%)
Patients with any TEAE leading to study withdrawal, n (%)	10 (7.1%)	6 (4.3%)	2 (1.4%)	5 (3.6%)	13 (3.1%)
Patients with any TEAE leading to death, n (%)	0	0	0	0	0

IV, intravenous; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; TEAE, treatment-emergent adverse event.

Supplementary Table 4. Summary of AEs with >3% incidence during the post-treatment follow-up period by System Organ Class and Preferred Term (safety analysis set)

		Fasinumab			
Primary System Organ Class Preferred Term	**Placebo (n=140)**	**6 mg SC Q4W (n=139)**	**9 mg SC Q4W (n=139)**	**9 mg IV Q8W (n=140)**	**Combined (N=418)**
Number of post-treatment AEs	45	73	58	64	195
Patients with at least one post-treatment AE, n (%)	39 (27.9%)	42 (30.2%)	39 (28.1%)	44 (31.4%)	125 (29.9%)
Musculoskeletal and connective tissue disorders	20 (14.3%)	32 (23.0%)	28 (20.1%)	33 (23.6%)	93 (22.2%)
Arthralgia	13 (9.3%)	16 (11.5%)	9 (6.5%)	13 (9.3%)	38 (9.1%)
Back pain	4 (2.9%)	9 (6.5%)	12 (8.6%)	8 (5.7%)	29 (6.9%)
Pain in extremity	1 (0.7%)	7 (5.0%)	4 (2.9%)	10 (7.1%)	21 (5.0%)
Rapidly progressive osteoarthritis	1 (0.7%)	5 (3.6%)	4 (2.9%)	6 (4.3%)	15 (3.6%)
Musculoskeletal pain	2 (1.4%)	6 (4.3%)	3 (2.2%)	5 (3.6%)	14 (3.3%)
Infections and infestations	20 (14.3%)	17 (12.2%)	14 (10.1%)	14 (10.0%)	45 (10.8%)
Nasopharyngitis	7 (5.0%)	8 (5.8%)	7 (5.0%)	6 (4.3%)	21 (5.0%)
Upper respiratory tract infection	7 (5.0%)	5 (3.6%)	6 (4.3%)	2 (1.4%)	13 (3.1%)
Bronchitis	1 (0.7%)	3 (2.2%)	5 (3.6%)	4 (2.9%)	12 (2.9%)
Urinary tract infection	5 (3.6%)	1 (0.7%)	0	4 (2.9%)	5 (1.2%)

Post-treatment AEs included any AEs reported during the post-treatment follow-up period with an onset more than 4 weeks from the last dose of SC study drug or 8 weeks from the last dose of IV study drug.

MedDRA (Version 18.0) coding applied.

A patient who reported 2 or more AEs with the same preferred term is counted only once for that term.

A patient who reported 2 or more AEs with different preferred terms within the same system organ class is counted only once in that system organ class.

For system organ classes, the table is sorted by decreasing frequency in combined fasinumab group. Within each system organ class, preferred terms are sorted by decreasing frequency count in combined fasinumab group.

AE; adverse event; IV, intravenous; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous.

Dakin P, *et al*. *Ann Rheum Dis* 2020;0:1–9. doi: 10.1136/annrheumdis-2020-217259

Supplementary Table 5. Summary of SAEs during the on-treatment period by System Organ Class and Preferred Term (safety analysis set)

Primary System Organ Class Preferred Term	Placebo (n=140)	Fasinumab			
		6 mg SC Q4W (n=139)	9 mg SC Q4W (n=139)	9 mg IV Q8W (n=140)	Combined (N=418)
Number of serious TEAEs	4	4	3	5	12
Patients with at least one serious TEAE, n (%)	4 (2.9%)	2 (1.4%)	3 (2.2%)	5 (3.6%)	10 (2.4%)
Injury, poisoning and procedural complications	1 (0.7%)	1 (0.7%)	0	2 (1.4%)	3 (0.7%)
Concussion	0	1 (0.7%)	0	0	1 (0.2%)
Craniocerebral injury	0	1 (0.7%)	0	0	1 (0.2%)
Meniscus injury	0	0	0	1 (0.7%)	1 (0.2%)
Patella fracture	0	0	0	1 (0.7%)	1 (0.2%)
Skull fracture	0	1 (0.7%)	0	0	1 (0.2%)
Eye injury	1 (0.7%)	0	0	0	0
Cardiac disorders	0	1 (0.7%)	0	0	1 (0.2%)
Angina pectoris	0	1 (0.7%)	0	0	1 (0.2%)
General disorders and administration site conditions	0	0	0	1 (0.7%)	1 (0.2%)

Pyrexia	0	0	0	1 (0.7%)	1 (0.2%)
Infections and infestations	0	0	1 (0.7%)	0	1 (0.2%)
Diverticulitis	0	0	1 (0.7%)	0	1 (0.2%)
Musculoskeletal and connective tissue disorders	0	0	1 (0.7%)	0	1 (0.2%)
Osteoarthritis	0	0	1 (0.7%)	0	1 (0.2%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.7%)	0	0	1 (0.7%)	1 (0.2%)
Adenocarcinoma of colon	0	0	0	1 (0.7%)	1 (0.2%)
Tongue carcinoma stage IV	1 (0.7%)	0	0	0	0
Nervous system disorders	1 (0.7%)	0	1 (0.7%)	0	1 (0.2%)
Haemorrhagic stroke	0	0	1 (0.7%)	0	1 (0.2%)
Cerebrovascular accident	1 (0.7%)	0	0	0	0
Vascular disorders	0	0	0	1 (0.7%)	1 (0.2%)
Hypotension	0	0	0	1 (0.7%)	1 (0.2%)
Investigations	1 (0.7%)	0	0	0	0
Blood creatine phosphokinase increased	1 (0.7%)	0	0	0	0

MedDRA (Version 18.0) coding applied.

A patient who reported 2 or more TEAEs with the same preferred term is counted only once for that term.

A patient who reported 2 or more TEAEs with different preferred terms within the same system organ class is counted only once in that system organ class.

For SOCs, the table is sorted by decreasing frequency in combined fasinumab group. Within each SOC, PTs are sorted by decreasing frequency count in combined fasinumab group.

AE; adverse event; IV, intravenous; PT, preferred term; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; SOC, system organ class; TEAE, treatment-emergent adverse event.

Dakin P, *et al*. *Ann Rheum Dis* 2020;0:1–9. doi: 10.1136/annrheumdis-2020-217259

Supplementary Table 6. Summary of SAEs during the post-treatment follow-up period by System Organ Class and Preferred Term (safety analysis set)

Primary System Organ Class Preferred Term	Placebo (n=140)	Fasinumab			
		6 mg SC Q4W (n=139)	9 mg SC Q4W (n=139)	9 mg IV Q8W (n=140)	Combined (N=418)
Number of serious post-treatment AEs	7	9	7	12	28
Patients with at least one serious post-treatment AE, n (%)	6 (4.3%)	9 (6.5%)	6 (4.3%)	10 (7.1%)	25 (6.0%)
Musculoskeletal and connective tissue disorders	0	3 (2.2%)	3 (2.2%)	5 (3.6%)	11 (2.6%)
Rapidly progressive osteoarthritis	0	1 (0.7%)	1 (0.7%)	5 (3.6%)	7 (1.7%)
Back pain	0	2 (1.4%)	1 (0.7%)	0	3 (0.7%)
Synovial cyst	0	0	1 (0.7%)	0	1 (0.2%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.7%)	2 (1.4%)	0	2 (1.4%)	4 (1.0%)
Bladder cancer	0	0	0	1 (0.7%)	1 (0.2%)
Endometrial adenocarcinoma	0	0	0	1 (0.7%)	1 (0.2%)
Large intestine benign neoplasm	0	1 (0.7%)	0	0	1 (0.2%)
Mediastinum neoplasm	0	0	0	1 (0.7%)	1 (0.2%)
Small cell lung cancer metastatic	0	1 (0.7%)	0	0	1 (0.2%)

Lung neoplasm malignant	1 (0.7%)	0	0	0	0
Cardiac disorders	0	0	2 (1.4%)	0	2 (0.5%)
Atrial fibrillation	0	0	2 (1.4%)	0	2 (0.5%)
Infections and infestations	0	1 (0.7%)	0	1 (0.7%)	2 (0.5%)
Abscess limb	0	0	0	1 (0.7%)	1 (0.2%)
Septic shock	0	1 (0.7%)	0	0	1 (0.2%)
Injury, poisoning and procedural complications	1 (0.7%)	0	1 (0.7%)	1 (0.7%)	2 (0.5%)
Radius fracture	0	0	1 (0.7%)	0	1 (0.2%)
Stress fracture	0	0	0	1 (0.7%)	1 (0.2%)
Ulna fracture	0	0	1 (0.7%)	0	1 (0.2%)
Ankle fracture	1 (0.7%)	0	0	0	0
Nervous system disorders	0	2 (1.4%)	0	0	2 (0.5%)
Cervical radiculopathy	0	1 (0.7%)	0	0	1 (0.2%)
Multiple sclerosis	0	1 (0.7%)	0	0	1 (0.2%)
Psychiatric disorders	0	0	0	1 (0.7%)	1 (0.2%)
Personality disorder	0	0	0	1 (0.7%)	1 (0.2%)
Vascular disorders	0	1 (0.7%)	0	0	1 (0.2%)
Hypertension	0	1 (0.7%)	0	0	1 (0.2%)

Gastrointestinal disorders	2 (1.4%)	0	0	0	0
Intestinal obstruction	1 (0.7%)	0	0	0	0
Pancreatitis acute	1 (0.7%)	0	0	0	0
Hepatobiliary disorders	1 (0.7%)	0	0	0	0
Cholelithiasis	1 (0.7%)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.7%)	0	0	0	0
Haemoptysis	1 (0.7%)	0	0	0	0
Surgical and medical procedures	1 (0.7%)	0	0	0	0
Joint arthropathy	1 (0.7%)	0	0	0	0

MedDRA (Version 18.0) coding applied.

A patient who reported 2 or more AEs with the same preferred term is counted only once for that term.

A patient who reported 2 or more AEs with different preferred terms within the same system organ class is counted only once in that system organ class. For SOCs, the table is sorted by decreasing frequency in combined fasinumab group. Within each SOC, PTs are sorted by decreasing frequency count in combined fasinumab group.

AE; adverse event; IV, intravenous; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; SOC, system organ class.

Supplementary Table 7. Overview of AA events by treatment group, number of scheduled doses, screening K-L score and medical history (safety analysis set)

Treatment group	Number of scheduled doses received	Screening K-L score of affected joint(s)	Maximum K-L score of any joint	Medical history of OA	AA category	Days to first event
Placebo	2 (Day 1, Week 4)	3 (right hip)	4	Y	RPOA1 of the right hip	246
Fasinumab 6 mg SC Q4W	3 (Day 1, Week 4, Week 8)	2 (left knee)	3	Y	RPOA1 of the left knee	269
Fasinumab 6 mg SC Q4W	4 (Day 1, Week 4, Week 8, Week 12)	3 (left knee) 3 (right knee)	3	Y	RPOA1, RPOA2 of the left knee RPOA1, SIF of the right knee	250
Fasinumab 6 mg SC Q4W	3 (Day 1, Week 4, Week 8)	1 (right knee)	1	Y	RPOA1, SIF of right knee	324
Fasinumab 6 mg SC Q4W	4 (Day 1, Week 4, Week 8, Week 12)	2 (left knee) N/A (right shoulder)	3	Y	RPOA1 of the left knee RPOA1 of the right shoulder	251
Fasinumab 6 mg SC Q4W	1 (Day 1)	2 (left hip)	2	Y	RPOA1 of the left hip	259
Fasinumab 9 mg SC Q4W	3 (Day 1, Week 4, Week 8)	2 (right hip)	2	Y	RPOA1 of the right hip	253
Fasinumab 9 mg SC Q4W	4 (Day 1, Week 4, Week 8, Week 12)	2 (left hip)	3	N	RPOA1 of the left hip	379
Fasinumab 9 mg SC Q4W	2 (Day 1, Week 4)	2 (left knee)	2	N	RPOA1 of the left knee	132
Fasinumab 9 mg SC Q4W	2 (Day 1, Week 4)	1 (left knee)	1	Y	RPOA1, SIF of the left knee	254

