Fulranumab for treatment of diabetic peripheral neuropathic pain

A randomized controlled trial

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ABSTRACT

Objective: To assess efficacy and safety of fulranumab, a fully human monoclonal antibody against nerve growth factor, in patients with diabetic peripheral neuropathic pain (DPNP).

Methods: In this phase II, double-blind, placebo-controlled trial, patients with moderate to severe DPNP were randomized to treatments with fulranumab (1, 3, or 10 mg) or placebo administered subcutaneously every 4 weeks.

Results: Because of early study termination (clinical hold) by the US Food and Drug Administration, 77 (intent-to-treat) of the planned 200 patients were enrolled. The primary endpoint, the mean reduction of average daily pain at week 12 compared with baseline, showed a positive dose-response relationship ($p = 0.014$, 1-sided); the pair-wise comparison between the 10-mg group and placebo was significant (unadjusted $p = 0.040$, 2-sided). An exploratory responder analysis revealed that a greater proportion of patients in the 10-mg group reported $\geq 30\%$ reduction in the average DPNP intensity compared with placebo at week 12 ($p = 0.006$). Although not statistically significant, several secondary endpoints showed directionally similar results to the primary efficacy dose-response relationship. During the combined efficacy and safety extension phases, the top 3 treatment-emergent adverse events in the combined fulranumab group were arthralgia (11%), edema peripheral (11%), and diarrhea (9%). No cases of joint replacement or death were reported.

Conclusion: Despite early study termination, fulranumab treatment resulted in dose-dependent efficacy and was generally well tolerated.

Classification of evidence: This study provides Class I evidence that in patients with DPNP, fulranumab 10 mg reduces pain by 1.2 points on an 11-point scale compared with placebo. *Neurology*® 2014;83:628-637

GLOSSARY

CI = confidence interval; **DB** = double-blind; **DPNP** = diabetic peripheral neuropathic pain; **FDA** = US Food and Drug Administration; **LS** = least squares; **NGF** = nerve growth factor; **NPSI** = Neuropathic Pain Symptom Inventory; **NRS** = numeric rating scale; **SAE** = serious adverse event; **TEAE** = treatment-emergent adverse event; **TNSn** = total neuropathy score-nurse.

Approximately 16% of patients with diabetes have diabetic peripheral neuropathic pain (DPNP), but it is estimated that 2 of 5 such cases do not receive any treatment for the pain.¹⁻³ DPNP seriously affects quality of life and represents an ongoing management challenge for patients and physicians.^{2,4} Although many pharmacotherapies are available for DPNP, including antidepressants, anticonvulsants, and opioids, the effect size of these treatments is limited.⁵⁻⁷

Nerve growth factor (NGF) contributes to persistent pain in a variety of animal models of inflammatory and neuropathic pain.⁸⁻¹² Blocking the activity of NGF has shown potential for normalizing neuronal hyperactivity and producing sustained clinical pain relief.¹³⁻¹⁷ The role of NGF in neuropathic pain and the implications for the development of novel therapeutics are of great interest.^{18,19}

Fulranumab is a fully human recombinant immunoglobulin G2 monoclonal antibody that has a specific capacity to neutralize the biological actions of human NGF. It has shown efficacy

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in the treatment of moderate to severe knee and hip osteoarthritis pain.²⁰ In the present study, we evaluated the efficacy and safety of fulranumab, compared with placebo, in patients with moderate to severe DPNP that was not adequately controlled by standard pain therapies.

METHODS **Standard protocol approvals, registrations, and patient consents.** The study was approved by an independent ethics committee or an institutional review board. Written informed consent was obtained from all participants at screening. The trial was registered with clinicaltrials.gov (NCT00993018).

