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# Fulranumab in Patients With Pain Associated With Postherpetic Neuralgia and Postraumatic Neuropathy

## Efficacy, Safety, and Tolerability Results From a Randomized, Double-blind, Placebo-controlled, Phase-2 Study

Hao Wang, PhD,* Gary Romano, MD, PhD,† Margaret Fedgchin, PharmD,†
Lucille Russell, MD,† Panna Sanga, MD,† Kathleen M. Kelly, MD,†
Mary Ellen Frustaci, MAS,† and John Thipphawong, MD†

**Objective:** Fulranumab is an antibody that specifically neutralizes the biological activity of human nerve growth factor. This multicenter, phase-2, randomized, double-blind (DB), placebo-controlled study evaluated the analgesic efficacy and safety of fulranumab in postherpetic neuralgia (PHN) and posttraumatic neuropathy (PTN) patients.

**Methods:** Patients (18 to 80 y) with inadequately controlled moderate-to-severe pain received study medication (subcutaneous injection) every 4 weeks. PHN patients were randomized (3:2:2:3) to receive either placebo or one of 3 doses of fulranumab: 1 mg (1 mgQ4 wk), 3 mg (3 mgQ4 wk), or 10 mg (10 mgQ4 wk). PTN patients were randomized (1:1) to receive either placebo or fulranumab 10 mgQ4 wk.

**Results:** The US Food and Drug Administration placed a clinical hold (December 23, 2010) on all trials of antinerve growth factor drugs, including fulranumab, due to identified risks of osteonecrosis or rapidly progressing osteoarthritis; therefore, only 49 (of 150 planned) PHN patients and 34 (of 50 planned) PTN patients completed the DB efficacy evaluation. There was no significant difference ($P > 0.05$, fulranumab vs. placebo) for change in 7-day average of daily pain intensity scores from DB baseline to end of 12-week DB efficacy phase in PHN or PTN patients (primary endpoint). No significant difference was found with fulranumab versus placebo ($P > 0.05$) in other efficacy measures in either PHN or PTN patients. The most common treatment-emergent adverse events (> 10% incidence) in PTN patients were sinusitis, carpal tunnel syndrome, and headache, whereas in PHN patients it was arthralgia.

**Discussion:** Fulranumab did not demonstrate efficacy in either PHN or PTN patients, but was generally well-tolerated in this small underpowered and abbreviated study.

**Key Words:** antinerve growth factor, fulranumab, neuropathic pain, postherpetic neuralgia, posttraumatic neuropathy

The prevalence of pain of predominantly neuropathic origin is significant (up to 8% of the general population).[1,2] Neuropathic pain due to postherpetic neuralgia (PHN) and posttraumatic neuropathy (PTN) are distinct clinical conditions.[3,4] PTN develops after nerve injury by trauma or surgery[5] and is often difficult to treat and may progress to persistent pain and disability. PHN as a consequence of herpes zoster (HZ: shingles) is debilitating and difficult to manage and is characterized by chronic pain after the onset of rash or following cutaneous healing.[6]

Approved treatments for pain associated with PHN include first-line (tricyclic antidepressants, serotonin-noradrenaline reuptake inhibitors, pregabalin, and gabapentin), second-line (lidocaine patches, capsaicin high-concentration patches, and tramadol), and third-line therapy (strong opioids and botulinum toxin).[7] Some of these drugs often require several weeks to reach target plasma levels and have undesirable side effects, resulting in poor patient compliance to the treatment. Treatments for PTN include nonsteroidal anti-inflammatory drugs, opioids, and gabapentin.[8] Both PHN and PTN can significantly impair quality of life and can lead to increased health care utilization costs.[9,10] More effective therapies for management of neuropathic pain remain an important unmet medical need.[11,12]

Inhibiting the effect of nerve growth factor (NGF) has shown potential for normalizing neuronal hyperactivity

and producing sustained clinical pain relief.[13–17] There is, therefore, significant interest in considering NGF as a potential drug target in neuropathic pain. Fulranumab is a fully human recombinant immunoglobulin-G2 inhibitor that specifically neutralizes biological actions of human NGF. Recent clinical studies have demonstrated that fulranumab is effective in treatment of pain related to knee and hip osteoarthritis and painful diabetic peripheral neuropathy.[18,19] The current study was conducted to explore the analgesic efficacy, safety, and tolerability of subcutaneous (SC) fulranumab for the treatment of PHN and PTN.

