Efficacy, Safety, and Tolerability of Fulranumab as an Adjunctive Therapy in Patients With Inadequately Controlled, Moderate-to-Severe Chronic Low Back Pain: A Randomized, Double-blind, Placebo-controlled, Dose-ranging, Dose-loading Phase II Study

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ABSTRACT

Purpose: Fulranumab is an investigational, fully human recombinant monoclonal antibody (IgG2) that neutralizes the biological actions of human nerve growth factor. Low back pain is a common cause of noncancer chronic pain and represents one of the most significant socioeconomic health-related problems in developed countries. This randomized, double-blind, placebo-controlled study was conducted to evaluate the analgesic effect of fulranumab in patients with moderate-to-severe chronic low back pain.

Methods: Patients (aged 18–80 years) were randomized to receive subcutaneous injections every 4 weeks in 1 of 5 parallel treatment groups: placebo or fulranumab 1mg (1mgQ4wk), 3mg (3mgQ4wk), 3mg after a 6mg loading dose (6mgLD+3mgQ4wk), or 10mg (10mgQ4wk) every 4 weeks.

Findings: A total of 385 patients (median age, 53 years; women, 54%) received at least 1 injection of study medication. No statistically significant differences were observed in improvement of pain intensity scores between the fulranumab treatment regimens and the placebo group at week 12 (primary end point; mean [SD], placebo: –2.0 [2.17], 1mgQ4wk: –1.9 [2.14], 3mgQ4wk: –2.2 [1.89], 6mgLD+3mgQ4wk: –2.0 [1.72] and 10mgQ4wk: –2.1 [2.18]). Results for secondary efficacy parameters (change in the Oswestry Disability Index, Brief Pain Inventory–Short Form, and Patient Global Assessment scales) were consistent with the primary outcome. A placebo effect was observed; the overall percentage of patients with treatment-emergent adverse events (TEAEs) was similar between the placebo (76%) and fulranumab treatment groups (77%–90%). Across all phases, the most common TEAEs in at least 10% of patients (combined fulranumab group vs placebo) were arthralgia (15% vs 12%), back pain (15% vs 18%), upper respiratory tract infection (15% vs 8%), paresthesia (14% vs 8%), diarrhea (12% vs 4%), headache (12% vs 8%), hypoesthesia (11% vs 5%), pain in extremity (11% vs 8%), sinusitis (10% vs 5%), and nasopharyngitis (10% vs 9%). Across all phases, neurologic TEAEs were less frequent in the placebo group (14%) versus the fulranumab treatment groups (25%). In the posttreatment phase, 8 patients had joint replacement operations, which were considered a result of normal progression of osteoarthritis. One case in the 10-mg group was determined to be rapid progession of osteoarthritis and was considered to be possibly related to study drug.

Implications: Fulranumab did not demonstrate efficacy compared with placebo in patients with chronic low back pain but was generally well-tolerated. ClinicalTrials.gov identifier: NCT00973024. (*Clin Ther*. 2016;38:1435–1450) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: Anti-nerve growth factor, chronic low back pain, efficacy, fulranumab, safety.

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INTRODUCTION

Low back pain (LBP) is pain, muscle tension, or stiffness localized below the costal margin and above the inferior gluteal folds, with or without referred leg pain.[1] Because of a lack of agreement on its diagnostic classification, the epidemiology of LBP has been difficult to assess. Nonspecific chronic LBP (cLBP) is defined as back pain without a specific cause when symptoms persist for 12 weeks or more.[2] According to the 2010 Global Burden of Disease Study, LBP is among the top 10 diseases and injuries that account for the highest number of disability-adjusted life-years worldwide.[3] The lifetime prevalence of LBP in developed countries is estimated to be 60% to 70%.[3] Each year, approximately 15% to 45% of adults have LBP,[4] and 5% present to a healthcare facility with a new episode of back pain.[5] Overall, 10% of patients with LBP were unable to work,[6] and approximately 20% had persistent symptoms at 1 year.[7] Despite the low proportion of chronic cases, cLBP accounts for most disability and costs associated with LBP.[8,9] Treatment of this condition is multidisciplinary, consisting of pharmacotherapies (eg, NSAIDs, opioids), antidepressents (eg, duloxetine), topical ointments, intra-articular injections, nonpharmacologic treatments (eg, lifestyle modification, education, exercise), surgical treatment (eg, spinal fusions, laminectomies, vertebroplasty, or kyphoplasty), and psychological counseling.[10–13] However, pharmacotherapies, which are an important component of the treatment approach, are associated with low tolerability due to gastrointestinal, cardiovascular, and central nervous system disorders.[14–16] These tolerability issues, along with limited effectiveness ($<30\%$),[15] result in insufficient pain relief and reduced treatment adherence.[17,18] In addition, long-term use of opioids in patients has led to aberrant drug-related behaviors, including abuse and addiction.[19] Given the limitations and lack of data on long-term effectiveness of the current therapies, there remains an unmet need for a tolerable analgesic intervention that is effective in the treatment of nonspecific cLBP.

Nerve growth factor (NGF), a neurotrophin, is associated with inflammatory and neuropathic pain.[20–23] An elevated level of NGF, resulting from tissue damage or other causes, is known to cause pain and hyperalgesia.[20] Rodent studies have found that antagonism of NGF leads to prevention of pain-related behavior[24–26] and is the rationale for use of anti-NGF agents to provide effective relief from chronic pain. Moreover, blocking NGF's activity with anti-NGF antibodies or with IgG fusion proteins resulted in reduction of hyperalgesia and pain.[27–29]

Fulranumab is a fully human recombinant monoclonal antibody (IgG2) directed against NGF and specifically neutralizes the biological activity of human NGF.[30] Recent clinical studies have found that fulranumab is highly effective in patients for the treatment of osteoarthritis pain[30] and diabetic peripheral neuropathic pain[31] that is inadequately controlled by standard pain therapies. The present study was undertaken to evaluate the efficacy and safety profile of fulranumab when given as an adjuvant, compared with placebo, in patients with moderate-to-severe cLBP insufficiently controlled by standard pain therapy (NSAIDs, opioids).

METHODS

This was a phase II, randomized, double-blind (DB), placebo-controlled, dose-ranging, dose-loading study conducted at 62 sites across 3 countries (Belgium, Canada, and the United States) from September 2009 through May 2011. The study protocol was approved by an independent ethics committee or an institutional review board at each study site, and the study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, consistent with Good Clinical Practices, and applicable regulatory requirements. Written informed consent was obtained from all participants at screening before initiation of protocol-specified procedures.