Study design. This was a phase II, randomized, placebo-controlled, double-blind (DB), dose-ranging study conducted at 16 sites from November 9, 2009 through June 23, 2011. The planned study included 5-week screening, 12-week DB efficacy, 40-week DB extension, 52-week open-label extension, and 26-week posttreatment phases. All patients still in the dosing phases stopped treatment on December 23, 2010, when the US Food and Drug Administration (FDA) placed ongoing fulranumab studies on clinical hold because of the concern that the entire class of anti-NGF antibodies may be associated with a condition representing either rapidly progressing osteoarthritis or osteonecrosis.

Patients were randomized 3:2:2:3, via an interactive voice response system, to 1 of 4 treatments (placebo, fulranumab 1, 3, or 10 mg) administered subcutaneously into the thigh or the abdomen every 4 weeks. To maintain the blinding, placebo-treated patients were randomized equally in a 1:1:1 ratio to receive a volume of placebo that matched the volume of the 3 fulranumab groups (1, 3, and 10 mg). Randomization was stratified by current DPNP medication use (yes or no). Patients had clinic visits every 4 weeks (week 1 through week 105).

Patients. Patients must have been 18 to 80 years of age (inclusive), with chronic DPNP (persistent for >6 months) that was not adequately controlled by standard of care treatment. Patients must have had pain (had to begin in the feet and with relatively symmetrical onset for >6 months) due to bilateral peripheral neuropathy caused by type 1 or type 2 diabetes mellitus, with bilateral decrease or absent reflexes at the ankles, or bilateral decrease of a sensory sign in the distal lower extremities based on medical history, or physical/neurologic examination.

Patients assessed pain using an 11-point numeric rating scale (NRS)²¹ of 0 to 10 (0 = no pain; 10 = pain as bad as you can imagine), and had an average pain intensity score of ≥ 5 but <10, over 7 consecutive days before randomization, with a minimum of 5 assessments required. Use of ≤ 2 of the following medications, each one from a different class, was permitted: anticonvulsants ($\leq 1,800$ mg/d gabapentin or ≤ 300 mg/d pregabalin); opioid analgesics (≤ 60 mg/d oxycodone equivalent or ≤ 200 mg/d tramadol); antidepressants (≤ 75 mg/d amitriptyline equivalent tricyclic antidepressants, ≤ 60 mg/d duloxetine, or ≤ 150 mg/d venlafaxine). Patients taking medications for neuropathic pain at screening could choose to continue, reduce the dose or number to within acceptable limits, or discontinue their current pain medications with an appropriate washout period.

Key exclusion criteria included severe autonomic dysfunction or loss of pinprick sensation above the knees or wrists; other chronic, more severe pain conditions than DPNP; and pregnancy or lactation.

Efficacy. The primary efficacy endpoint was the mean of the daily evening assessment of average pain intensity over the last

24 hours for the last 7 days of the DB efficacy phase minus the mean from the 7-day baseline period. Secondary efficacy outcomes included changes from baseline in (1) the 7-day mean of daily evening assessment of pain at its worst in the last 24 hours to the end of week 12; (2) the monthly Brief Pain Inventory–Short Form²² subscale scores; (3) the monthly Neuropathic Pain Symptom Inventory (NPSI)²³ total and subscale scores; and (4) the monthly Patient Global Impression of Change score. An exploratory responder analysis included $\geq 30\%$ or $\geq 50\%$ improvement in NRS pain intensity from baseline to the end of week 12.

A post hoc exploratory analysis was conducted to examine the relationship between pain reduction and NPSI baseline subscale scores.

Safety. Safety assessments included treatment-emergent adverse events (TEAEs), 12-lead ECG, clinical laboratory tests, vital signs, physical examinations, and investigator evaluation of the injection site. Nerve safety evaluation included neurologic examination, total neuropathy scores–nurse (TNSn), skin biopsy,²⁴ and nerve conduction studies.²⁵ We collected 2 adjacent skin biopsies from the distal thigh to determine the intraepidermal nerve fiber density, expressed as the number of fibers per millimeter length of the skin biopsy.^{26,27} Nerve conduction studies included measures of nerve conduction velocity and amplitude in the distal segments of 2 sensory nerves (ulnar and median) and 2 motor nerves (ulnar and peroneal) using standard surface recording techniques.²⁸ Details of skin biopsy, nerve conduction studies, and TNSn are described in a separate report.