## METHODS

This phase-2, randomized, placebo-controlled, double-blind (DB) study was conducted between August 2009 and July 2011 at 36 sites across 3 countries (Belgium, Spain, and United States). The protocol for this study 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 originating in the Declaration of Helsinki and in accordance with the ICH Good Clinical Practice guidelines, applicable regulatory requirements, and in compliance with the protocol. All patients provided written informed consent to participate in the study.

### Patients

Men and women, between 18 and 80 years (inclusive) of age, diagnosed with either PHN or PTN, having moderate-to-severe chronic neuropathic pain (pain persistent for > 6 mo), who were intolerant to, not willing to use, or whose pain was not adequately controlled by standard-of-care, were included. Concomitant pain medications were allowed but patients had to have received ≤ 2 pain medications each from a different class, consisting of anticonvulsants (gabapentin [≤ 1800 mg/d] or pregabalin [≤ 300 mg/d]), opioid analgesics (≤ 60 mg/d oxycodone equivalent) or tramadol (≤ 200 mg/d), antidepressants (tricyclic antidepressants [≤ 75 mg/d amitriptyline equivalent], duloxetine [≤ 60 mg/d], or venlafaxine [≤ 150 mg/d]), or equivalent drugs and doses, for inclusion in the study. Pain scores were entered by patient through the Interactive Voice Response System (IVRS). Patients were required to have an average daily pain intensity score between 5 and 10 recorded on an 11-point (0 = no pain, 10 = worst possible pain) numerical rating scale (NRS) over 7 consecutive days during the IVRS baseline period and have a Mini-Mental State Examination (MMSE) score > 26 (at least 5 d of scores required). Women of childbearing potential had to have a negative serum β-human chorionic gonadotropin pregnancy test at screening and a negative urine β-human chorionic gonadotropin pregnancy test at randomization (day 1).

Key exclusion criteria included a severe pain condition that would confound the assessment of neuropathic pain under investigation, PTN characterized by complex regional pain syndrome type I, patients whose nerve injury or pain was expected to recover in the next 4 months, history of lumbosacral radiculopathy within 6 months before screening, active or prior history of herpes simplex virus infection within the past 2 years, failed low-back surgery, spinal cord injury, and diabetes.

### Study Medication

Fulranumab (10 mg/mL) was provided as a clear, sterile, frozen solution (approximately 1 mL fill volume) in 5 mL single-use glass vials. Matching placebo was supplied in the same manner.

### Study Design, Randomization, and Blinding

The study included a 4-week screening (28 d before the first dose of study drug), 12-week double-blind (DB) efficacy, 40-week DB safety extension and 52-week open-label (OL) safety extension, and 26-week posttreatment/follow-up phases. The study was prematurely terminated because the United States Food and Drug Administration (FDA) placed a clinical hold (December 23, 2010) on all trials of anti-NGF drugs, including fulranumab, due to concerns around the occurrence of rapidly progressing osteoarthritis (RPOA).

All eligible patients were randomized through an IVRS to placebo or one of the 3 treatments (fulranumab 1 mg every 4 wk [1 mgQ4 wk], 3 mg every 4 wk [3 mgQ4 wk], or 10 mg every 4 wk [10 mgQ4 wk]) for patients with PHN, and 2 treatments (placebo or 10 mgQ4 wk) for patients with PTN. Patients received a single, SC injection of study medication every 28 days. During the 12-week DB efficacy and DB safety extension phase, patients with PHN received a total of 3 SC injections of either placebo or one of 3 fulranumab treatment regimens. To maintain 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 diagnostic groups (PHN or PTN) and concurrent pain medication use (yes or no). Patients who completed all assessments during the 12-week DB efficacy phase, including the week 12 visit, were considered to have completed the DB efficacy phase of the study. Because of the clinical hold, all treatments were stopped and patients entered the posttreatment phase per protocol.

### Study Evaluations

#### Efficacy

Primary efficacy endpoint included average pain intensity over the last 24 hours. Patient assessment of average pain intensity over the last 24 hours was performed once daily, in the evening, using an 11-point NRS, where 0 = no pain and 10 = pain as bad as you can imagine, collected through IVRS. Secondary endpoints included daily assessment of "worst pain in the past 24 hours" (11-point NRS, where 0 = no pain and 10 = pain as bad as you can imagine) collected through IVRS, neuropathic pain symptom inventory (NPSI),[20] Brief Pain Inventory-short form (BPI-SF),[21] Patient Global Assessments of Change (PGIC),[22] and pain responder analysis (a responder was defined as a patient showing a 30% and 50% decrease from baseline in average NRS pain).