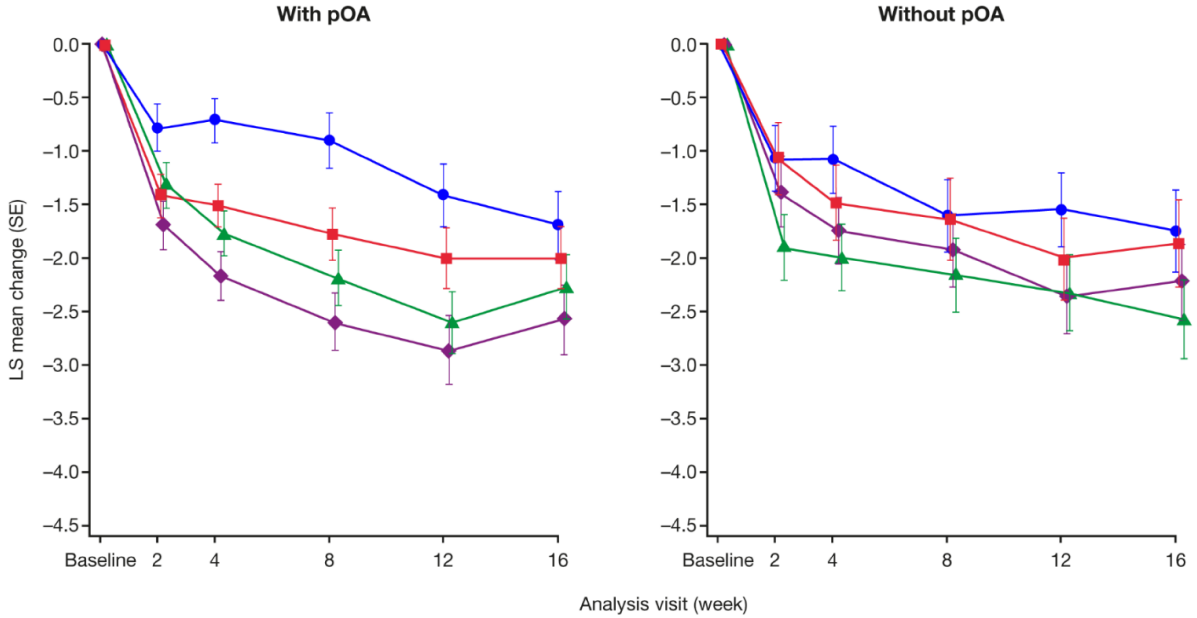
Fasinumab 9 mg IV Q8W	2 (Day 1, Week 8)	2 (right knee)	2	Y	RPOA1 of the right knee	254
Fasinumab 9 mg IV Q8W	2 (Day 1, Week 8)	2 (right knee)	2	Y	RPOA1 of the right knee	280
Fasinumab 9 mg IV Q8W	1 (Day 1)	3 (right hip) N/A (right shoulder)	3	Y	RPOA1 of the right hip RPOA1 of the right shoulder	106
Fasinumab 9 mg IV Q8W	2 (Day 1, Week 8)	3 (right knee)	3	Y	RPOA1 of the right knee	448
Fasinumab 9 mg IV Q8W	2 (Day 1, Week 8)	0 (right knee)	2*	N	RPOA1 of the right knee	398
Fasinumab 9 mg IV Q8W	2 (Day 1, Week 8)	3 (left knee)	3	Y	RPOA2 of the left knee	93
Fasinumab 9 mg IV Q8W	2 (Day 1, Week 8)	3 (left knee)	3	Y	SIF of the left knee	134

*Patient included in non-pOA subgroup; all other patients with AA events were included in the pOA subgroup based on medical history of OA and/or K-L score ≥2 in hip or ≥3 in knee.

K-L scores at screening were only assessed for hip and knee joints; in two shoulder joints, screening radiographs documented one with moderate OA and one with severe OA.

AA, adjudicated arthropathy; IV, intravenous; K-L, Kellgren-Lawrence; OA, osteoarthritis; Q4W, every 4 weeks; Q8W, every 8 weeks; RPOA1, rapid progressive OA type 1; RPOA2, rapid progressive OA type 2; SC, subcutaneous; SIF, subchondral insufficiency fracture.

Supplementary Figure 1. Least squares mean change from baseline in average daily LBPI NRS score by pOA subgroup (mITT analysis set)

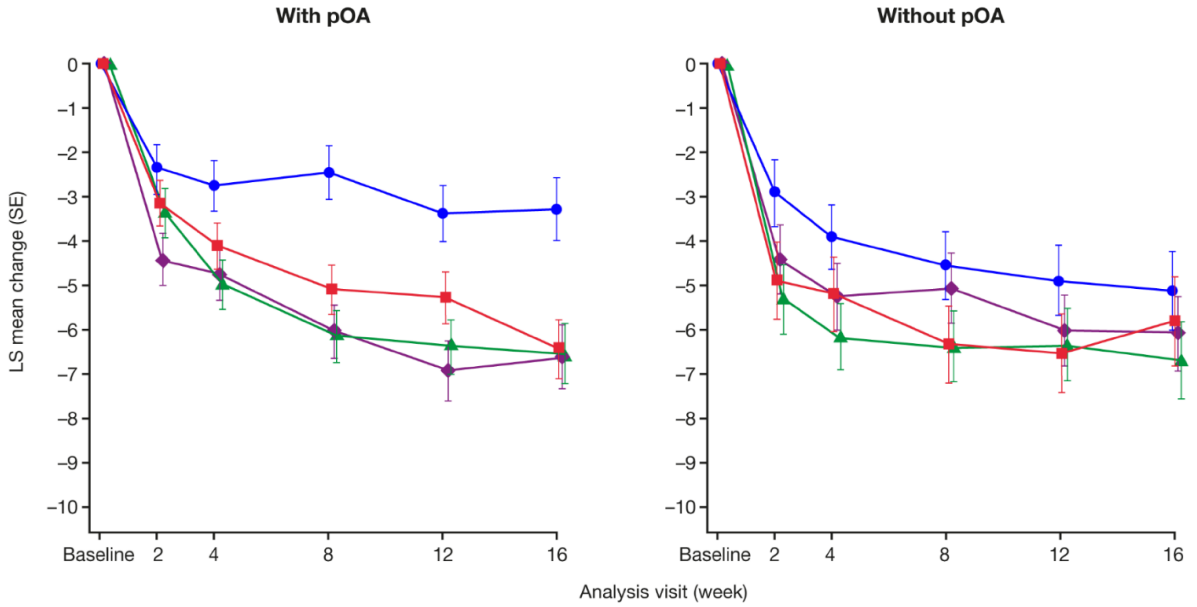


	Baseline	Week 2		Week 4		Week 8		Week 12		Week 16		Baseline	Week 2		Week 4		Week 8		Week 12		Week 16	
	N	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	N	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)
Placebo	81	78	−0.8 (0.21)	77	−0.7 (0.21)	54	−0.9 (0.25)	40	−1.4 (0.29)	31	−1.7 (0.30)	58	58	−1.1 (0.30)	56	−1.1 (0.30)	41	−1.6 (0.33)	29	−1.5 (0.34)	18	−1.7 (0.37)
Fasinumab 6 mg SC Q4W	90	87	−1.4 (0.20)	87	−1.5 (0.19)	61	−1.8 (0.24)	42	−2.0 (0.27)	32	−2.0 (0.29)	47	46	−1.1 (0.34)	45	−1.5 (0.34)	37	−1.6 (0.37)	27	−2.0 (0.37)	16	−1.9 (0.40)
Fasinumab 9 mg SC Q4Wa	68	67	−1.7 (0.22)	61	−2.2 (0.22)	51	−2.6 (0.26)	32	−2.9 (0.31)	26	−2.6 (0.32)	71	68	−1.4 (0.31)	67	−1.7 (0.31)	54	−1.9 (0.34)	42	−2.4 (0.34)	29	−2.2 (0.35)
Fasinumab 9 mg IV Q8W	78	76	−1.3 (0.21)	74	−1.8 (0.21)	59	−2.2 (0.25)	43	−2.6 (0.28)	34	−2.3 (0.29)	62	62	−1.9 (0.30)	58	−2.0 (0.31)	44	−2.2 (0.34)	33	−2.3 (0.34)	22	−2.6 (0.37)

pOA defined by medical history and/or K-L score ≥2 in hip or ≥3 in knee.

IV, intravenous; K-L, Kellgren-Lawrence; LBPI NRS, low back pain intensity numeric rating scale; LSM, least squares mean; mITT, modified intent-to-treat; pOA, peripheral osteoarthritis; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; SE, standard error.

Supplementary Figure 2. Least squares mean change from baseline in RMDQ total score by pOA subgroup (mITT analysis set)

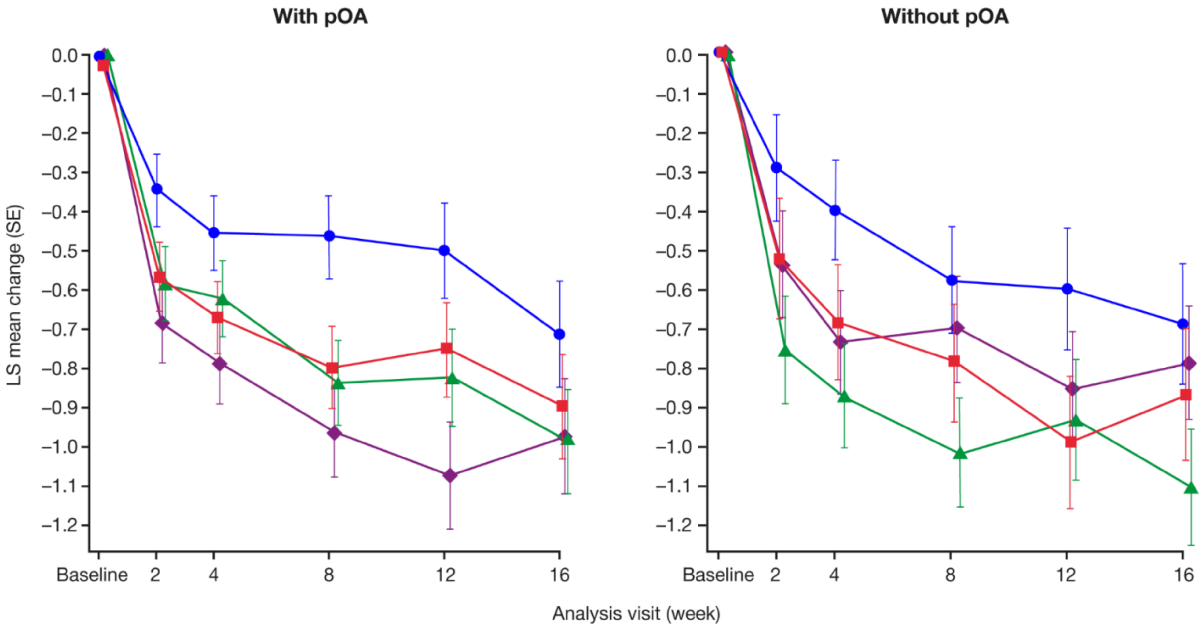


	With pOA										Without pOA									
	Baseline	Week 2		Week 4		Week 8		Week 12		Week 16	Baseline	Week 2		Week 4		Week 8		Week 12		Week 16	
	N	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	N	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)
Placebo	74	70	−2.4 (0.55)	70	−2.7 (0.55)	50	−2.4 (0.59)	37	−3.4 (0.63)	28	−3.3 (0.69)	58	58	−2.9 (0.73)	57	−3.9 (0.72)	42	−4.5 (0.76)	30	−4.9 (0.78)	18	−5.1 (0.87)
Fasinumab 6 mg SC Q4W	90	87	−3.1 (0.50)	85	−4.1 (0.50)	61	−5.1 (0.54)	40	−5.3 (0.59)	31	−6.4 (0.64)	45	45	−4.9 (0.86)	42	−5.2 (0.84)	36	−6.3 (0.86)	26	−6.5 (0.89)	15	−5.8 (0.98)
Fasinumab 9 mg SC Q4W	67	65	−4.4 (0.57)	61	−4.7 (0.58)	50	−6.0 (0.60)	32	−6.9 (0.66)	26	−6.6 (0.71)	69	69	−4.4 (0.76)	65	−5.2 (0.75)	52	−5.0 (0.77)	41	−6.0 (0.79)	29	−6.1 (0.83)
Fasinumab 9 mg IV Q8W	75	72	−3.4 (0.54)	71	−5.0 (0.55)	57	−6.1 (0.57)	41	−6.4 (0.61)	32	−6.5 (0.66)	61	61	−5.3 (0.76)	57	−6.2 (0.75)	44	−6.4 (0.78)	33	−6.3 (0.80)	23	−6.7 (0.86)

pOA defined by medical history and/or K-L score ≥2 in hip or ≥3 in knee.