Predefined neurologic treatment-emergent events of interest were significant neurologic signs and symptoms that resulted in discontinuation of treatment, prolonged hypotension, and symptomatic bradycardia. All TEAEs were followed to satisfactory resolution or a clinically stable endpoint. An independent data monitoring committee was established to monitor unblinded safety data, including the protocol predefined events of interest, to ensure the continuing safety of the enrolled patients.

Statistical analysis. This study was designed to enroll 200 patients to provide $\geq 85\%$ power at a 1-sided 5% significance level to assess a dose-response relationship, assuming a variance of 2.4 and an effect size of 1.25.

The intent-to-treat population for the efficacy analysis included all randomized patients who received at least 1 dose of fulranumab or placebo. Daily evening assessment of average pain scores for the 7 days before the first dose of study drug were averaged to determine the baseline pain score; those for the last 7 days before the time point of interest (4, 8, and 12 weeks) were averaged to define the pain score for that time point. The last observation carried forward and baseline observation carried forward methods were used for data imputation.

The dose response of the primary efficacy endpoint was evaluated using the MCP-Mod procedure²⁹ at a 1-sided, 5% level of significance. The decision to use a 1-tailed test of significance for the primary endpoint was prespecified. This approach was deemed appropriate because (1) the focus of this phase II pilot study was on a positive dose-response relationship, not an inverse dose-response, and (2) at this early phase, the type 1 error rate is primarily of concern to the sponsor regarding the risk of moving forward into later development stage. The linear, exponential, and Emax models were tested for dose-response relationship using the optimal contrast test for the original fixed allocation ratio of 3:2:2:3 for placebo, fulranumab 1, 3, or 10 mg. The treatment magnitude for each dosage was estimated in 3 pair-wise comparisons of each individual dosage group against placebo using the

Figure 1 Patient flowchart

*The study was discontinued by the sponsor because of the clinical hold.

analysis of covariance model (2-sided at a 5% level). The Cochran-Mantel-Haenszel test and the baseline observation carried forward method were applied to the exploratory responder analysis. All continuous secondary efficacy endpoints were analyzed based on analysis of covariance with treatment and concomitant medication as factors, and baseline score as a covariate. The least squares (LS) means and treatment differences relative to placebo with the corresponding 95% confidence intervals (CIs) and *p* values were provided. Unadjusted, nominal *p* values were presented for all secondary efficacy comparisons. Safety results were summarized descriptively.

The relationship between the baseline NPSI score and change from baseline in NRS pain intensity was explored post hoc using a logistic regression model with current baseline pain medication and NPSI score category (below or above a threshold) as factors and baseline NRS pain score as a covariate.

Classification of evidence. This interventional study provides class I evidence that in patients with DPNP, fulranumab decreased average pain intensity from baseline to the end of the DB efficacy phase in a positive dose-dependent manner (*p* = 0.014, 1-sided). Fulranumab 10 mg reduced pain by 1.2 points

(95% CI −2.44 to −0.06; unadjusted *p* = 0.040) on an 11-point scale compared with placebo.

RESULTS Baseline characteristics. At the time of the clinical hold, 312 patients had been screened and 77 qualified patients had been randomized into 4 treatment groups (figure 1).

Sixty-two patients (81%) completed the DB efficacy phase, while 13 of 55 patients (24%) completed the DB extension phase, with most patients discontinued by the sponsor because of the clinical hold. All 12 patients entering the open-label phase were withdrawn because of the clinical hold. Patient demographics and baseline characteristics were generally balanced across treatment groups (table 1). During the DB efficacy phase, most patients (62 of 77) received all 3 medication doses. The median treatment exposure was 85 days for the DB efficacy phase, and 194 days for the DB safety phase.