Study Population

Male and female patients, 18 through 80 years of age, with moderate-to-severe cLBP not adequately controlled by standard analgesic therapy (NSAIDs, opioids) were enrolled. Patients had a documented clinical diagnosis of LBP (category 1 or 2, classified according to the Quebec Task Force Classification for Spinal Disorders) that was present for ≥ 20 days per month, ≥ 3 hours per day, or ≥ 6 months; a average pain intensity rating of ≥ 5 (11-point pain intensity numerical rating scale [NRS]) during 3 days before randomization; and Beck Depression Inventory II score of ≤ 29 at screening. Patients had to be receiving stable doses of NSAIDs or immediate-release opioids for a minimum of 5 days per week or long-acting

opioids (not exceeding 200 mg of oral morphine equivalents per day) for 4 weeks before screening.

Key exclusion criteria included LBP classified as category 3 or 4 by the Quebec Task Force Classification for Spinal Disorders; history of seizure disorder, intrathecal therapy, epidural therapy and ventricular shunts, mild or moderate traumatic brain injury, stroke, transient ischemic attack, or meningitis within the past year before screening; history of brain injury within the past 15 years, resulting in a change in consciousness and with residual sequelae history of epilepsy or multiple sclerosis; current diagnosis of fibromyalgia, complex regional pain syndrome (including reflex sympathetic dystrophy or causalgia), acute spinal cord compression, bowel or bladder dysfunction as a result of cauda equina compression, back pain caused by secondary infection, or pain caused by confirmed or suspected neoplasm; and/or any new or unresolved neurologic deficits, including progressive deficits, within 6 months before screening.

Study Medication

Study medication was supplied by Amgen Inc (Thousand Oaks, California). Fulranumab was a clear, sterile, frozen solution (approximately 1-mL fill volume) in 5-mL, single-use glass vials. The fulranumab solution contained fulranumab at a concentration of 10 mg/mL. Matching placebo was supplied as a clear, sterile solution (approximately 1-mL fill volume) in 5-mL, single-use glass vials.

Study Design

The planned study consisted of 3-week screening, 12-week DB efficacy, 92-week DB extension, and 26-week posttreatment phases. All eligible patients were randomized (1:1:1:1:1) to receive 1 of 5 treatments (placebo, fulranumab 1 mg every 4 weeks [1mgQ4wk], 3 mg every 4 weeks [3mgQ4wk], 3 mg every 4 weeks after a 6-mg loading dose [6mgLD+3mgQ4wk], or 10 mg every 4 weeks [10mgQ4wk]) based on a computer-generated randomization schedule. The Interactive Voice Response System assigned a unique treatment code that was not provided to the investigator. During the DB efficacy and DB extension phases, the patients received 1 subcutaneous injection of study medication in the thigh every 4 weeks. To maintain blinding, placebo-treated patients were randomly assigned to 1 of the 4 volumes, matching the volumes of the 4 fulranumab treatment groups. The randomization was stratified by baseline opioid use (yes or no) and body weight (<85 or ≥ 85 kg). Dose reductions in study drug were allowed for patients who experienced new or worsening neurologic treatment-emergent adverse events (TEAEs). Patients who completed all assessments during the 12-week DB efficacy phase, including the last visit (ie, week 13) were considered to have completed the DB efficacy phase of the study. After completion of the 12-week DB efficacy phase, efficacy analysis was performed; dosing was stopped (October 2010) because of a lack of efficacy. All patients entered the posttreatment phase per protocol, which occurred 2 months before the clinical hold imposed by the US Food and Drug Administration on all anti-NGF studies because of concerns of possible increased risk of osteonecrosis and/or rapid progression of osteoarthritis (RPOA).

Concomitant Medications

The use of NSAIDs, immediate-release opioids, long-acting opioids, and acetaminophen (paracetamol; as rescue medication) was permitted. During the 12-week DB efficacy phase, patients were required to maintain their concurrent pain medications without change unless indicated for tolerability. However, they were allowed to change their concurrent pain medications as clinically needed during the DB extension phase.

Study Evaluations

Efficacy

The primary efficacy objective was the evaluation of change from baseline to the end of the 12-week DB efficacy phase in the mean LBP-related pain intensity score. The mean LBP NRS (0 indicating no pain to 10 indicating worst pain) during the past 12 hours was recorded twice daily. Baseline was a mean of 3 days before first injection, and the end point was a mean of the last 7 days during the DB efficacy phase. Secondary efficacy objectives included evaluation of the efficacy of fulranumab compared with placebo as measured by back pain disability with subscales and total scores of the Oswestry Disability Index (ODI; weeks 1, 5, 9, 13/discontinuation, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, and 105/discontinuation), pain severity and pain interference subscales, and total scores from the Brief Pain Inventory Short Form (BPI-SF; every 4 weeks) and Patient Global Assessment (PGA; every 4 weeks).

The ODI comprises 10 items or dimensions. Each item of the ODI score was assigned a score of 0 to 5 for the 6 response alternatives. The ODI total score was expressed as a percentage and was calculated as follows: total score = (sum of the nonmissing scores for individual items/total possible score) × 100%, where total possible score = 5 × total number of completed items.[32] The BPI-SF included 4 items that assessed pain intensity (pain intensity subscales) and 7 items that assessed how much this pain has interfered with daily activities (pain interference subscales).[33] The intensity of pain was assessed with 4 items using an 11-point NRS from 0 indicating no pain to 10 indicating pain "as bad as you can imagine." The pain interference items are scored by the respondent on a scale of 0 indicating does not interfere to 10 indicating completely interferes. If any of the individual components were missing, then the pain intensity subscale score was set to missing. The BPI-SF pain interference subscale score was calculated as the mean of the nonmissing scores from the individual components. This mean was computed only if at least 4 of the 7 items were nonmissing.[34] The PGA is a single item that the patients completed to indicate perception of his or her LBP problem on an 11-point NRS from 0 indicating very good to 10 indicating very bad.