#### Pharmacokinetics

Blood samples to determine fulranumab plasma concentrations were collected predose; at weeks 1, 5, 9, and 13 of the DB efficacy phase; at weeks 17, 21, 25, 29, 33, 37, 41, 45, 49, and 53 of the DB safety extension phase; and at week 85 of the OL safety extension phase; and at the final visit. Samples were assayed using enzyme-linked immunosorbent assay (ELISA). The lowest quantifiable

concentration in a sample for the serum fulranumab ELISA was 0.00156 µg/mL.

## Immunogenicity

Serum samples for the detection of antibodies to fulranumab were collected at weeks 1 and 13 of the DB efficacy phase, at weeks 37 and 53 of the DB safety extension phase, and at week 85 of the OL safety extension phase. Samples were also collected at the final visit. The presence of antidrug antibodies against fulranumab in serum was determined by a validated electrochemiluminescent immunoassay (ECLIA) on a Meso Scale Discovery platform (Gaithersburg, MD). The maximum observed sensitivity of the serum antidrug antibodies ECLIA was 0.77 ng/mL at a minimum required 1/20 dilution.

## Safety Evaluations

The following safety and tolerability information were monitored throughout the study: treatment-emergent adverse events (TEAEs), serious TEAEs, change in laboratory parameters, electrocardiogram, neurological evaluations, vital signs, investigator evaluation of the injection site, RPOA, and osteonecrosis. This included imaging data and/or historical patient data of any joint that was replaced, or in which a relevant joint-related TEAE occurred. Joint replacement surgeries were reported as serious TEAEs. An independent data monitoring committee was established to monitor unblinded safety data to ensure the continuing safety of the enrolled patients

## Statistical Analysis

### Analysis Set

All efficacy and safety analyses were performed on the intent-to-treat (ITT) analysis set, which included all patients who had received at least 1 dose of fulranumab or placebo.

### Sample Size Determination

For the PHN patients (150 who were planned to be randomized), the power of the multiple comparisons procedures and modeling (MCP-Mod) procedure to establish a dose-response relationship was ≥ 74% at a 1-sided 5% significance level, assuming a variance of 2.4 and the maximum effect of 1.25. The reduced sample size (N = 51) due to the clinical hold decreased the study power to 29% with a maximum effect of 1.0. For the PTN patients, assuming a 2-sided $\alpha = 0.1$ test with 25 patients per group (total = 50), there was 56% power to detect a true underlying difference of 1.25 points. With the reduced sample size due to the clinical hold (n = 32 allocated in a 17:15 ratio), the power was reduced to 42%.

The dose-response of primary efficacy endpoint was evaluated using MCP-Mod procedure to test a positive overall treatment effect (dose-response relationship, 1-sided test at a 5% level). Each individual active dose group were compared with placebo using the analysis of covariance (ANCOVA) model, with treatment and current pain mediation use as a factor; and baseline average pain intensity over 7 days as a covariate, at a 1-sided 5% significance level. Additional analysis was performed as sensitivity analyses to assess the robustness of the primary analysis. ANCOVA model with treatment and stratification variables as factors and baseline value as a covariate was applied for the analysis of change from baseline to the end

of week 16 for each coprimary endpoint. Missing data were imputed by multiple imputation based on discontinuation reasons and simple imputations of baseline observation carried forward (BOCF) and last observation carried forward (LOCF). Analyses of the secondary endpoints followed a similar approach to that used for the primary endpoint.

To explore the quantitative relationship between systemic exposure to fulranumab and clinical efficacy, the average pain intensity scores (LOCF and BOCF) at weeks 4, 8, and 12 in each type of pain subpopulation (PHN or PTN) were evaluated with respect to preinjection serum fulranumab concentration levels at week 5, 9, and 13 visit collections.

The number and percentage of patients reporting TEAEs were tabulated by system organ class and preferred term and summarized descriptively. Clinically significant changes in clinical laboratory tests, physical and neurological examinations, vital signs, 12-lead ECGs, and neurological evaluations (total neuropathy score-nurse, MMSE) were also summarized.

## RESULTS

## Patient Disposition and Demographics

At the time of clinical hold, 111 patients (PHN: 65 patients and PTN: 46 patients) were enrolled in the study (Fig. 1). In the ITT analysis set, 49 of the 65 randomized PHN patients (75%) and 34 of 46 PTN patients (74%) completed the DB efficacy phase. Of the total 111 patients enrolled, 73 patients (combined patients with PHN or PTN) entered the DB extension phase and 14 patients (19%) completed the DB extension phase. The major reason for discontinuation in the DB efficacy phase (PHN group: 8% and PTN group: 13%) and DB extension phase (49%) was the sponsor's decision to discontinue the study due to the clinical hold.