IV, intravenous; K-L, Kellgren-Lawrence; LSM, least squares mean; mITT, modified intent-to-treat; pOA, peripheral osteoarthritis; Q4W, every 4 weeks; Q8W, every 8 weeks; RMDQ, Roland-Morris Disability Questionnaire; SC, subcutaneous; SE, standard error.

Supplementary Figure 3. Least squares mean change from baseline in PGA of LBP score by pOA subgroup (mITT analysis set)



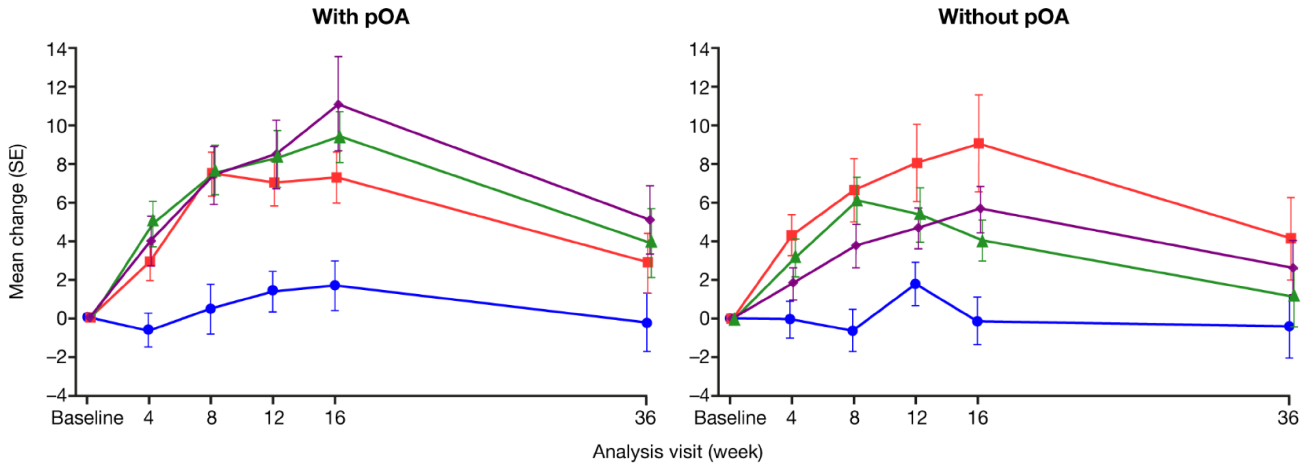
	Baseline	Week 2		Week 4		Week 8		Week 12		Week 16	
	N	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)
Placebo	82	78	−0.3 (0.09)	78	−0.5 (0.10)	58	−0.5 (0.11)	42	−0.5 (0.12)	32	−0.7 (0.13)
Fasinumab 6 mg SC Q4W	92	89	−0.6 (0.09)	87	−0.7 (0.09)	63	−0.8 (0.10)	42	−0.8 (0.12)	33	−0.9 (0.13)
Fasinumab 9 mg SC Q4W	68	66	−0.7 (0.10)	62	−0.8 (0.10)	51	−1.0 (0.11)	32	−1.1 (0.14)	26	−1.0 (0.15)
Fasinumab 9 mg IV Q8W	78	75	−0.6 (0.09)	74	−0.6 (0.10)	60	−0.8 (0.11)	43	−0.8 (0.12)	34	−1.0 (0.13)

	Baseline	Week 2		Week 4		Week 8		Week 12		Week 16	
	N	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)
Placebo	58	58	−0.3 (0.13)	57	−0.4 (0.13)	42	−0.6 (0.14)	30	−0.6 (0.15)	18	−0.7 (0.15)
Fasinumab 6 mg SC Q4W	47	46	−0.5 (0.15)	44	−0.7 (0.14)	38	−0.8 (0.15)	27	−1.0 (0.17)	15	−0.9 (0.17)
Fasinumab 9 mg SC Q4W	71	69	−0.5 (0.13)	67	−0.7 (0.13)	54	−0.7 (0.13)	43	−0.9 (0.15)	29	−0.8 (0.14)
Fasinumab 9 mg IV Q8W	62	61	−0.8 (0.14)	58	−0.9 (0.13)	44	−1.0 (0.14)	33	−0.9 (0.15)	23	−1.1 (0.15)

pOA defined by medical history and/or K-L score ≥2 in hip or ≥3 in knee.

IV, intravenous; K-L, Kellgren-Lawrence; LSM, least squares mean; mITT, modified intent-to-treat; PGA of LBP, Patient Global Assessment of Lower Back Pain; pOA, peripheral osteoarthritis; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; SE, standard error.

Supplementary Figure 4. Mean change from baseline in alkaline phosphatase (U/L) by pOA subgroup (safety analysis set)



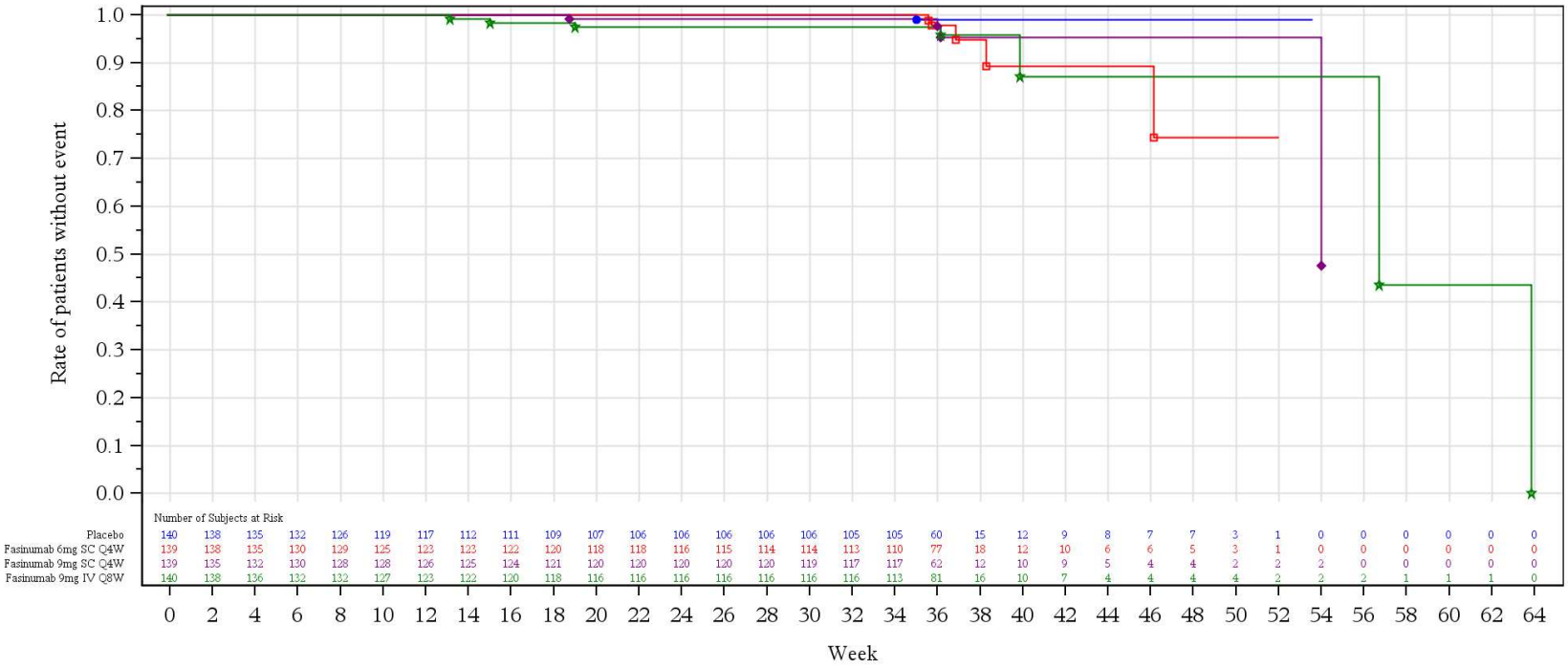
	Baseline	Week 4		Week 8		Week 12		Week 16		Week 36	
	N	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
Placebo	82	77	−0.6 (0.83)	71	0.5 (1.28)	67	1.4 (1.06)	64	1.7 (1.28)	59	−0.2 (1.48)
Fasinumab 6 mg SC Q4W	92	87	2.9 (0.90)	83	2.0 (1.13)	78	7.0 (1.15)	75	7.3 (1.43)	72	2.9 (1.45)
Fasinumab 9 mg SC Q4W	68	63	4.0 (1.26)	62	7.4 (1.46)	59	8.5 (1.73)	60	11.1 (2.41)	54	5.1 (1.78)
Fasinumab 9 mg IV Q8W	78	72	4.9 (1.17)	69	7.7 (1.29)	70	8.3 (1.45)	67	9.4 (1.27)	69	3.9 (1.73)

	Baseline	Week 4		Week 8		Week 12		Week 16		Week 36	
	N	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
Placebo	58	55	0.0 (0.98)	53	−0.6 (1.13)	47	2.0 (1.17)	44	−0.1 (1.30)	41	−0.4 (1.75)
Fasinumab 6 mg SC Q4W	47	45	4.7 (1.13)	42	7.2 (1.76)	39	8.7 (2.11)	38	9.8 (2.68)	36	4.5 (2.27)
Fasinumab 9 mg SC Q4W	71	67	2.0 (0.86)	66	4.1 (1.22)	64	5.1 (1.11)	61	6.1 (1.27)	62	2.9 (1.47)
Fasinumab 9 mg IV Q8W	62	58	3.4 (1.04)	57	6.6 (1.30)	54	5.8 (1.48)	51	4.4 (1.12)	48	1.2 (1.57)

pOA defined by medical history and/or K-L score ≥2 in hip or ≥3 in knee.

IV, intravenous; K-L, Kellgren-Lawrence; mITT, modified intent-to-treat; pOA, peripheral osteoarthritis; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; SE, standard error; U/L, units per litre.

Supplementary Figure 5. Kaplan-Meier curve of time to event for patients with AA events (safety analysis set)



AA, adjudicated arthropathy; IV, intravenous; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous.