Table 1 Demographics and baseline characteristics

	Placebo (n = 24)	Fulranumab			Total (N = 77)
		1 mg (n = 16)	3 mg (n = 14)	10 mg (n = 23)	
Mean age (SD), y	58.0 (9.47)	57.9 (7.15)	57.1 (11.36)	60.9 (9.90)	58.7 (9.48)
Age category, n (%)					
<65 y	16 (66.7)	14 (87.5)	11 (78.6)	13 (56.5)	54 (70.1)
≥65 y	8 (33.3)	2 (12.5)	3 (21.4)	10 (43.5)	23 (29.9)
Sex, n (%)					
Female	12 (50.0)	6 (37.5)	6 (42.9)	10 (43.5)	34 (44.2)
Male	12 (50.0)	10 (62.5)	8 (57.1)	13 (56.5)	43 (55.8)
Race, n (%)					
White	19 (79.2)	12 (75.0)	11 (78.6)	21 (91.3)	63 (81.8)
Black or African American	5 (20.8)	3 (18.8)	1 (7.1)	2 (8.7)	11 (14.3)
Asian	0	0	2 (14.3)	0	2 (2.6)
Other	0	1 (6.2)	0	0	1 (1.3)
Mean weight (SD), kg	91.6 (18.23)	102.8 (20.86)	99.2 (20.23)	102.9 (20.68)	98.7 (20.13)
Body mass index (SD), kg/m ²	31.9 (5.44)	34.0 (6.76)	34.8 (7.69)	35.5 (6.01)	33.9 (6.38)
Current pain medication use, n (%)	12 (50.0)	8 (50.0)	7 (50.0)	12 (52.2)	39 (50.6)

Efficacy. The MCP-Mod test results indicated that the linear model was the best fitted one (using the Akaike information criterion) and fulranumab significantly ($p = 0.014$, 1-sided) decreased average pain intensity from baseline to the end of week 12 in a dose-dependent manner (figure 2A). The p value corresponded to the minimum t statistic (the smaller the more significant, when accounting for the negative sign). At the end of week 12, the reduction of average pain intensity with the fulranumab 10-mg treatment group was significant compared with placebo (LS mean difference -1.2 , 95% CI -2.44 to -0.06 , unadjusted $p = 0.040$; figure 2B), and the 10-mg group had significantly more responders with a $\geq 30\%$ reduction in average pain intensity than placebo (unadjusted $p = 0.006$; table 2). Although not significant, the improvement from baseline to the end of week 12 in worst pain intensity, NPSI total score and several subscales, and most Brief Pain Inventory–Short Form subscales increased with increasing doses (table 2), consistent with the primary efficacy trend.

A post hoc exploratory analysis showed that the likelihood of being a responder was related to baseline NPSI levels of burning spontaneous pain ($\leq 5 / > 5$) and pressing spontaneous pain ($\leq 3.5 / > 3.5$) ($p = 0.012$ and $p = 0.045$, respectively). Other NPSI baseline subscales were not found to contribute to the responder patient population.

Safety. During the combined DB efficacy and safety extension phases, the overall percentage of patients with TEAEs was similar among placebo (75%) and

fulranumab (81%–86%) groups, with no dose relationship observed among the fulranumab groups (table 3).

Among fulranumab-treated patients, the 3 most common TEAEs (percentage of patients) were arthralgia (11%), edema peripheral (11%), and diarrhea (9%), compared with arthralgia (13%), constipation (8%), diarrhea (8%), hypertension (8%), nausea (8%), and sinusitis (8%) in the placebo group. Two patients (4%) in the combined fulranumab treatment groups vs none in the placebo group discontinued because of TEAEs: one in the 1-mg group had type III immune complex mediated reaction and the other in the 10-mg group had vesicular lesions in the upper chest. Both TEAEs were moderate in severity and considered by the investigator as probably or possibly related to the study drug. The events resolved after study drug withdrawal.