Patient demographics and baseline characteristics were generally balanced across the treatment groups. There were more women than men across all the treatment groups except in the 3 mgQ4 wk group (Table 1). The majority of patients were white and of non-Hispanic ethnicity. More patients with PTN (34 [73.9%]) than PHN (30 [46.2%]) used pain medication at baseline.

## Efficacy Results

### Primary Efficacy Endpoints

It was hypothesized that fulranumab would demonstrate a positive dose-response relationship in PHN with respect to reducing average pain intensity, as measured by the mean of the daily evening assessment of average pain intensity over 24 hours for the last days of the DB efficacy phase minus the mean from the 7-day baseline period. No significant dose-response was observed in the PHN patients. No significant changes in paired-wise analysis in average pain intensity were observed from baseline to the end of the study (week 12) for both the PHN and PTN populations compared with placebo (Tables 2 and 3) at either week 4 or week 8 of the 12-week DB efficacy phase, except for the 10 mg group ($P = 0.02$; week 4 BOCF imputation) in PHN patients.
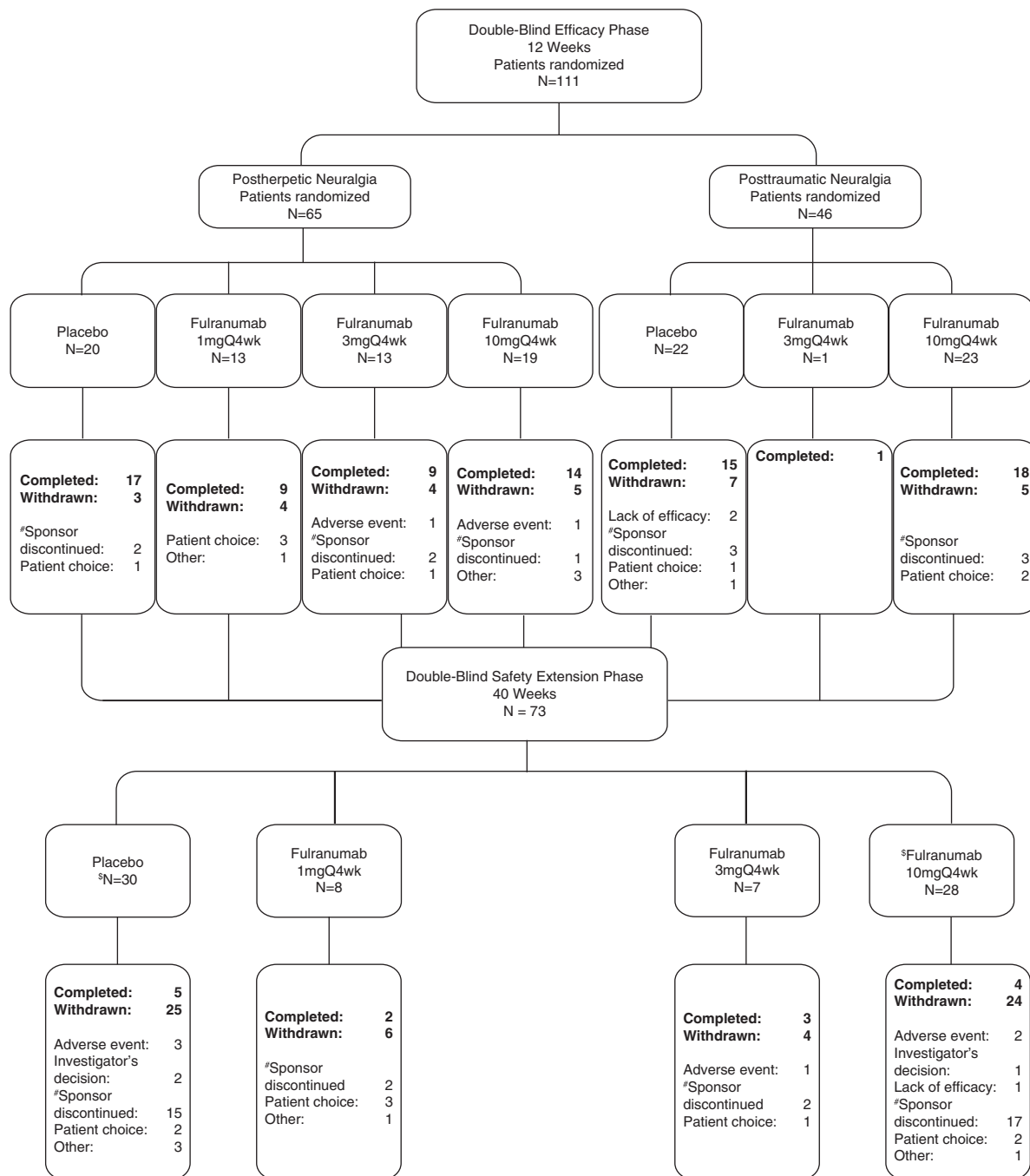
**FIGURE 1.** Study design and patient disposition, intent-to-treat analysis set. #Patients who were discontinued by sponsor due to clinical hold. During double-blind extension phase, in placebo and fulranumab 10 mgQ4 wk groups, "n" represents patients from both PHN and PTN populations. A total of 111 patients who either completed or withdrew from study at various stages entered posttreatment follow-up phase (26 wk). PHN indicates postherpetic neuralgia; PTN, posttraumatic neuropathy.