Supplementary Materials

Efficacy and safety of fasinumab in patients with chronic low back pain: a phase II/III randomized clinical trial

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Supplementary Methods

Inclusion criteria

A patient must have met all of the following criteria to be eligible for inclusion in the study:

1. Male or female ≥35 years of age at the screening visit
2. Provided signed informed consent
3. Body mass index ≤39 kg/m^2
4. Clinical diagnosis of chronic moderate-to-severe LBP for ≥3 months (prior to the screening visit)
    a. Quebec taskforce category 1 (pain without radiation) or category 2 (pain with proximal radiation above the knee)
    b. Primary pain location between 12th thoracic vertebra and lower gluteal fold
    c. At both the screening and the randomization visit, an LBPI NRS score of ≥4 over the previous 24 hours
    d. During the pre-randomization period, mean daily LBPI score of ≥4
    e. At the screening visit, PGA of LBP of fair, poor, or very poor
5. History of regular analgesic medication, such as NSAIDs, COX-2 inhibitors, opioids, paracetamol/acetaminophen, or a combination thereof
    a. Taking medication >4 days per week in the month prior to screening

   b. Willing to discontinue current opioid pain medications starting at pre-randomization visit through the week 16 study visit

   c. Willing to discontinue current NSAID pain medications (oral or topical) starting at pre-randomization visit through 16 weeks after last dose of study drug

6. A history of inadequate pain relief or intolerance to analgesics used for chronic LBP as defined by:

   a. Intolerance or inadequate pain relief from paracetamol/acetaminophen, and

   b. Intolerance or inadequate pain relief from at least 1 oral NSAID, and

   c. Intolerance or inadequate pain relief from at least 1 opioid, unwillingness to take opioid therapy, or lack of access to opioid therapy

7. Willing to consider TJR surgery, if necessary
   NOTE: This inclusion criterion was added in protocol amendment 2

8. Willing and able to comply with clinic visits and study-related procedures

9. Able to understand and complete study-related questionnaires

Exclusion criteria

A patient who met any of the following criteria was excluded from the study:

1. Four or more consecutive LBPI NRS data entries missed during the pre-randomization period.

2. History of Quebec taskforce category >2 (pain with proximal radiation above the knee) lumbosacral radiculopathy within the past 2 years prior to the screening visit

3. Patient was not a candidate for MRI

4. Evidence on baseline lumbar spine MRI (or lumbar spine X-ray, if requested) of severe spinal stenosis, disc herniation with substantial neural encroachment, recent vertebral fracture, an active destructive process, or marked segmental instability (as indicated by bone marrow oedema or Modic type I change, respectively)

5. History of major trauma, or back surgery in the past 6 months prior to the screening visit.

6. History or presence of pyriformis syndrome

7. History or presence at the screening visit of non-OA inflammatory joint disease (e.g. rheumatoid arthritis, lupus erythematosus, psoriatic arthritis, pseudogout, joint infections), multiple sclerosis, seronegative spondyloarthropathy, Paget's disease of the spine, pelvis, or femur, fibromyalgia, or tumours or infections of the spinal cord

8. Use of extended-release opioids or long-acting opioids such as oxycodone controlled-release, oxymorphone extended release, hydromorphone, transdermal fentanyl, or methadone within 3 months prior to the screening visit

9. Use of a monoamine reuptake inhibitor, tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors for treatment of pain within 4 weeks prior to the screening visit
10. Systemic (i.e. oral or intramuscular) corticosteroids or intra-articular corticosteroid injections within 30 days prior to the screening visit
11. Epidural steroid injections within 3 months prior to the screening visit
12. Botox injections for LBP within 6 months prior to the screening visit
13. History or presence on imaging of arthropathy (osteonecrosis, subchondral insufficiency fracture, rapidly progressing OA type 1 or type 2), stress or recent fracture, neuropathic joint arthropathy, hip dislocation (prosthetic hip dislocation is eligible), knee dislocation (patella dislocation is eligible), congenital hip dysplasia with degenerative joint disease, extensive subchondral cysts, evidence of bone fragmentation or collapse, or primary metastatic tumour with the exception of chondromas or pathological fractures during the screening period
14. Was scheduled for a joint replacement surgery during the study period
15. Signs and symptoms of carpal tunnel syndrome within 6 months of screening
16. History or presence at the screening visit of autonomic neuropathy, diabetic neuropathy, or other peripheral neuropathy including reflex sympathetic dystrophy
17. Evidence of autonomic neuropathy at the screening visit, as defined in the Survey of Autonomic Symptoms

18. History or diagnosis of chronic autonomic failure syndrome including pure autonomic failure and multiple system atrophy (Shy-Drager syndrome)

19. Poorly controlled diabetes (Haemoglobin A1c [HbA1c] >9.0%) at the screening visit

20. Confirmed elevated screening alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5x upper limit of normal (ULN)
    NOTE: This inclusion criterion was added in protocol amendment 1

21. Resting heart rate of <50 beats per minute (bpm) at the screening, pre-randomization, or randomization visits

22. History or presence of 2nd or 3rd degree heart block, 1st degree heart block with abnormal QRS, or bifascicular block by ECG at the screening visit

23. History or presence of orthostatic hypotension at the screening, pre-randomization, or baseline visits

24. Poorly controlled hypertension

    - Systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥110 mm Hg at the screening visit

    - Systolic blood pressure of 160 mm Hg to 179 mm Hg or diastolic blood pressure of 100 mm Hg to 109 mm Hg at the screening visit, AND a history of end-organ damage (including history of left ventricular hypertrophy, heart failure, angina, myocardial infarction, stroke, transient ischemic attack (TIA), peripheral arterial disease, and moderate to advanced retinopathy [haemorrhages or exudates, papilledema])

25. Congestive heart failure with NY Heart Classification of stage 3 or 4

26. TIA or cerebrovascular accident within the past 12 months prior to the screening visit, or myocardial infarction or acute coronary syndromes within the past 6 months prior to the screening visit

27. Significant concomitant illness including, but not limited to, psychiatric, cardiac, renal, hepatic, neurological, endocrinological, metabolic, or lymphatic disease that, in the opinion of the investigator, would adversely affect the patient's participation in the study

28. New major illness diagnosed within 2 months prior to the screening visit

29. Known history of ocular herpes simplex virus, herpes simplex virus pneumonia, or herpes simplex virus encephalitis

30. Known history of human immunodeficiency virus infection

31. Known history of infection with hepatitis B virus. Patients with a history of hepatitis B are eligible if there is documentation of a negative test for hepatitis B surface antigen and a positive test for antibodies to the hepatitis B virus surface antigen

32. Known history of infection with hepatitis C virus. Patients with a history of hepatitis C are eligible if there is documentation of a negative hepatitis C virus RNA test

33. History or presence of malignancy within the last 5 years prior to screening, except patients who have been treated successfully with no recurrence for >1

year of basal cell or squamous cell carcinoma of the skin or in-situ cervical cancer

34. Known allergy or sensitivity to doxycycline or related compounds, or monoclonal antibodies

35. History of (within 5 years prior to the screening visit) current alcoholism, alcohol abuse, substance abuse, or abuse of prescription pain medication

36. History of cannabis use for the treatment of pain within the past 6 months prior to the screening visit

37. History of hospital admission for depression or suicide attempt within 5 years or active, severe major depression at screening

38. Current or pending worker's compensation, litigation, disability, or any other monetary settlement related to LBP

39. Ongoing participation in a clinical research study evaluating another investigational drug or having received another investigational product within 30 days or 5 half-lives, whichever is longer

40. Exposure to an anti-NGF antibody within 6 months prior to the screening visit or known sensitivity or intolerance to anti-NGF antibodies

41. Pregnant or breast-feeding women

42. Women of childbearing potential who had a positive pregnancy test result or did not have their pregnancy test result at baseline

43. Women of childbearing potential who were unwilling to use acceptable contraceptive methods during the study and for 20 weeks after the last dose of study drug. Acceptable methods of contraception included combined (oestrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal); progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable); intrauterine device; intra-uterine hormone-releasing system; bilateral tubal occlusion; vasectomized partner; sexual abstinence; or condom in combination with either cap, diaphragm, or sponge with spermicide (double-barrier contraception).

Safety monitoring

An independent data monitoring committee (DMC), consisting of statistical and medical experts, met periodically to review unblinded data as the study progressed. The DMC assessed the safety of fasinumab, with a focus on joint-related adverse events, sympathetic nervous system dysfunction, and neurosensory disturbances. The DMC made recommendations to the sponsor based on the conduct of the study, however no action was requested during the study period.

An independent blinded adjudication committee composed of musculoskeletal radiologists reviewed images for joint AEs, pre-operative images in patients undergoing joint replacements, and routine study scheduled images of suspicious findings by the central reader, for AAs. Positive adjudications met the definition for one or more of the following categories: rapidly progressive osteoarthritis (RPOA) type 1 (RPOA1), RPOA type 2 (RPOA2), subchondral insufficiency fracture (SIF), or primary osteonecrosis. RPOA1 was defined as joint space narrowing exceeding pre-

specified thresholds. For knee joints with a baseline joint space width (JSW) ≥2 mm, reduction had to be ≥2 mm or 50% from baseline at any time point during the study, whichever was greater. For knee joints with baseline JSW <2 mm, a reduction of JSW to 0 mm qualified as RPOA1. For hip joints; if JSW was >1.5 mm at baseline, a reduction of >1.5 mm from baseline qualified as RPOA1. If JSW was <1.5 mm at baseline, then a reduction in JSW to 0 mm also qualified as RPOA1. RPOA2 was defined as changes in bone structure on plain film or magnetic resonance imaging (MRI), atypical of advanced OA. Subchondral insufficiency fracture was defined as subchondral radiolucency, which could have a possible sclerotic linear component and articular surface flattening, confirmed by MRI. Primary osteonecrosis was defined as a focal circumscribed or extended region of mottled radiolucency without evidence of subchondral collapse or bone fragmentation, confirmed by MRI. Because the categories are not always considered mutually exclusive, particularly when reviewing MRIs, the adjudication process across the fasinumab program was updated during the conduct of the study such that the adjudication committee had the option to select more than one category simultaneously in a single joint. All patients received x-rays of the knees, hips, and shoulders at screening as well as MRI of any knee or hip with K-L score ≥3.

Analysis sets

The safety analysis set included all randomized patients who received any study drug. The full analysis set included all randomized patients and was based on the treatment allocated (as randomized). The full analysis set was used to perform sensitivity analysis for the primary and selected secondary endpoints.

A modified intent-to-treat set (mITT) was specified in the final SAP, before database lock, in response to the unplanned early termination of dosing in the study. This set included all randomized patients who received at least one dose of study drug based on the treatment allocated (as randomized) including data up to 5 weeks after the last dose of study drug. Originally, the efficacy data in the study was to be analyzed based on data collected up to week 16, which was 4 weeks after the last planned dose of study therapy for patients receiving fasinumab Q4W. However, with the early cessation of dosing, many patients at week 16 would have discontinued dosing more than 5 weeks before the week 16 visit and thus would not be expected to continue to derive efficacy from the study drug. Thus, this modification to the treatment set was implemented.

Statistical analysis

The primary efficacy endpoint, change from baseline to week 16 in LBPI NRS score, was analysed using a mixed-effect model repeated measures approach based on the mITT analysis set. The model included the randomization strata, baseline LBPI score, treatment, study week, and treatment-by-week interaction. Denominator degrees of freedom were estimated using Kenward-Roger's approximation. Data from all patients, including data collected after discontinuing treatment up to the earlier of withdrawal of consent, week 16, or 5 weeks after the last dose of study drug, were used in the primary efficacy analyses according to the intent-to-treat principle using the MMRM approach with no imputation for missing data. Additional sensitivity analysis was performed using the full analysis set, which included all randomized patients, for the primary and secondary endpoints.

Supplementary Results

Patient disposition

Approximately 30% (166 patients) of the 563 randomized patients completed the week 16 end of treatment visit before the study was placed on partial clinical hold. Of these patients, six discontinued treatment early due to an AE (three patients), physician decision (two patients), or withdrawal by patient (one patient). The remaining 70% (397 patients) did not complete dosing through the end of the treatment period (week 16 visit) before the study was placed on partial clinical hold. Across the treatment groups, 42% to 54% of these patients were followed for safety and completed their remaining visits to week 36 following the partial clinical hold.

Dakin P, *et al. Ann Rheum Dis* 2020;0:1–9. doi: 10.1136/annrheumdis-2020-217259

Supplementary Table 1. Study drug administration (safety analysis set)

		Fasinumab			
	Placebo (n=140)	**6 mg SC Q4W (n=139)**	**9 mg SC Q4W (n=139)**	**9 mg IV Q8W (n=140)**	**Total (N=558)**
SC study drug injection*					
Compliance (%), mean (SD)	94.3 (15.0)	95.1 (14.1)	97.5 (11.6)	95.0 (14.4)	95.5 (13.9)
Number of SC injections (% of patients)					
1	33 (23.6%)	32 (23.0%)	33 (23.7%)	34 (24.3%)	132 (23.7%)
2	33 (23.6%)	32 (23.0%)	28 (20.1%)	28 (20.0%)	121 (21.7%)
3	23 (16.4%)	26 (18.7%)	19 (13.7%)	22 (15.7%)	90 (16.1%)
4	51 (36.4%)	49 (35.3%)	59 (42.4%)	56 (40.0%)	215 (38.5%)
IV study drug infusion					
Compliance (%), mean (SD)	95.7 (14.1)	95.3 (15.8)	98.9 (7.3)	97.5 (10.9)	96.9 (12.5)
Number of IV injections (% of patients)					
1	68 (48.6%)	67 (48.2%)	61 (43.9%)	64 (45.7%)	260 (46.6%)
2	72 (51.4%)	71 (51.1%)	78 (56.1%)	76 (54.3%)	297 (53.2%)
Missing	0	1	0	0	1
Mean total fasinumab dose/patient, mg	N/A	22.0	33.7	13.9	N/A

*SC treatment included loading dose as well as nominal dose on day of first study drug treatment

Compliance = (Number of actual injections or infusions of study drug during exposure period)/(Number of planned injections or infusions of study drug during exposure period on or before the time that the patient discontinued from the study) x 100%.