Pharmacokinetic Properties

Pharmacokinetic (PK) end points included evaluation of the PK properties of fulranumab after multiple-dose administrations of fulranumab and a population PK approach to characterize the disposition characteristics of fulranumab in this study. Venous blood samples for measuring serum fulranumab concentrations were scheduled to be collected at weeks 1, 5, 9, 13, 17, 21, 25, 29, 33, 37, 57, 81, and 105 and at week 26 after the last dose of study drug. Samples were collected at the final visit for patients who discontinued from the study. An additional blood sample was collected randomly at a clinic visit anytime between week 5 and week 13. Serum fulranumab concentrations were measured using a validated ELISA. The lowest quantifiable concentration in a sample for the serum fulranumab ELISA was 0.00156 μg/mL. In addition, serum fulranumab concentrations were summarized by baseline body weight (<85 or ≥85 kg). Concentrations below the lowest quantifiable concentration in a sample were treated as 0 in these summaries.

Immunogenicity

Serum samples for the detection of antibodies to fulranumab were collected at weeks 1, 13, 37, 57, 81, and 105 and at week 26 after the last dose of study medication. Samples were collected at the final visit for patients who were terminated from the study. The presence of antidrug antibodies against fulranumab in serum was determined by a validated electrochemiluminescent immunoassay on a Meso Scale Discovery platform (Gaithersburg, Maryland). The maximum observed sensitivity of the serum antidrug antibody electrochemiluminescent immunoassay was 0.77 ng/mL at a minimum required 1/20 dilution.

Safety Profile

Safety profile measurements were performed throughout the study and included evaluations of TEAEs, monitoring of injection site, clinical laboratory tests, ECGs, vital signs, physical examination, and neurologic assessments (Total Neuropathy Score–nurse[35] and the Mini-Mental State Examination).[36] In addition, examination of joint safety profile was instituted and included collection of all imaging and requests for tissue specimens of excised and replaced joints from the time of the clinical hold until the end of posttreatment phase. An independent data monitoring committee was appointed before the start of the study to review all unblinded safety profile data.

Statistical Evaluations

Sample Size Determination

It was estimated that with 72 patients per group (360 patients in total) the study would have 84% power to detect a treatment difference versus placebo of 1.4 for change from baseline to the end of the 12-week DB phase in average pain intensity score, assuming an SD of 2.5 for each group and a 20% withdrawal rate, using a type I error rate of 0.05 and a 2-sided, 2-sample *t* test.

Analysis Set

All efficacy and safety profile analyses were based on the intent-to-treat analysis set, which included all randomly assigned patients who received at least 1 dose of fulranumab or placebo.

Statistical Analyses

Demographic and baseline characteristics were summarized descriptively. Change from baseline to

week 12 in average pain score was analyzed using ANCOVA, with treatment, baseline body weight (<85 or ≥ 85 kg), and baseline opioid use (yes or no) as factors and baseline average pain score as the covariate. A step-down procedure was planned, at a 2-sided, 0.05 level of significance for each step, in the following order of fulranumab doses versus placebo: (1) 10mgQ4wk, (2) 6mgLD+3mgQ4wk, (3) 3mgQ4wk, and (4) 1mgQ4wk. The primary analysis used the last observation carried forward imputation method for the missing data. All analyses based on the last observation carried forward were also replicated using the baseline observation carried forward imputation method. Sensitivity analyses of the primary efficacy results were performed using a model of mixed-effects repeated measures for observed cases.

Change from baseline to week 12 in ODI total scores, pain severity, and pain interference subscales of the BPI-SF and PGA scores were analyzed using the same ANCOVA, with the corresponding baseline as a covariate. There were no multiplicity adjustments for secondary efficacy comparisons. The incidence and titers of antibodies to fulranumab were summarized by treatment group for all treated patients. Patients were classified as positive or negative for antibodies to fulranumab. Descriptive statistics were provided for PK data, and PK end points included mean, SD, median, and range.

All evaluations for safety profile were summarized descriptively. The incidence of patients reporting TEAEs was tabulated by system-organ class and preferred terms.

RESULTS

Patient Disposition and Demographic Characteristics

Overall, 625 patients were screened, of whom 389 eligible patients were randomly assigned to 5 treatment groups, and 385 patients received at least 1 dose of the study medication (Figure 1). Overall, 330 (84.8%) of 389 randomized patients completed the DB efficacy phase, and 317 patients entered the DB extension phase. The major reason for withdrawal from the DB extension phase was sponsor discontinued the study (72%, because of a lack of efficacy in the DB efficacy phase). Most patients (76%) completed the posttreatment phase.

Patient demographic characteristics and baseline characteristics were generally balanced across the treatment groups (Table I). Among these patients (mean age, 53.2 years), 54.0% were women, 45.5% were taking opioids at baseline, and 52.7% were in the <85 kg subgroup. A total of 51.7% patients had LBP pain with no radiation, with the highest percentage of patients in the placebo group (60.5%); a total of 48.1% of patients had LBP with some radiation into proximal extremity, with the highest percentage of patients in the fulranumab 1mgQ4wk group (55.8%).

Most patients received 3 injections of the study medications during the DB efficacy phase (82%–91%), and most patients (59%–67%) received 6 injections in the DB extension phase. Six patients did not receive all 3 planned injections (due to neurologic adverse event, missed visit, or other reasons not provided by the investigator). Only 1 patient (in the 10mgQ4wk group) had a dose reduction from the day 29 to the day 57 dose due to a neurosensory TEAE. The median treatment duration during the DB phases was similar across all treatment groups: approximately 9 to 9.4 months (275–282.5 days), with approximately 3 of those months during the DB efficacy phase. The duration of the extension phase that was to be approximately 92 weeks was curtailed because of the early termination of the study.

No significant change from baseline to end of the DB efficacy phase in the average daily dose of rescue medication was noted. In the 6mgLD+3mgQ4wk and 10mgQ4wk fulranumab groups (18.6% each), the lowest median percentage of days taking rescue medication was observed compared with the placebo group (34.5%) and other fulranumab groups (25.0% [1mgQ4wk] and 22.5% [3mgQ4wk]) during the entire 12-week DB efficacy phase.