Neurologic-related TEAEs were reported in 8% (placebo), 25% (1 mg), 14% (3 mg), and 30% (10 mg) of patients during the combined DB efficacy and safety phases (table 3). The incidence of neurologic TEAEs was higher among fulranumab-treated patients (25% overall) than placebo (8%); however, no apparent fulranumab dose relationship was detected. The most common neurologic TEAEs in all fulranumab groups were neuropathic pain (4%), neuropathy (4%), and carpal tunnel syndrome (4%), compared with paresthesia (4%), peripheral neuropathy aggravated (4%), and fecal incontinence (4%) in the placebo group. All neurologic TEAEs were mild or moderate in severity. Twelve of 19 neurologic TEAEs were resolved with durations of 3 to 253 days; 7 of 19 had no end date.

Figure 2 Efficacy results

(A) Estimated linear dose response for the intent-to-treat population using the MCP-Mod procedure with 80% point-wise confidence interval (CI). (B) Mean change from baseline in average pain intensity score to 4, 8, and 12 weeks in the double-blind efficacy phase (intent-to-treat population). Locf = last observation carried forward.

During the combined DB efficacy and safety extension phases, serious adverse events (SAEs) occurred in 2 patients (13%) of the 1-mg group and 6 (26%) of the 10-mg group. These SAEs included hyperglycemia and type III immune complex-mediated reaction (1-mg group), and arthralgia, bacteremia, cellulitis, diverticulitis, localized infection, mental status changes, and urinary

Table 2 Secondary efficacy outcomes at the end of the 12-week double-blind efficacy phase

		Fulranumab		
		Placebo (n = 24)	1 mg (n = 16)	3 mg (n = 14)
Worst pain intensity				
Baseline mean (SD)	7.1 (1.33)	6.7 (1.52)	7.1 (1.75)	7.1 (1.25)
Diff. of LS means ^a (95% CI)	—	0.4 (−0.97, 1.79)	−0.6 (−1.99, 0.88)	−1.1 (−2.38, 0.11)
p Value (minus placebo)	—	0.554	0.443	0.073
NPSI: burning spontaneous pain subscale				
Baseline mean (SD)	5.1 (2.52)	5.6 (1.71)	5.7 (2.92)	5.9 (2.27)
Diff. of LS means ^a (95% CI)	—	0.6 (−1.09, 2.31)	−0.2 (−2.00, 1.55)	−1.0 (−2.59, 0.54)
p Value (minus placebo)	—	0.478	0.800	0.194
NPSI: pressing spontaneous pain subscale				
Baseline mean (SD)	4.6 (2.15)	3.8 (2.66)	3.9 (3.11)	3.8 (2.80)
Diff. of LS means ^a (95% CI)	—	0.0 (−1.48, 1.51)	−1.3 (−2.86, 0.25)	−0.7 (−2.06, 0.68)
p Value (minus placebo)	—	0.980	0.099	0.318
NPSI: paroxysmal subscale				
Baseline mean (SD)	4.5 (2.65)	4.9 (2.53)	4.3 (2.77)	4.9 (2.90)
Diff. of LS means ^a (95% CI)	—	−1.2 (−2.56, 0.09)	−1.0 (−2.35, 0.42)	−1.7 (−2.93, −0.51)
p Value (minus placebo)	—	0.067	0.168	0.006
NPSI: evoked pain subscale				
Baseline mean (SD)	4.2 (3.03)	3.8 (2.25)	5.0 (2.96)	4.2 (2.61)
Diff. of LS means ^a (95% CI)	—	−0.9 (−2.13, 0.23)	−0.4 (−1.68, 0.79)	−0.2 (−1.27, −0.88)
p Value (minus placebo)	—	0.114	0.479	0.718
NPSI: paresthesia/dysesthesia subscale				
Baseline mean (SD)	6.4 (1.84)	5.8 (1.91)	5.3 (2.91)	5.3 (2.24)
Diff. of LS means ^a (95% CI)	—	0.3 (−1.22, 1.75)	−0.9 (−2.50, 0.62)	−1.0 (−2.33, 0.42)
p Value (minus placebo)	—	0.724	0.235	0.170
NPSI: total score				
Baseline mean (SD)	48.8 (20.42)	46.0 (17.61)	47.7 (23.40)	46.4 (19.07)
Diff. of LS means ^a (95% CI)	—	−3.9 (−14.34, 6.60)	−7.7 (−18.56, 3.23)	−8.1 (−17.63, 1.51)
p Value (minus placebo)	—	0.464	0.165	0.097
BPI-SF: pain intensity subscale				
Baseline mean (SD)	5.8 (1.46)	5.8 (1.72)	5.8 (1.61)	5.8 (1.40)
Diff. of LS means ^a (95% CI)	—	0.1 (−1.17, 1.42)	−1.0 (−2.32, 0.38)	−1.1 (−2.27, 0.10)
p Value (minus placebo)	—	0.844	0.156	0.072
BPI-SF: treatment relief subscale				
Baseline mean (SD)	21.7 (24.44)	19.4 (22.35)	31.4 (29.31)	18.2 (25.38)
Diff. of LS means ^a (95% CI)	—	−15.6 (−35.81, 4.61)	10.4 (−10.81, 31.68)	6.2 (−12.28, 24.72)
p Value (minus placebo)	—	0.128	0.331	0.505
BPI-SF: pain interference subscale				
Baseline mean (SD)	5.0 (2.09)	5.4 (2.15)	4.5 (3.07)	4.7 (2.34)
Diff. of LS means ^a (95% CI)	—	−0.6 (−1.90, 0.63)	−0.6 (−1.96, 0.68)	−0.8 (−1.97, 0.35)
p Value (minus placebo)	—	0.322	0.339	0.170
PGIC: reporting minimally, much, or very much improved in neuropathic pain				
Patients, n (%)	14 (58)	8 (50)	8 (57)	18 (82)