IV, intravenous; N/A, not applicable; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; SD, standard deviation.

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Supplementary Table 2. Change from baseline to week 16 in the average daily LBPI NRS, RMDQ, and PGA of LBP scores in patients with and without OA of the peripheral joints (mITT analysis set)

		Fasinumab		
	Placebo	**6 mg SC Q4W**	**9 mg SC Q4W**	**9 mg IV Q8W**
		LBPI NRS		
Patients with OA of the peripheral joints, n	82	92	68	78
Baseline average daily LBPI NRS score, mean (SD); n	6.4 (1.2); 81	6.6 (1.3); 90	6.7 (1.4); 68	6.2 (1.1); 78
Week 8				
Average daily LBPI NRS score, mean (SD); n	5.6 (2.1); 55	4.8 (2.1); 62	3.9 (2.3); 51	4.0 (2.2); 59
Change from baseline to week 8, mean (SD); n	–1.0 (2.0)	–1.9 (2.1)	–2.7 (1.9)	–2.2 (2.0)
LS mean (SE)	–0.9 (0.3)	–1.8 (0.2)	–2.6 (0.3)	–2.2 (0.3)
95% CI	(–1.39, –0.40)	(–2.24, –1.31)	(–3.11, –2.08)	(–2.67, –1.70)
Difference vs placebo, LS mean (SE)		–0.9 (0.3)	–1.7 (0.4)	–1.3 (0.3)
95% CI		(–1.53, –0.22)	(–2.40, –1.00)	(–1.96, –0.62)
Week 16				
Average daily LBPI NRS score, mean (SD); n	4.5 (2.4); 32	4.2 (2.1); 32	3.6 (2.2); 26	4.0 (2.5); 34
Change from baseline to week 16, mean (SD); n	–2.1 (2.4); 31	–2.5 (2.0); 32	– 2.9 (1.8); 26	–2.2 (2.0); 34
LS mean (SE)	–1.7 (0.3)	–2.0 (0.3)	–2.6 (0.3)	–2.3 (0.3)
95% CI	(–2.26, –1.09)	(–2. 56, –1.43)	(–3.20, –1.94)	(–2.84, –1.70)

Difference vs placebo, LS mean (SE)		–0.3 (0.4)	–0.9 (0.4)	–0.6 (0.4)
95% CI		(–1.11, 0.48)	(–1.73, –0.04)	(–1.39, 0.21)
Patients without OA of the peripheral joints, n	58	47	71	62
Baseline average daily LBPI NRS score, mean (SD); n	6.6 (1.4); 58	6.3 (1.3); 47	6.7 (1.2); 71	6.7 (1.2); 62
Week 8				
Average daily LBPI NRS score, mean (SD); n	4.9 (2.0); 41	4.5 (1.7); 37	4.6 (2.5); 54	4.3 (2.6); 44
Change from baseline to week 8, mean (SD); n	–1.7 (1.4); 41	–1.8 (1.5); 37	–2.1 (2.4); 54	–2.3 (2.6); 44
LS mean (SE)	–1.6 (0.3)	–1.6 (0.4)	–1.9 (0.3)	–2.2 (0.3)
95% CI	(–2.26, –0.94)	(–2.37, –0.90)	(–2.58, –1.26)	(–2.82, –1.49)
Difference vs placebo, LS mean (SE)		–0.0 (0.4)	–0.3 (0.4)	–0.6 (0.40)
95% CI		(–0.87, 0.80)	(–1.08, 0.44)	(–1.34, 0.23)
Week 16				
Average daily LBPI NRS score, mean (SD); n	4.9 (1.2); 18	4.6 (1.4); 16	4.7 (2.2); 29	3.8 (2.4); 22
Change from baseline to week 16, mean (SD); n	–1.4 (1.5); 18	–1.5 (1.5); 16	–2.4 (2.1); 29	–2.9 (2.5); 22
LS mean (SE)	–1.7 (0.4)	–1.9 (0.4)	–2.2 (0.4)	–2.6 (0.4)
95% CI	(–2.47, –1.01)	(–2.66, –1.06)	(–2.91, –1.53)	(–3.29, –1.84)
Difference vs placebo, LS mean (SE)		–0.1 (0.5)	–0.5 (0.4)	–0.8 (0.5)
95% CI		(–1.08, 0.84)	(–1.34, 0.38)	(–1.73, 0.07)

RMDQ

Patients with OA of the peripheral joints, n	82	92	68	78
Baseline RMDQ total score, mean (SD); n	11.1 (4.8); 74	11.4 (5.1); 90	10.3 (5.0); 67	11.7 (5.4); 75
Week 8				
RMDQ total score, mean (SD); n	8.7 (5.5); 58	6.2 (5.4); 63	4.8 (4.9); 51	5.5 (5.0); 60
Change from baseline to week 8, mean (SD); n	–2.6 (4.1); 50	–5.5 (5.7); 61	–5.3 (5.1): 50	–7.0 (5.4); 57
LS mean (SE)	–2.4 (0.6)	–5.1 (0.5)	–6.0 (0.6)	–6.1 (0.6)
95% CI	(–3.60, –1.27)	(–6.16, –4.05)	(–7.22, –4.85)	(–7.27, –5.02)
Difference vs placebo, LS mean (SE)		–2.7 (0.8)	–3.6 (0.8)	–3.7 (0.8)
95% CI		(–4.19, –1.15)	(–5.23, –1.98)	(–5.28, –2.14)
Week 16				
RMDQ total score, mean (SD); n	6.5 (5.8); 32	4.6 (4.4); 33	3.5 (3.0); 26	4.9 (4.9); 34
Change from baseline to week 16, mean (SD); n	–3.9 (4.5); 28	–7.2 (6.0); 31	–6.8 (4.5); 26	–6.6 (5.7); 32
LS mean (SE)	–3.3 (0.7)	-6.4 (0.6)	–6.6 (0.7)	–6.5 (0.7)
95% CI	(–4.64, –1.92)	(–7.69, –5.16)	(–7.99, –5.19)	(–7.82, –5.23)
Difference vs placebo, LS mean (SE)		–3.1 (0.9)	–3.3 (1.0)	–3.2 (0.9)
95% CI		(–4.96, –1.33)	(–5.24, –1.39)	(–5.08, –1.42)
Patients without OA of the peripheral joints	58	47	71	62
Baseline RMDQ total score, mean (SD); n	10.6 (5.9); 58	9.7 (5.1); 45	11.1 (6.3); 69	11.6 (5.1); 61
Week 8				
RMDQ total score, mean (SD); n	6.7 (5.6); 42	5.0 (4.8); 38	6.9 (6.1); 54	5. 9 (6.0); 44

Change from baseline to week 8, mean (SD); n	–3.8 (5.6); 42	–5.2 (4.6); 36	–4.2 (4.6); 52	–5.1 (5.3)
LS mean (SE)	–4.5 (0.8)	–6.3 (0.9)	–5.0 (0.7)	–6.4 (0.8)
95% CI	(–6.04, –3.05)	(–8.02, –4.62)	(–6.57, –3.52)	(–7.90, –4.83)
Difference vs placebo, LS mean (SE)		–1.8 (1.0)	–0.5 (0.9)	–1.8 (0.9)
95% CI		(–3.69, 0.13)	(–2.23, 1.23)	(–3.61, –0.04)
Week 16				
RMDQ total score, mean (SD); n	6.7 (5.4); 18	6.2 (5.9); 15	6.0 (5.4); 29	5.2 (5.9); 23
Change from baseline to week 16, mean (SD); n	–3.7 (4.6); 18	–3.7 (4.4); 15	–5.7 (5.0); 29	–6.7 (5.6); 23
LS mean (SE)	–5.1 (0.9)	–5.8 (1.0)	–6.1 (0.8)	–6.7 (0.9)
95% CI	(–6.82, –3.37)	(–7.74, –3.85)	(–7.71, –4.44)	(–8.38, –4.98)
Difference vs placebo, LS mean (SE)		–0.7 (1.2)	–1.0 (1.0)	–1.6 (1.1)
95% CI		(–3.02, 1.63)	(–3.03, 1.07)	(–3.71, 0.54)
		PGA of LBP		
Patients with OA of the peripheral joints, n	82	92	68	78
Baseline PGA, mean (SD); n	3.5 (0.7); 82	3.5 (0.7); 92	3.3 (0.9); 68	3.4 (0.6); 78
Week 8				
PGA, mean (SD); n	3.1 (0.8); 58	2.7 (0.9); 63	2.4 (0.9); 51	2.6 (0.9); 60
Change from baseline to week 8, mean (SD); n	–0.5 (0.8); 58	–0.8 (1.0); 63	–0.9 (1.1); 51	–0.9 (0.9); 60
LS mean (SE)	–0.5 (0.1)	–0.8 (0.1)	–1.0 (0.1)	–0.8 (0.1)
95% CI	(–0.67, –0.25)	(–1.00, –0.60)	(–1.19, –0.74)	(–1.05, –0.63)
Difference vs placebo, LS mean (SE)		–0.3 (0.1)	–0.5 (0.2)	–0.4 (0.2)

95% CI		(–0.61, –0.05)	(–0.80, –0.20)	(–0.66, –0.08)
Week 16				
PGA, mean (SD); n	2.7 (0.8); 32	2.4 (0.9); 33	2.3 (0.9); 26	2.3 (1.0); 34
LS mean (SE)	–0.7 (0.1)	–0.9 (0.1)	–1.0 (0.2)	–1.0 (0.1)
95% CI	(–0.98, –0.45)	(–1.16, –0.64)	(–1.26, –0.68)	(–1.25, –0.73)
Difference vs placebo, LS mean (SE)		–0.2 (0.2)	–0.3 (0.2)	–0.3 (0.2)
95% CI		(–0.55, 0.18)	(–0.65, 0.13)	(–-0.64, 0.09)
Patients without OA of the peripheral joints, n	58	47	71	62
Baseline PGA, mean (SD); n	3.6 (0.7); 58	3.4 (0.7); 47	3.4 (0.7); 71	3.4 (0.8); 62
Week 8				
PGA, mean (SD); n	3.0 (0.7); 42	2.7 (0.8); 38	2.7 (0.9); 54	2.5 (1.1); 44
Change from baseline to week 8, mean (SD); n	–0.6 (0.9); 42	–0.8 (0.8); 38	–0.7 (0.8); 54	–0.9 (1.0); 44
LS mean (SE)	–0.6 (0.1)	–0.8 (0.2)	–0.7 (0.1)	–1.0 (0.1)
95% CI	(–0.84, –0.31)	(–1.08, –0.50)	(–0.97, –0.44)	(–1.28, –0.74)
Difference vs placebo, LS mean (SE)		–0.2 (0.2)	–0.1 (0.2)	–0.4 (0.2)
95% CI		(–0.55, 0.13)	(–0.43, 0.19)	(–0.76, –0.12)
Week 16				
PGA, mean (SD); n	3.0 (0.6); 18	2.7 (1.0); 15	2.7 (1.0); 29	2.4 (0.9); 23
Change from baseline to week 16, mean (SD); n	–0.6 (0.6); 18	–0.5 (1.1); 15	–0.8 (0.8); 29	–1.0 (0.9); 23
LS mean (SE)	–0.7 (0.2)	–0.9 (0.2)	–0.8 (0.1)	–1.1 (0.2)
95% CI	(–0.99, –0.39)	(–1.20, –0.54)	(–1.06, –0.51)	(–1.39, –0.81)

Difference vs placebo, LS mean (SE)	–0.2 (0.2)	–0.1 (0.2)	–0.4 (0.2)
95% CI	(–0.58, 0.22)	(–0.45, 0.25)	(–0.78, –0.05)

Analyses are based on MMRM model with baseline randomization strata, baseline score, treatment, visit, and treatment-by-visit interaction.