Efficacy Outcomes

Primary End Points

No significant differences were observed in the improvement of pain intensity scores between the fulranumab treatment regimens compared with the placebo group at week 12. The least square mean change from baseline was −1.9 (1mgQ4wk), −2.2 (3mgQ4wk), −2.0 (6mgLD+3mgQ4wk), −2.1 (10mgQ4wk) and −2.0 (placebo) (Table II). The numerical reduction of pain over time (weeks 4, 8, and 12) with fulranumab treatment revealed a consistent pattern of improvement

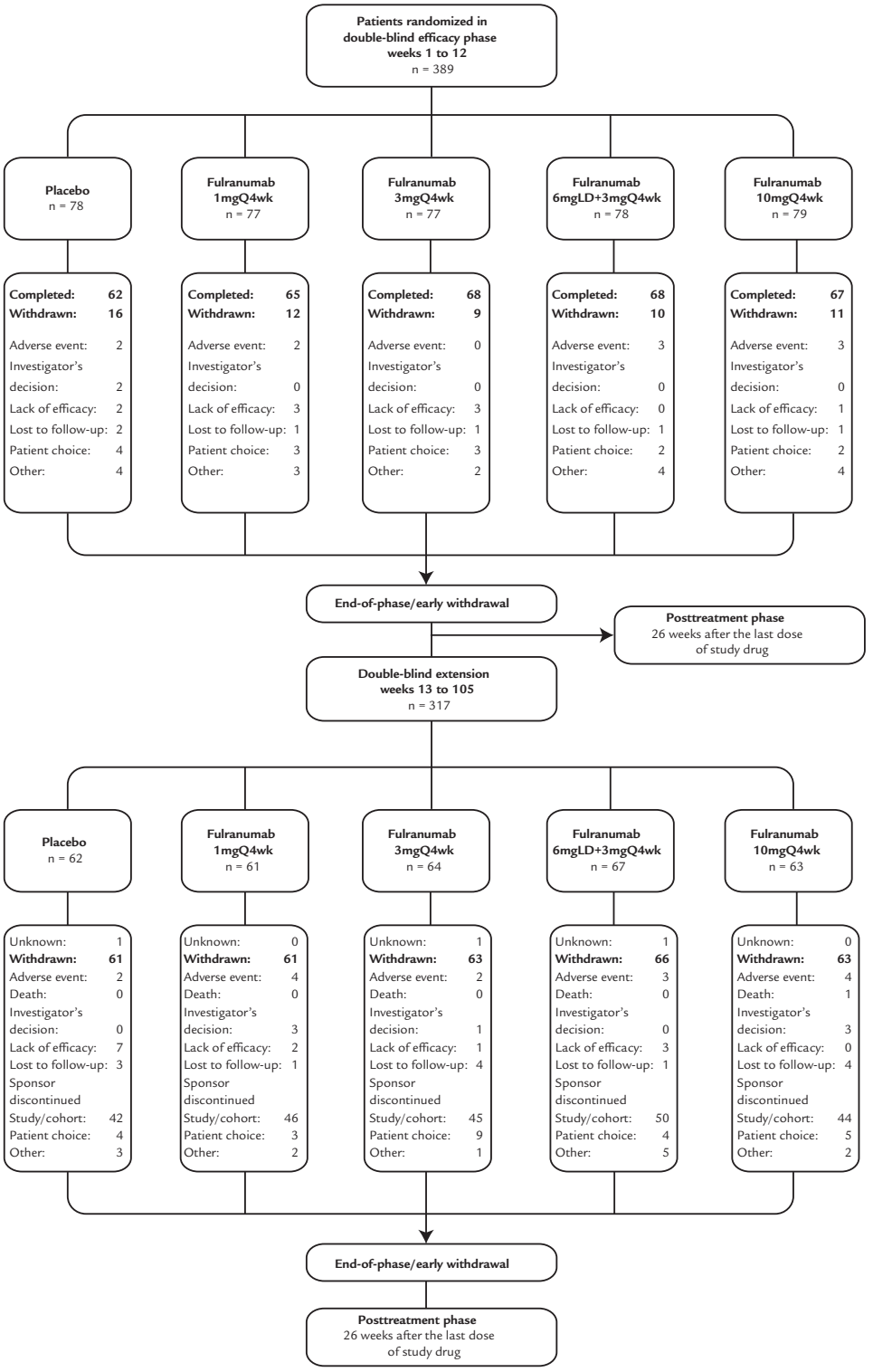


Figure 1. Study design and patient disposition (all randomized patients analysis set). One patient in the 1 mg of fulranumab every 4 weeks (1mgQ4wk) group never received an injection in the double-blind extension phase before being withdrawn (reason: other). LD = loading dose.

Table I. Demographic and baseline characteristics (intent-to-treat analysis set).

Characteristic	Placebo (n = 76)	Fulranumab 1mgQ4wk (n = 77)	Fulranumab 3mgQ4wk (n = 77)	Fulranumab 6mgLD+3mgQ4wk (n = 78)	Fulranumab 10mgQ4wk (n = 77)	Total (n = 385)
Age, mean (SD), y	54.9 (11.72)	51.7 (11.58)	53.2 (13.46)	54.1 (10.77)	51.9 (12.48)	53.2 (12.03)
Age group, No. (%)						
≥65 years	15 (19.7)	13 (16.9)	14 (18.2)	13 (16.7)	15 (19.5)	70 (18.2)
<65 years	61 (80.3)	64 (83.1)	63 (81.8)	65 (83.3)	62 (80.5)	315 (81.8)
Women, No. (%)	43 (56.5)	39 (50.6)	37 (48.1)	47 (60.3)	42 (54.5)	208 (54.0)
Race, No. (%)						
White	65 (85.5)	70 (90.9)	64 (83.1)	65 (83.3)	61 (79.2)	325 (84.4)
Black or African American	8 (10.5)	4 (5.2)	7 (9.1)	9 (11.5)	12 (15.6)	40 (10.4)
Asian	2 (2.6)	1 (1.3)	2 (2.6)	2 (2.6)	1 (1.3)	8 (2.1)
American Indian or Alaskan native	0	2 (2.6)	0	1 (1.3)	1 (1.3)	4 (1.0)
Other/multiple	0	0	4 (5.2)	1 (1.3)	1 (1.3)	6 (1.6)
Not reported	1 (1.3)	0	0	0	1 (1.3)	2 (0.5)
Baseline BMI, mean (SD), kg/m^2	29.2 (5.28)	29.4 (4.65)	29.2 (4.60)	28.9 (5.45)	28.8 (6.47)	29.1 (5.31)
Strata 1 – baseline opioid use, No. (%)						
No opioids	42 (55.3)	42 (54.5)	42 (54.5)	42 (53.8)	42 (54.5)	210 (54.5)
Use of opioids	34 (44.7)	35 (45.5)	35 (45.5)	36 (46.2)	35 (45.5)	175 (45.5)
Strata 2 – baseline weight group, No. (%)						
<85 kg	40 (52.6)	41 (53.2)	40 (51.9)	42 (53.8)	40 (51.9)	203 (52.7)
≥85 kg	36 (47.4)	36 (46.8)	37 (48.1)	36 (46.2)	37 (48.1)	182 (47.3)
Quebec Task Force classification of spinal disorder, No. (%)						
Low back pain with no radiation	46 (60.5)	33 (42.9)	41 (53.2)	40 (51.3)	39 (50.6)	199 (51.7)
Low back pain with some radiation into proximal extremity	30 (39.5)	43 (55.8)	36 (46.8)	38 (48.7)	38 (49.4)	185 (48.1)
Low back pain with radiation and positive neurologic findings	0	1 (1.3)	0	0	0	1 (0.3)

LD = loading dose; Q = every.