Continued

Table 2 Continued

		Fulranumab			
		Placebo (n = 24)	1 mg (n = 16)	3 mg (n = 14)	10 mg (n = 23)
Responder: pain assessment ≥30% improved					
Yes, n (%)	5 (20.8)	7 (43.8)	6 (42.9)	14 (60.9)	
p Value (minus placebo) ^b	—	0.110	0.153	0.006	
Responder: pain assessment ≥50% improved					
Yes, n (%)	2 (8.3)	3 (18.8)	4 (28.6)	7 (30.4)	
p Value (minus Placebo) ^b	—	0.329	0.105	0.056	

Abbreviations: BPI-SF = Brief Pain Inventory–Short Form; CI = confidence interval; diff. = difference; LS = least squares; NPSI = Neuropathic Pain Symptom Inventory; PGIC = Patient Global Impression of Change.

^aDiff. of LS means: 12-week double-blind efficacy phase result minus baseline result.

^bPairwise comparison: generalized Cochran-Mantel-Haenszel test for general association controlling for stratum 1 (baseline current pain medication). Unadjusted, nominal p values are displayed.

retention (10-mg group). There were only 2 patients in the fulranumab 10-mg group who had SAEs (localized infection and urinary retention) during the efficacy phase. At the end of the efficacy phase when efficacy was evaluated, the mean (SD) change in average pain scores from baseline for all 23 patients in the fulranumab 10-mg group was -2.7 (1.8). By comparison, the reductions in average pain intensity from baseline for these 2 patients were respectively -1.3 and 0.4 . Thus, these SAEs did not distract those 2 patients from their neuropathic pain during the efficacy phase. All SAEs were resolved within 30 days, except one (right hip joint pain) with no end date.

We observed no clinically important changes in laboratory, ECG, and vital sign findings in any patient during the study. No cases of joint replacement surgery or death were reported during the study. There were no clinically significant changes from baseline in neurologic examination findings, TNSn, or Mini-Mental State Examination score. The assessments of skin biopsy and nerve conduction studies (detailed in a separate report) do not support the hypothesis that fulranumab treatment was associated with improved pain secondary to decreased or damaged nerve function in patients with DPNP.