CI, confidence interval; IV, intravenous; LBPI NRS, low back pain intensity numeric rating scale; LS, least squares; OA, osteoarthritis; PGA, patient global assessment; Q4W, every 4 weeks; Q8W, every 8 weeks; RMDQ, Roland-Morris Disability Questionnaire; SD, standard deviation; SE, standard error; SC, subcutaneous; TEAE, treatment-emergent adverse event.

Supplementary Table 3. Summary of TEAEs during the on-treatment period (safety analysis set)

		Fasinumab			
	Placebo (n=140)	**6 mg SC Q4W (n=139)**	**9 mg SC Q4W (n=139)**	**9 mg IV Q8W (n=140)**	**Combined (N=418)**
Patients with any TEAE, n (%)	94 (67.1%)	85 (61.2%)	95 (68.3%)	94 (67.1%)	274 (65.6%)
Patients with any serious TEAE, n (%)	4 (2.9%)	2 (1.4%)	3 (2.2%)	5 (3.6%)	10 (2.4%)
Patients with any severe TEAE, n (%)	5 (3.6%)	4 (2.9%)	2 (1.4%)	3 (2.1%)	9 (2.2%)
Patients with any TEAE leading to study drug discontinuation, n (%)	9 (6.4%)	5 (3.6%)	5 (3.6%)	5 (3.6%)	15 (3.6%)
Patients with any TEAE leading to study withdrawal, n (%)	10 (7.1%)	6 (4.3%)	2 (1.4%)	5 (3.6%)	13 (3.1%)
Patients with any TEAE leading to death, n (%)	0	0	0	0	0

IV, intravenous; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; TEAE, treatment-emergent adverse event.

Supplementary Table 4. Summary of AEs with >3% incidence during the post-treatment follow-up period by System Organ Class and Preferred Term (safety analysis set)

		Fasinumab			
Primary System Organ Class Preferred Term	**Placebo (n=140)**	**6 mg SC Q4W (n=139)**	**9 mg SC Q4W (n=139)**	**9 mg IV Q8W (n=140)**	**Combined (N=418)**
Number of post-treatment AEs	45	73	58	64	195
Patients with at least one post-treatment AE, n (%)	39 (27.9%)	42 (30.2%)	39 (28.1%)	44 (31.4%)	125 (29.9%)
Musculoskeletal and connective tissue disorders	20 (14.3%)	32 (23.0%)	28 (20.1%)	33 (23.6%)	93 (22.2%)
Arthralgia	13 (9.3%)	16 (11.5%)	9 (6.5%)	13 (9.3%)	38 (9.1%)
Back pain	4 (2.9%)	9 (6.5%)	12 (8.6%)	8 (5.7%)	29 (6.9%)
Pain in extremity	1 (0.7%)	7 (5.0%)	4 (2.9%)	10 (7.1%)	21 (5.0%)
Rapidly progressive osteoarthritis	1 (0.7%)	5 (3.6%)	4 (2.9%)	6 (4.3%)	15 (3.6%)
Musculoskeletal pain	2 (1.4%)	6 (4.3%)	3 (2.2%)	5 (3.6%)	14 (3.3%)
Infections and infestations	20 (14.3%)	17 (12.2%)	14 (10.1%)	14 (10.0%)	45 (10.8%)
Nasopharyngitis	7 (5.0%)	8 (5.8%)	7 (5.0%)	6 (4.3%)	21 (5.0%)
Upper respiratory tract infection	7 (5.0%)	5 (3.6%)	6 (4.3%)	2 (1.4%)	13 (3.1%)
Bronchitis	1 (0.7%)	3 (2.2%)	5 (3.6%)	4 (2.9%)	12 (2.9%)
Urinary tract infection	5 (3.6%)	1 (0.7%)	0	4 (2.9%)	5 (1.2%)

Post-treatment AEs included any AEs reported during the post-treatment follow-up period with an onset more than 4 weeks from the last dose of SC study drug or 8 weeks from the last dose of IV study drug.

MedDRA (Version 18.0) coding applied.

A patient who reported 2 or more AEs with the same preferred term is counted only once for that term.

A patient who reported 2 or more AEs with different preferred terms within the same system organ class is counted only once in that system organ class.

For system organ classes, the table is sorted by decreasing frequency in combined fasinumab group. Within each system organ class, preferred terms are sorted by decreasing frequency count in combined fasinumab group.

AE; adverse event; IV, intravenous; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous.

Dakin P, *et al*. *Ann Rheum Dis* 2020;0:1–9. doi: 10.1136/annrheumdis-2020-217259

Supplementary Table 5. Summary of SAEs during the on-treatment period by System Organ Class and Preferred Term (safety analysis set)

Primary System Organ Class Preferred Term	Placebo (n=140)	Fasinumab			
		6 mg SC Q4W (n=139)	9 mg SC Q4W (n=139)	9 mg IV Q8W (n=140)	Combined (N=418)
Number of serious TEAEs	4	4	3	5	12
Patients with at least one serious TEAE, n (%)	4 (2.9%)	2 (1.4%)	3 (2.2%)	5 (3.6%)	10 (2.4%)
Injury, poisoning and procedural complications	1 (0.7%)	1 (0.7%)	0	2 (1.4%)	3 (0.7%)
Concussion	0	1 (0.7%)	0	0	1 (0.2%)
Craniocerebral injury	0	1 (0.7%)	0	0	1 (0.2%)
Meniscus injury	0	0	0	1 (0.7%)	1 (0.2%)
Patella fracture	0	0	0	1 (0.7%)	1 (0.2%)
Skull fracture	0	1 (0.7%)	0	0	1 (0.2%)
Eye injury	1 (0.7%)	0	0	0	0
Cardiac disorders	0	1 (0.7%)	0	0	1 (0.2%)
Angina pectoris	0	1 (0.7%)	0	0	1 (0.2%)
General disorders and administration site conditions	0	0	0	1 (0.7%)	1 (0.2%)

Pyrexia	0	0	0	1 (0.7%)	1 (0.2%)
Infections and infestations	0	0	1 (0.7%)	0	1 (0.2%)
Diverticulitis	0	0	1 (0.7%)	0	1 (0.2%)
Musculoskeletal and connective tissue disorders	0	0	1 (0.7%)	0	1 (0.2%)
Osteoarthritis	0	0	1 (0.7%)	0	1 (0.2%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.7%)	0	0	1 (0.7%)	1 (0.2%)
Adenocarcinoma of colon	0	0	0	1 (0.7%)	1 (0.2%)
Tongue carcinoma stage IV	1 (0.7%)	0	0	0	0
Nervous system disorders	1 (0.7%)	0	1 (0.7%)	0	1 (0.2%)
Haemorrhagic stroke	0	0	1 (0.7%)	0	1 (0.2%)
Cerebrovascular accident	1 (0.7%)	0	0	0	0
Vascular disorders	0	0	0	1 (0.7%)	1 (0.2%)
Hypotension	0	0	0	1 (0.7%)	1 (0.2%)
Investigations	1 (0.7%)	0	0	0	0
Blood creatine phosphokinase increased	1 (0.7%)	0	0	0	0

MedDRA (Version 18.0) coding applied.

A patient who reported 2 or more TEAEs with the same preferred term is counted only once for that term.

A patient who reported 2 or more TEAEs with different preferred terms within the same system organ class is counted only once in that system organ class.

For SOCs, the table is sorted by decreasing frequency in combined fasinumab group. Within each SOC, PTs are sorted by decreasing frequency count in combined fasinumab group.

AE; adverse event; IV, intravenous; PT, preferred term; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; SOC, system organ class; TEAE, treatment-emergent adverse event.

Dakin P, *et al*. *Ann Rheum Dis* 2020;0:1–9. doi: 10.1136/annrheumdis-2020-217259

Supplementary Table 6. Summary of SAEs during the post-treatment follow-up period by System Organ Class and Preferred Term (safety analysis set)

Primary System Organ Class Preferred Term	Placebo (n=140)	Fasinumab			
		6 mg SC Q4W (n=139)	9 mg SC Q4W (n=139)	9 mg IV Q8W (n=140)	Combined (N=418)
Number of serious post-treatment AEs	7	9	7	12	28
Patients with at least one serious post-treatment AE, n (%)	6 (4.3%)	9 (6.5%)	6 (4.3%)	10 (7.1%)	25 (6.0%)
Musculoskeletal and connective tissue disorders	0	3 (2.2%)	3 (2.2%)	5 (3.6%)	11 (2.6%)
Rapidly progressive osteoarthritis	0	1 (0.7%)	1 (0.7%)	5 (3.6%)	7 (1.7%)
Back pain	0	2 (1.4%)	1 (0.7%)	0	3 (0.7%)
Synovial cyst	0	0	1 (0.7%)	0	1 (0.2%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.7%)	2 (1.4%)	0	2 (1.4%)	4 (1.0%)
Bladder cancer	0	0	0	1 (0.7%)	1 (0.2%)
Endometrial adenocarcinoma	0	0	0	1 (0.7%)	1 (0.2%)
Large intestine benign neoplasm	0	1 (0.7%)	0	0	1 (0.2%)
Mediastinum neoplasm	0	0	0	1 (0.7%)	1 (0.2%)
Small cell lung cancer metastatic	0	1 (0.7%)	0	0	1 (0.2%)

Lung neoplasm malignant	1 (0.7%)	0	0	0	0
Cardiac disorders	0	0	2 (1.4%)	0	2 (0.5%)
Atrial fibrillation	0	0	2 (1.4%)	0	2 (0.5%)
Infections and infestations	0	1 (0.7%)	0	1 (0.7%)	2 (0.5%)
Abscess limb	0	0	0	1 (0.7%)	1 (0.2%)
Septic shock	0	1 (0.7%)	0	0	1 (0.2%)
Injury, poisoning and procedural complications	1 (0.7%)	0	1 (0.7%)	1 (0.7%)	2 (0.5%)
Radius fracture	0	0	1 (0.7%)	0	1 (0.2%)
Stress fracture	0	0	0	1 (0.7%)	1 (0.2%)
Ulna fracture	0	0	1 (0.7%)	0	1 (0.2%)
Ankle fracture	1 (0.7%)	0	0	0	0
Nervous system disorders	0	2 (1.4%)	0	0	2 (0.5%)
Cervical radiculopathy	0	1 (0.7%)	0	0	1 (0.2%)
Multiple sclerosis	0	1 (0.7%)	0	0	1 (0.2%)
Psychiatric disorders	0	0	0	1 (0.7%)	1 (0.2%)
Personality disorder	0	0	0	1 (0.7%)	1 (0.2%)
Vascular disorders	0	1 (0.7%)	0	0	1 (0.2%)
Hypertension	0	1 (0.7%)	0	0	1 (0.2%)

Gastrointestinal disorders	2 (1.4%)	0	0	0	0
Intestinal obstruction	1 (0.7%)	0	0	0	0
Pancreatitis acute	1 (0.7%)	0	0	0	0
Hepatobiliary disorders	1 (0.7%)	0	0	0	0
Cholelithiasis	1 (0.7%)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.7%)	0	0	0	0
Haemoptysis	1 (0.7%)	0	0	0	0
Surgical and medical procedures	1 (0.7%)	0	0	0	0
Joint arthropathy	1 (0.7%)	0	0	0	0

MedDRA (Version 18.0) coding applied.

A patient who reported 2 or more AEs with the same preferred term is counted only once for that term.

A patient who reported 2 or more AEs with different preferred terms within the same system organ class is counted only once in that system organ class. For SOCs, the table is sorted by decreasing frequency in combined fasinumab group. Within each SOC, PTs are sorted by decreasing frequency count in combined fasinumab group.

AE; adverse event; IV, intravenous; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; SOC, system organ class.