Table II. Change from baseline to 12-week end point in average pain intensity score (last observation carried forward) in the intent-to-treat analysis set.

Variable	Placebo (n = 76)	Fulranumab 1mgQ4wk (n = 77)	Fulranumab 3mgQ4wk (n = 77)	Fulranumab 6mgLD+3mgQ4wk (n = 78)	Fulranumab 10mgQ4wk (n = 77)
Baseline, mean (SD)	7.2 (1.20)	6.8 (1.26)	7.0 (1.25)	7.0 (1.06)	7.0 (1.13)
Baseline, median (range)	7.1 (5–10)	6.8 (5–10)	7.0 (5–10)	6.8 (5–10)	7.0 (5–10)
Week 12, mean (SD)	5.1 (2.29)	4.9 (2.26)	4.8 (2.27)	4.9 (1.94)	4.9 (2.51)
Week 12, median (range)	5.2 (0–9)	5.0 (1–10)	4.7 (0–10)	5.1 (1–9)	5.0 (0–10)
Change from baseline, mean (SD)	−2.0 (2.17)	−1.9 (2.14)	−2.2 (1.89)	−2.0 (1.72)	−2.1 (2.18)
Change from baseline, median (range)	−1.4 (−8 to 2)	−1.3 (−6 to 3)	−2.2 (−7 to 1)	−1.8 (−7 to 1)	−1.8 (−8 to 1)
LS mean change	−2.0	−1.9	−2.2	−2.0	−2.1
Difference of LS means (95% CI)		0.04 (−0.60 to 0.68)	−0.24 (−0.88 to 0.40)	−0.05 (−0.68 to 0.59)	−0.15 (−0.79 to 0.49)
P value (minus placebo)[*,†]		0.91	0.46	0.89	0.65

LD = loading dose; LS = least square; Q = every.
[*] *P* values and LS means from ANCOVA model with treatment, baseline opioid use (use/no use), and baseline body weight (<85 or ≥85 kg) as factors and baseline average pain score as covariate.
[†] Nominal unadjusted *P* values are presented.

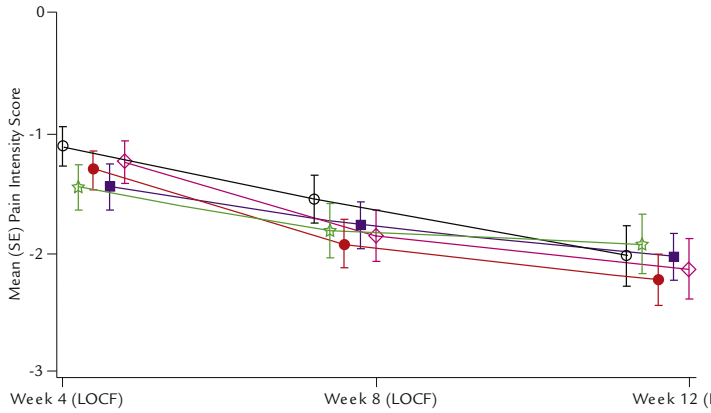
similar to placebo (Figure 2). However, there were no significant changes in average pain intensity for any of the fulranumab treatment groups versus placebo. The placebo effect improved over time and reached a least square mean change from baseline of −2.0 at week 12. No significant change from baseline in average pain scores across all fulranumab treatment groups compared with the placebo group at week 12 of the DB efficacy phase was noted based on the baseline observation carried forward and mixed-effects repeated-measures sensitivity analyses.

Secondary End Points

Across all fulranumab treatment groups, no significant change from baseline to end point in ODI scores was observed compared with placebo (Table III). However, numerically greater improvements in scores from baseline to end point were noted in the 3mgQ4wk and 10mgQ4wk treatment groups compared with placebo. For the BPI-SF pain intensity and pain interference subscale scores, no consistent dose-related improvement from baseline was observed at the end of the DB efficacy phase. However, a significant improvement from baseline was observed for the treatment relief in the fulranumab 10mgQ4wk group (mean [SD] change from baseline, 18.0 [34.76]) compared with placebo (mean [SD] change from baseline, 4.9 [30.56]) ($P = 0.008$). There were no significant differences versus placebo for changes in PGA scores from baseline to the end of the DB efficacy phase.

PK Properties

After a subcutaneous injection of fulranumab, mean trough serum fulranumab concentrations increased in an approximately dose-proportional or greater than dose-proportional manner across all dosing regimens (data not shown). Steady-state serum fulranumab concentrations were generally achieved by week 17 after 1mgQ4wk, 3mgQ4wk, 6mgLD+3mgQ4wk, or 10mgQ4wk dosing.



	Week 4 Mean (SE)	Week 8 Mean (SE)	Week 12 Mean (SE)
Placebo (n = 76)	−1.12 (0.17)	−1.56 (0.20)	−2.03 (0.25)
Fulranumab 1mgQ4wk (n = 77)	−1.46 (0.19)	−1.82 (0.23)	−1.93 (0.24)
Fulranumab 3mgQ4wk (n = 77)	−1.31 (0.16)	−1.93 (0.20)	−2.23 (0.22)
Fulranumab 6mgLD+3mgQ4wk (n = 78)	−1.45 (0.19)	−1.77 (0.19)	−2.04 (0.19)
Fulranumab 10mgQ4wk (n = 77)	−1.24 (0.18)	−1.86 (0.21)	−2.14 (0.25)

Figure 2. Mean (SE) change from baseline in pain intensity score over time in the double-blind efficacy phase (last observation carried forward [LOCF]) in the intent-to-treat analysis set. LD = loading dose; Q = every.