DISCUSSION We evaluated the analgesic efficacy and safety of fulranumab (1, 3, and 10 mg administered every 4 weeks) in treating patients with moderate to severe DPNP. Because of the clinical hold by the FDA, only 39% (n = 77) of planned enrollment was achieved; 81% of the study patients (n = 62) received all 3 doses of study medication.

Fulranumab significantly decreased average DPNP intensity in a dose-dependent manner from baseline to the end of the efficacy phase. In addition, a significant pairwise difference from placebo and significantly more responders with a $\geq 30\%$ reduction in average pain intensity than placebo were observed in the fulranumab

10-mg group. The magnitude of the pain reduction in the 10-mg group could be considered as clinically meaningful pain relief.^{30,31} Consistent with the primary efficacy dose-response relationship, although not statistically significant, most secondary efficacy outcomes showed similar trends.

It is of scientific interest to understand whether patients with different phenotypic pain respond differently to anti-NGF treatment. NPSI includes 10 descriptors (plus 2 temporal items) that allow discrimination and quantification of 5 distinct clinically relevant dimensions of neuropathic pain syndromes. The psychometric properties of the NPSI suggest that this tool might be used to characterize subgroups of patients with neuropathic pain and verify whether they respond differentially to various pharmacologic agents or therapeutic interventions. The exploratory analysis revealed that patients with a baseline NPSI subscale score of >5 for burning spontaneous pain or >3.5 for pressing spontaneous pain tended to be more responsive to treatment. These findings (need to be verified in an appropriately sized future study) may help inform future research on whether patients with certain baseline phenotypes are likely to be more treatment responsive.

During the combined DB efficacy and safety extension phases, the overall rate of TEAEs was similar among placebo and fulranumab treatment groups, with no dose relationship apparent; however, the rate of neurologic-related TEAEs in the placebo group was approximately one-third of that in the combined fulranumab groups. Based on phase I results, hypoesthesia and paresthesia were expected and were closely monitored using a brief neurologic examination and TNSn assessments. The most common neurologic-related TEAEs in fulranumab-treated patients were those associated with large- and small-fiber sensory function, such as neuropathic pain, neuropathy, paresthesia, and carpal tunnel

Table 3 TEAEs during the combined double-blind efficacy and safety extension phases

Patients reporting, n (%)	Placebo (n = 24)	Fulranumab			
		1 mg (n = 16)	3 mg (n = 14)	10 mg (n = 23)	Drug overall (n = 53)
TEAEs	18 (75)	13 (81)	12 (86)	19 (83)	44 (83)
SAEs	0	2 (13)	0	6 (26)	8 (15)
Discontinued because of TEAEs	0	1 (6)	0	1 (4)	2 (4)
TEAEs reported by ≥5% of patients ^a					
Arthralgia	3 (13)	1 (6)	1 (7)	4 (17)	6 (11)
Edema peripheral	0	0	2 (14)	4 (17)	6 (11)
Diarrhea	2 (8)	2 (13)	1 (7)	2 (9)	5 (9)
Nasopharyngitis	1 (4)	2 (13)	1 (7)	1 (4)	4 (8)
Pain in extremity	0	0	0	4 (17)	4 (8)
Upper respiratory tract infection	1 (4)	2 (13)	2 (14)	0	4 (8)
Anemia	0	1 (6)	0	2 (9)	3 (6)
Arthritis	1 (4)	1 (6)	0	2 (9)	3 (6)
Blood creatine phosphokinase increased	0	2 (13)	0	1 (4)	3 (6)
Constipation	2 (8)	1 (6)	0	2 (9)	3 (6)
Influenza	0	1 (6)	0	2 (9)	3 (6)
Insomnia	0	1 (6)	1 (7)	1 (4)	3 (6)
Muscle spasms	1 (4)	0	0	3 (13)	3 (6)
Myalgia	0	1 (6)	1 (7)	1 (4)	3 (6)
Nausea	2 (8)	2 (13)	0	1 (4)	3 (6)
Neuropathy peripheral	1 (4)	2 (13)	0	1 (4)	3 (6)
Sinusitis	2 (8)	0	0	3 (13)	3 (6)
Urinary tract infection	0	0	1 (7)	2 (9)	3 (6)
Neurologic-related TEAEs	2 (8)	4 (25)	2 (14)	7 (30)	13 (25)
Burning sensation	0	0	0	1 (4)	1 (2)
Carpal tunnel syndrome	0	0	0	2 (9)	2 (4)
Diabetic neuropathy	0	1 (6)	0	0	1 (2)
Fecal incontinence	1 (4)	0	0	0	0
Hypoesthesia	0	0	0	1 (4)	1 (2)
Neuralgia	0	1 (6)	1 (7)	0	2 (4)
Neuropathy peripheral	1 (4)	2 (13)	0	1 (4)	3 (6)
Paresthesia	1 (4)	0	0	1 (4)	1 (2)
Sensory disturbance	0	0	1 (7)	0	1 (2)
Syncope	0	0	0	1 (4)	1 (2)