Supplementary Table 7. Overview of AA events by treatment group, number of scheduled doses, screening K-L score and medical history (safety analysis set)

Treatment group	Number of scheduled doses received	Screening K-L score of affected joint(s)	Maximum K-L score of any joint	Medical history of OA	AA category	Days to first event
Placebo	2 (Day 1, Week 4)	3 (right hip)	4	Y	RPOA1 of the right hip	246
Fasinumab 6 mg SC Q4W	3 (Day 1, Week 4, Week 8)	2 (left knee)	3	Y	RPOA1 of the left knee	269
Fasinumab 6 mg SC Q4W	4 (Day 1, Week 4, Week 8, Week 12)	3 (left knee) 3 (right knee)	3	Y	RPOA1, RPOA2 of the left knee RPOA1, SIF of the right knee	250
Fasinumab 6 mg SC Q4W	3 (Day 1, Week 4, Week 8)	1 (right knee)	1	Y	RPOA1, SIF of right knee	324
Fasinumab 6 mg SC Q4W	4 (Day 1, Week 4, Week 8, Week 12)	2 (left knee) N/A (right shoulder)	3	Y	RPOA1 of the left knee RPOA1 of the right shoulder	251
Fasinumab 6 mg SC Q4W	1 (Day 1)	2 (left hip)	2	Y	RPOA1 of the left hip	259
Fasinumab 9 mg SC Q4W	3 (Day 1, Week 4, Week 8)	2 (right hip)	2	Y	RPOA1 of the right hip	253
Fasinumab 9 mg SC Q4W	4 (Day 1, Week 4, Week 8, Week 12)	2 (left hip)	3	N	RPOA1 of the left hip	379
Fasinumab 9 mg SC Q4W	2 (Day 1, Week 4)	2 (left knee)	2	N	RPOA1 of the left knee	132
Fasinumab 9 mg SC Q4W	2 (Day 1, Week 4)	1 (left knee)	1	Y	RPOA1, SIF of the left knee	254

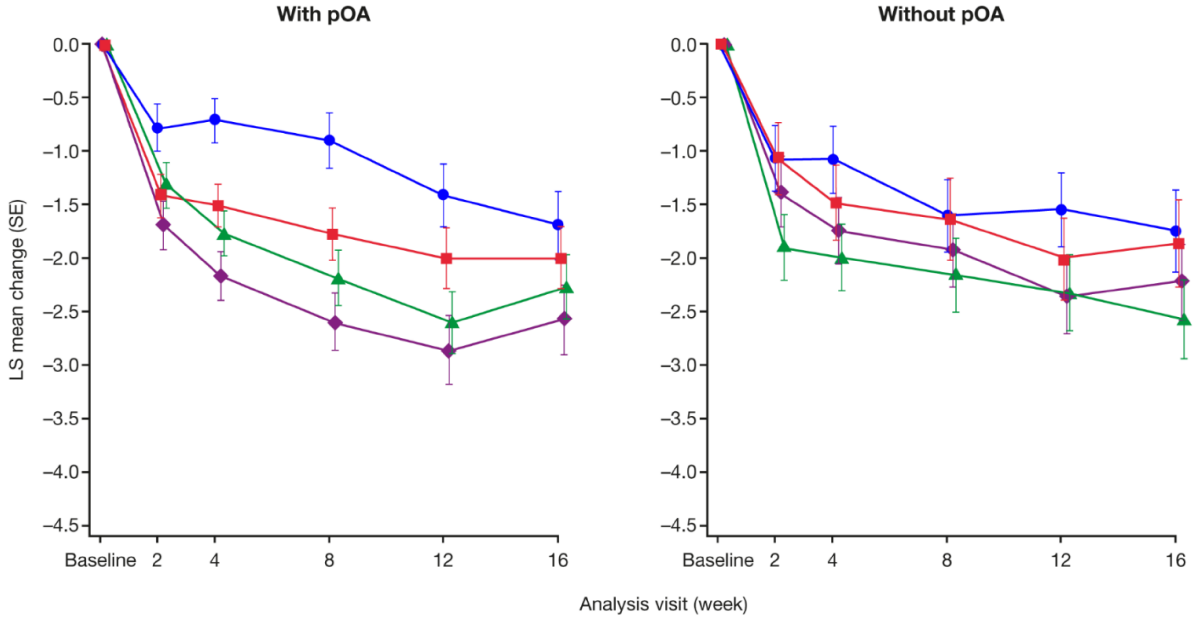
Fasinumab 9 mg IV Q8W	2 (Day 1, Week 8)	2 (right knee)	2	Y	RPOA1 of the right knee	254
Fasinumab 9 mg IV Q8W	2 (Day 1, Week 8)	2 (right knee)	2	Y	RPOA1 of the right knee	280
Fasinumab 9 mg IV Q8W	1 (Day 1)	3 (right hip) N/A (right shoulder)	3	Y	RPOA1 of the right hip RPOA1 of the right shoulder	106
Fasinumab 9 mg IV Q8W	2 (Day 1, Week 8)	3 (right knee)	3	Y	RPOA1 of the right knee	448
Fasinumab 9 mg IV Q8W	2 (Day 1, Week 8)	0 (right knee)	2*	N	RPOA1 of the right knee	398
Fasinumab 9 mg IV Q8W	2 (Day 1, Week 8)	3 (left knee)	3	Y	RPOA2 of the left knee	93
Fasinumab 9 mg IV Q8W	2 (Day 1, Week 8)	3 (left knee)	3	Y	SIF of the left knee	134

*Patient included in non-pOA subgroup; all other patients with AA events were included in the pOA subgroup based on medical history of OA and/or K-L score ≥2 in hip or ≥3 in knee.

K-L scores at screening were only assessed for hip and knee joints; in two shoulder joints, screening radiographs documented one with moderate OA and one with severe OA.

AA, adjudicated arthropathy; IV, intravenous; K-L, Kellgren-Lawrence; OA, osteoarthritis; Q4W, every 4 weeks; Q8W, every 8 weeks; RPOA1, rapid progressive OA type 1; RPOA2, rapid progressive OA type 2; SC, subcutaneous; SIF, subchondral insufficiency fracture.

Supplementary Figure 1. Least squares mean change from baseline in average daily LBPI NRS score by pOA subgroup (mITT analysis set)

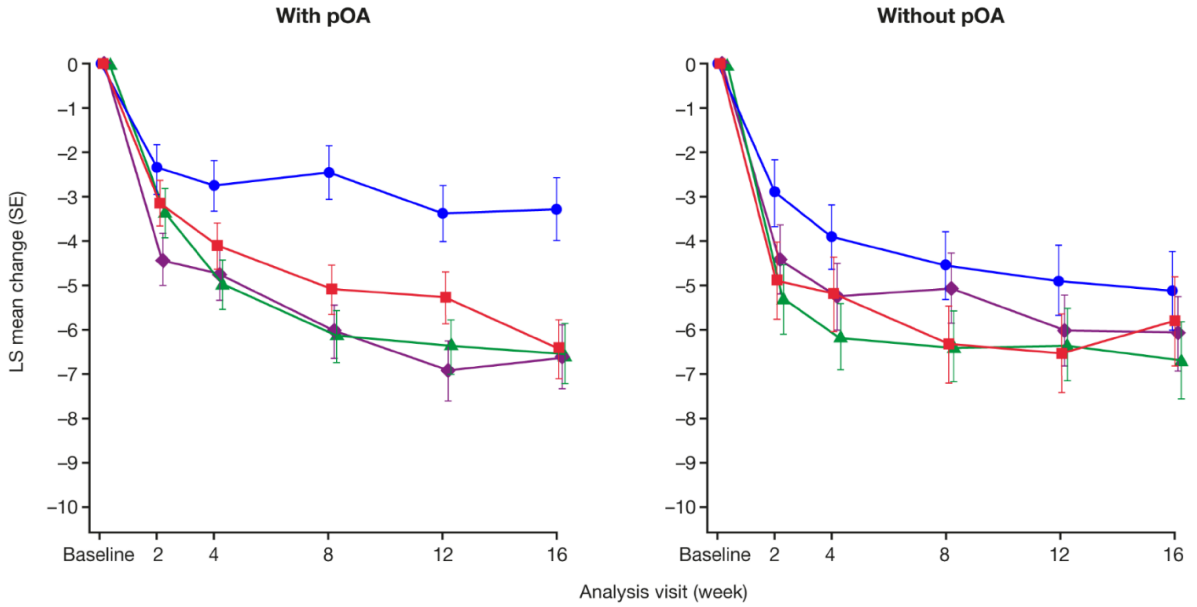


	Baseline	Week 2		Week 4		Week 8		Week 12		Week 16		Baseline	Week 2		Week 4		Week 8		Week 12		Week 16	
	N	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	N	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)
Placebo	81	78	−0.8 (0.21)	77	−0.7 (0.21)	54	−0.9 (0.25)	40	−1.4 (0.29)	31	−1.7 (0.30)	58	58	−1.1 (0.30)	56	−1.1 (0.30)	41	−1.6 (0.33)	29	−1.5 (0.34)	18	−1.7 (0.37)
Fasinumab 6 mg SC Q4W	90	87	−1.4 (0.20)	87	−1.5 (0.19)	61	−1.8 (0.24)	42	−2.0 (0.27)	32	−2.0 (0.29)	47	46	−1.1 (0.34)	45	−1.5 (0.34)	37	−1.6 (0.37)	27	−2.0 (0.37)	16	−1.9 (0.40)
Fasinumab 9 mg SC Q4Wa	68	67	−1.7 (0.22)	61	−2.2 (0.22)	51	−2.6 (0.26)	32	−2.9 (0.31)	26	−2.6 (0.32)	71	68	−1.4 (0.31)	67	−1.7 (0.31)	54	−1.9 (0.34)	42	−2.4 (0.34)	29	−2.2 (0.35)
Fasinumab 9 mg IV Q8W	78	76	−1.3 (0.21)	74	−1.8 (0.21)	59	−2.2 (0.25)	43	−2.6 (0.28)	34	−2.3 (0.29)	62	62	−1.9 (0.30)	58	−2.0 (0.31)	44	−2.2 (0.34)	33	−2.3 (0.34)	22	−2.6 (0.37)

pOA defined by medical history and/or K-L score ≥2 in hip or ≥3 in knee.

IV, intravenous; K-L, Kellgren-Lawrence; LBPI NRS, low back pain intensity numeric rating scale; LSM, least squares mean; mITT, modified intent-to-treat; pOA, peripheral osteoarthritis; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; SE, standard error.

Supplementary Figure 2. Least squares mean change from baseline in RMDQ total score by pOA subgroup (mITT analysis set)