Mean trough serum fulranumab concentrations were generally maintained at an approximate steady-state through week 37 when treated with 1mgQ4wk, 3mgQ4wk, or 10mgQ4wk maintenance dosing. Within each treatment group, the mean serum fulranumab concentrations in patients weighing ≥85 kg were generally lower than those levels observed at each respective sampling time point in patients weighing <85 kg.

Immunogenicity

Four patients in the fulranumab treatment groups developed antibodies to fulranumab by the end of study (data not shown). The incidence of antibodies to fulranumab occurred in the 1mgQ4wk and 10mgQ4wk dose groups. Overall, antibody responses to fulranumab were low (titers, 1:20–1:320), and none of these antibodies were able to reduce serum fulranumab concentrations or neutralize the biological effects of fulranumab in vitro.

Safety Profile Outcomes

Overall, fulranumab at all doses was generally well-tolerated. During the combined DB and posttreatment phase, the overall percentage of patients with TEAEs was similar between placebo (76%) and the fulranumab treatment groups (77%–90%), with no dose relationship observed among the fulranumab groups (Table IV). In the combined fulranumab group, upper respiratory tract infection, sinusitis, nasopharyngitis, back pain, arthralgia, pain in extremity, peripheral edema, paresthesia, headache, hypoesthesia, and diarrhea were the most common TEAEs. Across treatments, during all phases combined, the percentage of patients discontinuing due to TEAEs was low (26 patients [7%]), with no apparent dose relationship. Most TEAEs were mild or moderate in intensity. Serious TEAEs occurred in 33 patients (1mgQ4wk, 9 [12%]; 3mgQ4wk, 6 [8%]; 6mgLD+3mgQ4wk, 11 [14%]; and 10mgQ4wk, 7 [9%]) in the combined fulranumab group compared with 7 patients (9%) in the placebo group (Table IV). Most of the serious TEAEs were in musculoskeletal and connective tissue disorders and surgical and medical procedures system organ classes. One death was reported in the 10mgQ4wk group due to streptococcal pneumonia and malignant lung neoplasm.

Neurologic TEAEs were more frequent in the fulranumab treatment groups compared with placebo (1mgQ4wk, 12 [16%]; 3mgQ4wk, 20 [26%];

Table III. Change from baseline to 12-week end point in Oswestry Disability Index, Brief Pain Inventory, and patient global assessment (last observation carried forward) in the intent-to-treat analysis set.

		Fulranumab			
	Placebo (n = 76)[*]	1mgQ4wk (n = 77)[‖]	3mgQ4wk (n = 77)[‡]	6mgLD+3mgQ4wk (n = 78)[†]	10mgQ4wk (n = 77)[‡]
Oswestry Disability Index					
Baseline, mean (SD)	36.7 (13.47)	33.5 (12.03)	34.0 (14.0)	37.0 (13.51)	36.8 (13.55)
Baseline, median (range)	35.6 (6–76)	32.0 (4–64)	34.0 (4–72)	35.8 (12–72)	38.0 (8–64)
Change from baseline					
Mean (SD)	−6.5 (12.64)	−5.7 (11.82)	−8.0 (12.16)	−6.8 (11.35)	−7.9 (11.82)
Median (range)	−4.4 (−58 to 16)	−6.0 (−38 to 54)	−6.0 (−42 to 20)	−5.2 (−32 to 18)	−6.0 (−48 to 20)
P value (minus placebo)[§,‖]		1.00	0.24	0.89	0.47
Difference of LS means (95% CI)		0.0 (−3.69 to 3.69)	−2.2 (−5.90 to 1.50)	−0.3 (−3.95 to 3.41)	−1.4 (−5.04 to 2.34)
Brief Pain Inventory–Pain Intensity Subscale					
Baseline, mean (SD)	6.7 (1.29)	6.4 (1.25)	6.5 (1.34)	6.5 (1.20)	6.7 (1.28)
Baseline, median (range)	6.8 (3–9)	6.3 (3–10)	6.5 (4–10)	6.5 (4–10)	6.8 (4–10)
Change from baseline					
Mean (SD)	−1.6 (2.14)	−1.8 (2.02)	−2.1 (2.10)	−1.6 (1.76)	−2.1 (2.22)
Median (range)	−1.3 (−8 to 4)	−1.5 (−7 to 2)	−1.8 (−9 to 2)	−1.1 (−7 to 2)	−2.0 (−8 to 3)
P value (minus placebo)[§,‖]		0.46	0.10	0.72	0.14
Difference of LS means (95% CI)		−0.2 (−0.88 to 0.40)	−0.5 (−1.19 to 0.10)	−0.1 (−0.76 to 0.53)	−0.5 (−1.13 to 0.16)
Brief Pain Inventory–Pain Interference Subscale					
Baseline, mean (SD)	6.0 (1.85)	5.0 (1.89)	5.3 (2.34)	5.8 (1.61)	5.2 (1.78)
Baseline, median (range)	6.0 (1–9)	4.9 (0–9)	5.4 (0–10)	6.1 (1–9)	5.1 (1–9)
Change from baseline					
Mean (SD)	−1.6 (2.29)	−1.4 (2.10)	−2.0 (2.18)	−1.9 (1.75)	−1.6 (1.96)
Median (range)	−1.7 (−9 to 6)	−1.3 (−7 to 4)	−1.4 (−8 to 3)	−1.8 (−6 to 2)	−1.9 (−6 to 3)
P value (minus placebo)[§,‖]		0.87	0.09	0.36	0.65
Difference of LS means (95% CI)		−0.1 (−0.70 to 0.59)	−0.6 (−1.20 to 0.09)	−0.3 (−0.93 to 0.34)	−0.2 (−0.80 to 0.49)
Brief Pain Inventory–Treatment Relief, %					
Baseline, mean (SD)	38.8 (22.17)	39.3 (26.04)	35.3 (22.14)	34.7 (22.48)	37.3 (24.46)
Baseline, median (range)	40.0 (0–80)	40.0 (0–100)	30.0 (0–80)	30.0 (0–90)	40.0 (0–90)
Change from baseline					
Mean (SD)	4.9 (30.56)	11.6 (32.66)	10.1 (33.83)	8.9 (25.90)	18.0 (34.76)
Median (range)	10.0 (−70 to 90)	10.0 (−70 to 90)	10.0 (−80 to 90)	0.0 (−80 to 80)	20.0 (−70 to 100)
P value (minus placebo)[§,‖]		0.13	0.49	0.73	0.01[¶]
Difference of LS means (95% CI)		6.9 (−2.12 to 15.85)	3.2 (−5.84 to 12.21)	1.6 (−7.42 to 10.58)	12.1 (3.12–21.15)
Patient Global Assessment					
Baseline, mean (SD)	6.9 (1.50)	6.5 (1.49)	6.8 (1.59)	6.8 (1.29)	6.9 (1.41)
Baseline, median (range)	7.0 (3–10)	7.0 (3–10)	7.0 (3–10)	7.0 (4–10)	7.0 (3–10)

(continued)

Table III. (continued).