Abbreviations: SAE = serious adverse event; TEAE = treatment-emergent adverse event.

^aThis is based on all fulranumab groups combined and placebo group, respectively.

syndrome. The majority of neurologic TEAEs were mild to moderate in severity and not associated with clinically meaningful neurologic abnormalities. No neurologic-related SAEs were reported during the DB treatment phases. Although not definitive, nerve safety assessments (detailed in a separate report) do not support the hypothesis that fulranumab achieves neuropathic pain relief in DPNP by damaging or otherwise adversely affecting nerves or nerve function.

The FDA has identified rapid joint destruction and/or osteonecrosis as a specific safety concern for the anti-NGF class. No cases of osteonecrosis or joint replacement were reported or adjudicated in this trial, although 13 patients enrolled had a history of osteoarthritis. However, because of the limited sample size due to the clinical hold, we cannot conclude there is no risk. All future trials will incorporate prospective joint surveillance.

The limitations of this study include a small sample size because of the FDA clinical hold. In addition, patients who discontinued the study were often lost to follow-up for safety. However, the discontinuation rate due to TEAEs (4%) in fulranumab treatment groups compares favorably with those reported in other medications (approximately 20%) recommended for treatment of DPNP.³² In addition, neurologic TEAE characteristics of this drug class were typically reported as mild or moderate and investigators opted to continue treatment. Thus, fulranumab showed the potential to address the unmet need for a better tolerated and more effective option compared with currently marketed therapies.³³

Despite the limited sample size caused by early study termination, fulranumab treatment resulted in dose-dependent efficacy and was generally well tolerated, with the 10-mg dose demonstrating significant improvement over placebo. Long-term trials involving more patients are needed to fully characterize the efficacy, safety, and tolerability of this potentially new class of analgesic drug for treatment of DPNP.

AUTHOR CONTRIBUTIONS

Dr. Wang participated in the study design, study governance, supervising study recruitment, monitoring of data quality, and data analysis; contributed to the development of the manuscript and approved the final manuscript for submission. Dr. Romano participated in the study design; contributed to the development of the manuscript and approved the final manuscript for submission. Ms. Frustaci was the study statistician; contributed to the development of the manuscript and approved the final manuscript for submission. Dr. Bohidar participated in the study design; was the study statistician; contributed to the development of the manuscript and approved the final manuscript for submission. Dr. Ma drafted and revised the manuscript for intellectual content; contributed to the development of the manuscript and approved the final manuscript for submission. Dr. Sanga and Dr. Fedgchin participated in the study design, study governance, supervising study recruitment, monitoring of data quality, and data analysis; contributed to the development of the manuscript and approved the final manuscript for submission. Dr. Ness, Dr. Russell, Dr. Kelly, and Dr. Thippawong participated in study governance, supervising study recruitment, monitoring of data quality, and data analysis; contributed to the development of the manuscript and approved the final manuscript for submission.

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