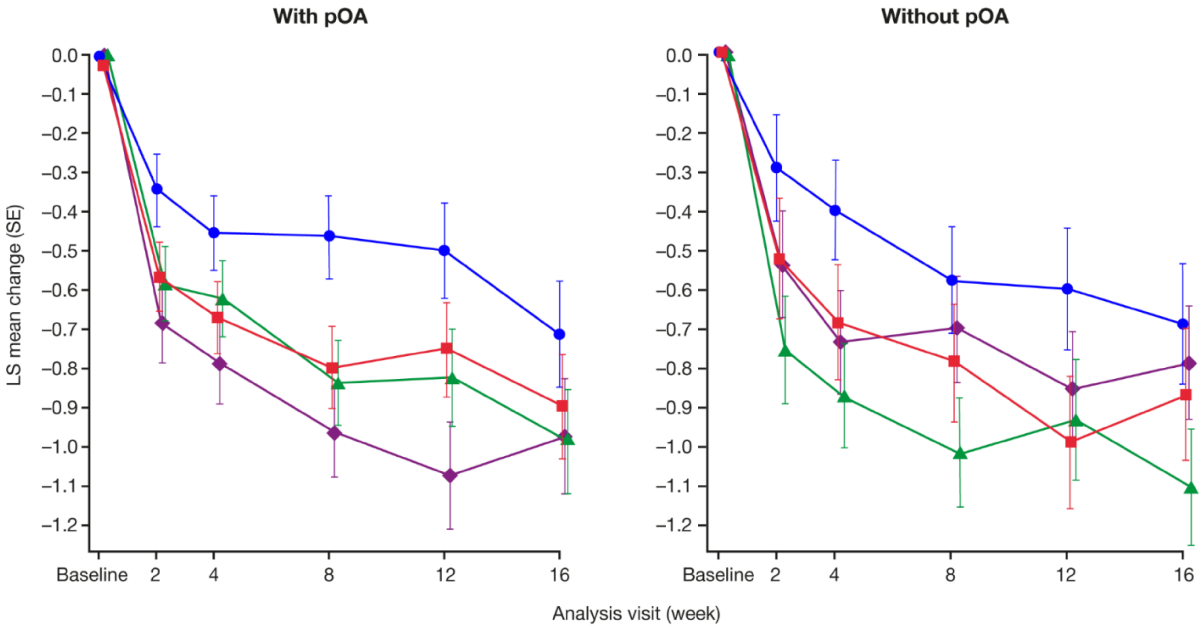


	With pOA										Without pOA									
	Baseline	Week 2		Week 4		Week 8		Week 12		Week 16	Baseline	Week 2		Week 4		Week 8		Week 12		Week 16	
	N	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	N	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)
Placebo	74	70	−2.4 (0.55)	70	−2.7 (0.55)	50	−2.4 (0.59)	37	−3.4 (0.63)	28	−3.3 (0.69)	58	58	−2.9 (0.73)	57	−3.9 (0.72)	42	−4.5 (0.76)	30	−4.9 (0.78)	18	−5.1 (0.87)
Fasinumab 6 mg SC Q4W	90	87	−3.1 (0.50)	85	−4.1 (0.50)	61	−5.1 (0.54)	40	−5.3 (0.59)	31	−6.4 (0.64)	45	45	−4.9 (0.86)	42	−5.2 (0.84)	36	−6.3 (0.86)	26	−6.5 (0.89)	15	−5.8 (0.98)
Fasinumab 9 mg SC Q4W	67	65	−4.4 (0.57)	61	−4.7 (0.58)	50	−6.0 (0.60)	32	−6.9 (0.66)	26	−6.6 (0.71)	69	69	−4.4 (0.76)	65	−5.2 (0.75)	52	−5.0 (0.77)	41	−6.0 (0.79)	29	−6.1 (0.83)
Fasinumab 9 mg IV Q8W	75	72	−3.4 (0.54)	71	−5.0 (0.55)	57	−6.1 (0.57)	41	−6.4 (0.61)	32	−6.5 (0.66)	61	61	−5.3 (0.76)	57	−6.2 (0.75)	44	−6.4 (0.78)	33	−6.3 (0.80)	23	−6.7 (0.86)

pOA defined by medical history and/or K-L score ≥2 in hip or ≥3 in knee.

IV, intravenous; K-L, Kellgren-Lawrence; LSM, least squares mean; mITT, modified intent-to-treat; pOA, peripheral osteoarthritis; Q4W, every 4 weeks; Q8W, every 8 weeks; RMDQ, Roland-Morris Disability Questionnaire; SC, subcutaneous; SE, standard error.

Supplementary Figure 3. Least squares mean change from baseline in PGA of LBP score by pOA subgroup (mITT analysis set)



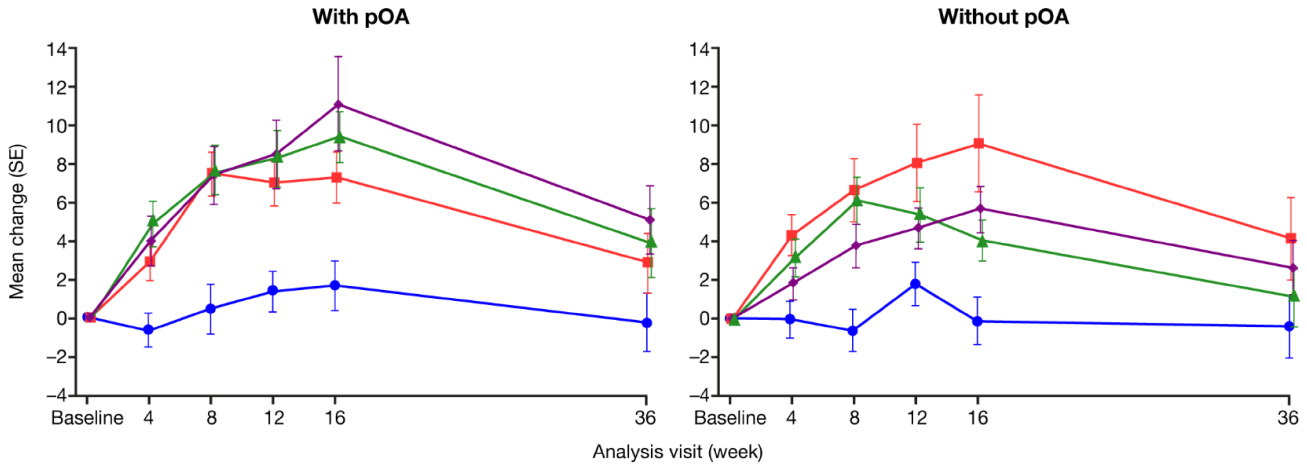
	Baseline	Week 2		Week 4		Week 8		Week 12		Week 16	
	N	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)
Placebo	82	78	−0.3 (0.09)	78	−0.5 (0.10)	58	−0.5 (0.11)	42	−0.5 (0.12)	32	−0.7 (0.13)
Fasinumab 6 mg SC Q4W	92	89	−0.6 (0.09)	87	−0.7 (0.09)	63	−0.8 (0.10)	42	−0.8 (0.12)	33	−0.9 (0.13)
Fasinumab 9 mg SC Q4W	68	66	−0.7 (0.10)	62	−0.8 (0.10)	51	−1.0 (0.11)	32	−1.1 (0.14)	26	−1.0 (0.15)
Fasinumab 9 mg IV Q8W	78	75	−0.6 (0.09)	74	−0.6 (0.10)	60	−0.8 (0.11)	43	−0.8 (0.12)	34	−1.0 (0.13)

	Baseline	Week 2		Week 4		Week 8		Week 12		Week 16	
	N	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)	n	LSM (SE)
Placebo	58	58	−0.3 (0.13)	57	−0.4 (0.13)	42	−0.6 (0.14)	30	−0.6 (0.15)	18	−0.7 (0.15)
Fasinumab 6 mg SC Q4W	47	46	−0.5 (0.15)	44	−0.7 (0.14)	38	−0.8 (0.15)	27	−1.0 (0.17)	15	−0.9 (0.17)
Fasinumab 9 mg SC Q4W	71	69	−0.5 (0.13)	67	−0.7 (0.13)	54	−0.7 (0.13)	43	−0.9 (0.15)	29	−0.8 (0.14)
Fasinumab 9 mg IV Q8W	62	61	−0.8 (0.14)	58	−0.9 (0.13)	44	−1.0 (0.14)	33	−0.9 (0.15)	23	−1.1 (0.15)

pOA defined by medical history and/or K-L score ≥2 in hip or ≥3 in knee.

IV, intravenous; K-L, Kellgren-Lawrence; LSM, least squares mean; mITT, modified intent-to-treat; PGA of LBP, Patient Global Assessment of Lower Back Pain; pOA, peripheral osteoarthritis; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; SE, standard error.

Supplementary Figure 4. Mean change from baseline in alkaline phosphatase (U/L) by pOA subgroup (safety analysis set)



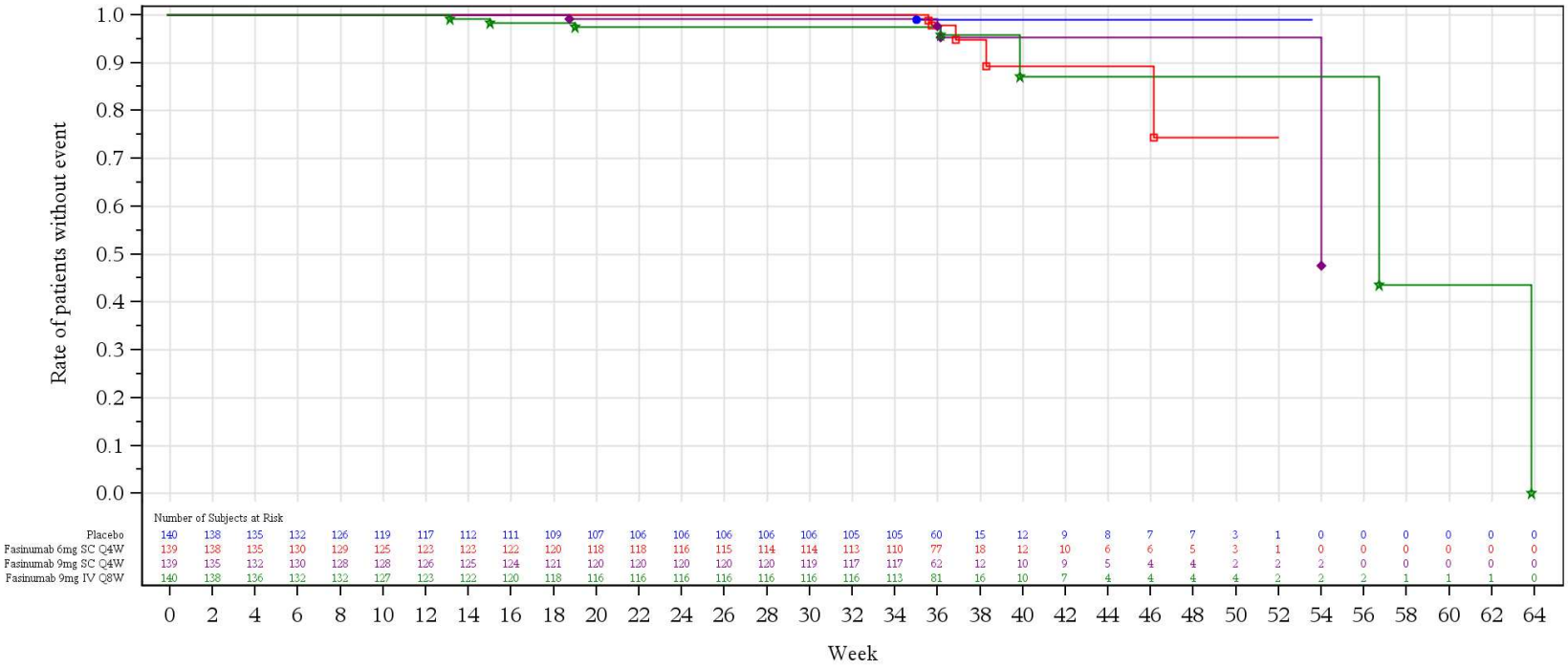
	Baseline	Week 4		Week 8		Week 12		Week 16		Week 36	
	N	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
Placebo	82	77	−0.6 (0.83)	71	0.5 (1.28)	67	1.4 (1.06)	64	1.7 (1.28)	59	−0.2 (1.48)
Fasinumab 6 mg SC Q4W	92	87	2.9 (0.90)	83	2.0 (1.13)	78	7.0 (1.15)	75	7.3 (1.43)	72	2.9 (1.45)
Fasinumab 9 mg SC Q4W	68	63	4.0 (1.26)	62	7.4 (1.46)	59	8.5 (1.73)	60	11.1 (2.41)	54	5.1 (1.78)
Fasinumab 9 mg IV Q8W	78	72	4.9 (1.17)	69	7.7 (1.29)	70	8.3 (1.45)	67	9.4 (1.27)	69	3.9 (1.73)

	Baseline	Week 4		Week 8		Week 12		Week 16		Week 36	
	N	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
Placebo	58	55	0.0 (0.98)	53	−0.6 (1.13)	47	2.0 (1.17)	44	−0.1 (1.30)	41	−0.4 (1.75)
Fasinumab 6 mg SC Q4W	47	45	4.7 (1.13)	42	7.2 (1.76)	39	8.7 (2.11)	38	9.8 (2.68)	36	4.5 (2.27)
Fasinumab 9 mg SC Q4W	71	67	2.0 (0.86)	66	4.1 (1.22)	64	5.1 (1.11)	61	6.1 (1.27)	62	2.9 (1.47)
Fasinumab 9 mg IV Q8W	62	58	3.4 (1.04)	57	6.6 (1.30)	54	5.8 (1.48)	51	4.4 (1.12)	48	1.2 (1.57)

pOA defined by medical history and/or K-L score ≥2 in hip or ≥3 in knee.

IV, intravenous; K-L, Kellgren-Lawrence; mITT, modified intent-to-treat; pOA, peripheral osteoarthritis; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous; SE, standard error; U/L, units per litre.

Supplementary Figure 5. Kaplan-Meier curve of time to event for patients with AA events (safety analysis set)



AA, adjudicated arthropathy; IV, intravenous; Q4W, every 4 weeks; Q8W, every 8 weeks; SC, subcutaneous.