	Placebo (n = 76)*	Fulranumab 1mgQ4wk (n = 77)‖	Fulranumab 3mgQ4wk (n = 77)‡	Fulranumab 6mgLD+3mgQ4wk (n = 78)†	Fulranumab 10mgQ4wk (n = 77)‡
Change from baseline					
Mean (SD)	−1.8 (2.42)	−2.0 (2.11)	−2.4 (2.51)	−1.8 (1.95)	−2.3 (2.71)
Median (range)	−2.0 (−7 to 5)	−2.0 (−8 to 2)	−2.0 (−9 to 3)	−1.5 (−6 to 2)	−3.0 (−8 to 5)
P value (minus placebo)§,‖		0.40	0.07	0.83	0.15
Difference of LS means (95% CI)		−0.3 (−1.03 to 0.41)	−0.7 (−1.39 to 0.05)	−0.1 (−0.80 to 0.64)	−0.5 (−1.24 to 0.20)

LD = loading dose; LS = least square; Q = every.

*n = 73 with assessments.

†n = 76 with assessments.

‡n = 75 with assessments.

§*P* values and LS means from ANCOVA model with treatment, baseline opioid use (use/no use), and baseline body weight (<85 or ≥85 kg) as factors and baseline total score as the covariate.

‖Nominal unadjusted *P* values are presented.

¶significant versus placebo.

6mgLD+3mgQ4wk, 21 [27%]; 10mgQ4wk, 24 [31%]; and placebo, 11 [14%]). The most frequently occurring neurologic TEAEs were paresthesia (combined fulranumab group, 14%; placebo, 8%) and hypoesthesia (combined fulranumab group, 11%; placebo, 5%). Two events were considered serious (lumbar radiculopathy in the 6mgLD+3mgQ4wk group and peripheral neuropathy in the 10mgQ4wk group). A low percentage of patients receiving fulranumab (total 1%) discontinued treatment because of neurologic events (paresthesia, hypoesthesia, peripheral neuropathy, peripheral sensory neuropathy, and muscular weakness). None of the neurologic TEAEs were serious except for 1 event in the 10mgQ4wk group (peripheral neuropathy), and that patient recovered. The overall percentage of patients with bradycardia-related TEAEs in all phases combined was low among the fulranumab treatment groups (2%) with a higher percentage than placebo (1 [1%]) in the 3mgQ4wk (3 [4%]) and 10mgQ4wk (2 [3%]) groups and an equal percentage in 6mgLD+3mgQ4wk group. None of the patients in 1mgQ4wk had bradycardia-related TEAEs. There were no TEAEs of bradycardia that were serious or led to discontinuation. Hypotension-related TEAEs occurred in 3 of the fulranumab treatment groups (3mgQ4wk, 1 [1%]; 6mgLD+3mgQ4wk, 1 [1%]; and 10mgQ4wk, 2 [3%]). One case of hypotension was considered serious, and no cases of hypotension led to treatment discontinuation. Elevated aspartate transaminase and alanine transaminase levels (≥ 5 the upper limit of normal) occurred in 3 patients (1mgQ4wk, 2; placebo, 1). There was no acute renal failure during the study in any treatment group.

Injection-site evaluations of mild or moderate rating were most common in the 10mgQ4wk group: 36% of patients had at least 1 evaluation of mild redness, and 16% had at least 1 evaluation of mild or moderate swelling in this group during the DB efficacy phase. No clinically significant changes in laboratory parameters, ECG readings, or vital signs were noted in any patient during the study. In addition, there were no clinically significant changes from baseline in Total Neuropathy Score–nurse and Mini-Mental State Examination. Neurologic TEAEs leading to a neurologic consultation with category grades >2 were noted in the 1mgQ4wk group (hypoesthesia, muscular weakness, and hypersensitivity, 1 patient each) and the 6mgLD+3mgQ4wk group (hypoesthesia and radiculopathy, 1 patient each). The

Table IV. TEAEs for all treatment groups for all combined phases.

TEAE	Placebo (n = 76), No. (%)	Fulranumab, No. (%)			
		1mgQ4wk (n = 77)	3mgQ4wk (n = 77)	6mgLD+3mgQ4wk (n = 78)	10mgQ4wk (n = 77)
Total patients with TEAEs	58 (76)	59 (77)	64 (83)	70 (90)	66 (86)
Serious TEAEs	7 (9)	9 (12)	6 (8)	11 (14)	7 (9)
TEAEs leading to discontinuation	5 (7)	6 (8)	2 (3)	6 (8)	7 (9)
TEAEs reported by ≥10% of patients in any group					
Back pain	14 (18)	15 (19)	11 (14)	10 (13)	11 (14)
Arthralgia	9 (12)	13 (17)	12 (16)	14 (18)	7 (9)
Sinusitis	4 (5)	11 (14)	4 (5)	11 (14)	5 (6)
Pain in extremity	6 (8)	9 (12)	1 (1)	11 (14)	12 (16)
Upper respiratory tract infection	6 (8)	8 (10)	14 (18)	12 (15)	11 (14)
Headache	6 (8)	8 (10)	10 (13)	9 (12)	9 (12)
Nasopharyngitis	7 (9)	5 (6)	11 (14)	7 (9)	7 (9)
Diarrhea	3 (4)	7 (9)	11 (14)	8 (10)	11 (14)
Edema peripheral	3 (4)	5 (6)	5 (6)	9 (12)	8 (10)
Neurologic TEAEs ≥10% of patients					
Paresthesia	6 (8)	5 (6)	16 (21)	12 (15)	10 (13)
Hypoesthesia	4 (5)	4 (5)	10 (13)	8 (10)	12 (16)

LD = loading dose; TEAE = treatment-emergent adverse event; Q = every.

incidence rate of joint replacement was 22 per 1000 person-years with fulranumab treatment (combined) and 13 per 1000 person-years with placebo treatment. An adjudication committee consisting of an expert, independent, and blinded panel was convened to adjudicate all joint replacement cases and cases with TEAEs that indicated possible joint destruction but without requiring joint replacement. In the posttreatment phase, 8 patients (placebo, 1; combined fulranumab, 7) had joint replacement operations of either the hip or knee or shoulder arthroplasty. Most of these cases (n=5) were determined by the adjudication committee to be from normal progression of osteoarthritis. One case that was adjudicated as RPOA occurred in a patient taking fulranumab (10mgQ4wk group) using regular concurrent NSAIDS and who had a history of osteoarthritis in the affected joint before study entry. Most joint replacements (n = 6) were assessed as not related to study drug; 1 (RPOA) was assessed as possibly related, and 1 was considered to have insufficient data for assessment of association.

DISCUSSION

Inhibition of NGF by fulranumab, a fully human recombinant monoclonal antibody, can result in reduction of chronic pain resulting from osteoarthritis[30] and diabetic peripheral neuropathy[31] and is thus proving to be a promising target in the search for new pain therapeutics. This dose-ranging, dose-loading study was conducted to evaluate the efficacy and safety profile of fulranumab when given as adjuvant compared with placebo in patients with moderate-to-severe cLBP insufficiently controlled by standard pain therapy. However, the primary objective to indicate that fulranumab was significantly better than placebo as measured by the change in

average pain intensity at the end of the 12-week DB efficacy phase was not achieved.

The total treatment exposure was curtailed because the study was terminated while patients were in the DB extension phase because of a negative efficacy outcome after the completion of the DB efficacy phase. However, most of the patients completed the DB extension phase of up to 12 months of exposure. Therefore, substantial treatment exposure data for the safety profile were collected in addition to that during the posttreatment phase.

The numerical reduction of pain over time (weeks 4, 8, and 12) with fulranumab treatment revealed a consistent pattern of improvement similar to placebo. However, there were no significant changes in average pain intensity for any of the fulranumab treatment groups compared with placebo. The placebo effect was strong in this study, improving over time and reaching a least square mean change from baseline of −2.0 at week 12. No dose response was observed in the primary end point among the fulranumab treatment groups. No significant results with fulranumab in secondary outcomes as measured by change from baseline in the ODI, BPI-SF subscales, and PGA scales were seen for any of the 4 treatment groups compared with placebo. These findings are in contrast to the earlier studies that evaluated the effectiveness of similar anti-NGF class treatment in patients with chronic osteoarthritis of the knee. In addition, a previous study on the efficacy and tolerability of fulranumab in patients with diabetic peripheral neuropathic pain found a mean reduction of average daily pain at week 12 compared with baseline and revealed a positive dose-response relationship.[31]

The mean trough serum fulranumab concentrations increased in a greater than dose proportional manner when comparing serum fulranumab concentrations in the 3mgQ4wk or 10mgQ4wk groups with those in the 1mgQ4wk group. Sparse sampling design, moderate-to-large interpatient variability in trough serum fulranumab concentrations, a large window for sample collection, and early termination of administration of the study drug may contribute as a whole to the variability in serum fulranumab concentrations. Thus, a definite conclusion regarding dose proportionality cannot be drawn. The steady-state serum fulranumab concentrations were achieved and maintained in those patients who tested positive for antibodies to fulranumab (low titers), indicating that development of antibodies to fulranumab did not reduce serum fulranumab concentrations. However, these results should be interpreted with caution because only 4 patients in the active treatment groups tested positive for antibodies to fulranumab through the end of the study.

During the combined DB and posttreatment phases, the overall rate of TEAEs was similar among placebo and fulranumab treatment groups, with no dose relationship apparent. This safety profile is similar to previous fulranumab studies.[30,31] The most frequently occurring TEAEs were seen in infections and infestations, musculoskeletal and connective tissue disorders, nervous system disorders, and gastrointestinal disorders system organ classes. These TEAEs have also been reported previously in an earlier study that evaluated the tolerability of fulranumab in the treatment of osteoarthritis.[30] The rate of neurologic TEAEs in the placebo group was less than that in the combined fulranumab groups. Most of these neurologic TEAEs generally were mild to moderate in severity and were those associated with large- and small-fiber sensory function, such as paresthesia and hypoesthesia. These results were consistent with earlier studies in patients with osteoarthritis pain and diabetic peripheral neuropathic pain.[30,31] Few withdrawals from the study resulted from these TEAEs. Administration of the anti-NGF class is known to be associated with a number of clinical events termed 'events of interest', such as bradycardia, hypotension, neurologic signs or symptoms, renal failure, and hepatic failure. No events of interest were due to study drug as judged by an unblinded independent data monitoring committee. There was 1 death in the fulranumab group due to the serious TEAE of streptococcal pneumonia and malignant lung neoplasm.

The US Food and Drug Administration has identified rapid joint destruction and/or osteonecrosis as a specific tolerability concern for the anti-NGF class.[37] RPOA has been described in the literature for decades predating the trials of anti-NGF compounds. The incidence of RPOA in the general osteoarthritis population has not been well defined. Progression of osteoarthritis is more rapid than routine osteoarthritis.[38] The single case of RPOA reported in this study appears to be associated with fulranumab and in patients with preexisting osteoarthritis. Data elucidating the underlying mechanism of NGF class inhibition and RPOA are not available. Future studies examining the link between the NGF class and RPOA are warranted.

A limitation of the study was that the study was terminated prematurely (sponsor's decision because of the lack of efficacy results from the DB efficacy phase). However, the DB efficacy phase was completed, and efficacy and safety profile were evaluated. Another limitation of the study is that a high placebo effect was observed. In recent years, in multiple clinical trials of neuropathic pain, a placebo response is increasingly observed, leading to lower separation between the drug and placebo arms.[39–41]

CONCLUSION

Analgesic efficacy of adjunctive fulranumab at a dose of up to 10 mg once every 4 weeks during a 12-week period was not significantly different from placebo in patients with moderate-to-severe cLBP. Fulranumab at all doses was generally well-tolerated.

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CONFLICTS OF INTEREST

All authors are employees of Janssen Research & Development LLC, a Johnson & Johnson company, and hold Johnson & Johnson stock. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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