## Secondary Efficacy Endpoints

Across all fulranumab treatment groups, no significant differences in worst pain in the past 24 hours were observed as compared with placebo in both the PHN and PTN populations, at the week 12 endpoint (Table 4). When measured by the BPI-SF scale, a significant improvement from baseline in treatment pain relief subscale was observed only for the fulranumab 3 mgQ4 wk group (*P* = 0.04) in the PHN population, but there was no improvement in the PTN population (Table 4). For the NPSI total scores, no improvements were observed from baseline to the end of DB efficacy phase in the fulranumab treatment groups as compared with placebo in either population (Table 4). At the 12-week endpoint, there were no significant differences noted for any of the fulranumab treatment groups compared with placebo as measured by responder analysis

**TABLE 1.** Demographic and Baseline Characteristics (Intent-to-Treat Analysis Set)

| Parameters | PHN | | | | PTN | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| | Placebo (N = 20) | Fulranumab 1 mg Q4 wk (N = 13) | Fulranumab 3 mg Q4 wk (N = 13) | Fulranumab 10 mg Q4 wk (N = 19) | Placebo (N = 22) | Fulranumab 3 mg Q4 wk (N = 1) | Fulranumab 10 mg Q4 wk (N = 23) |
| Sex (n [%]) | | | | | | | |
|   Women | 13 (65.0) | 8 (61.5) | 3 (23.1) | 10 (52.6) | 13 (59.1) | 1 (100) | 14 (60.9) |
|   Men | 7 (35.0) | 5 (38.5) | 10 (76.9) | 9 (47.4) | 9 (40.9) | - | 9 (39.1) |
| Race (n [%]) | | | | | | | |
|   White | 16 (80.0) | 12 (92.3) | 9 (69.2) | 19 (100) | 21 (95.5) | 1 (100) | 20 (87.0) |
|   Black or African American | 1 (5.0) | 1 (7.7) | 2 (15.4) | — | 1 (4.5) | — | 2 (8.7) |
|   Asian | 2 (10.0) | — | 1 (7.7) | — | — | — | — |
|   Other | 1 (5.0) | — | 1 (7.7) | — | — | — | 1 (4.3) |
| Ethnicity (n [%]) | | | | | | | |
|   Hispanic or Latino | 1 (5.0) | 1 (7.7) | — | — | 1 (4.5) | — | — |
|   Not Hispanic or Latino | 19 (95.0) | 12 (92.3) | 13 (100) | 19 (100) | 20 (90.9) | 1 (100) | 23 (100) |
|   Not reported | — | — | — | — | 1 (4.5) | — | — |
| Age (mean [SD]) (y) | 64.1 (9.94) | 66.5 (11.93) | 71.8 (10.02) | 66.1 (9.37) | 53.0 (12.25) | 46.0 (—) | 48.0 (13.06) |
| Baseline weight (mean [SD]) (kg) | 83.0 (22.38) | 79.8 (19.05) | 85.4 (19.39) | 78.0 (17.45) | 77.6 (14.91) | 65.5 (—) | 80.2 (14.59) |
| Baseline height (mean [SD]) (cm) | 164.3 (9.33) | 167.2 (12.83) | 173.7 (9.71) | 167.3 (10.50) | 170.8 (10.51) | 168.0 (—) | 171.2 (9.57) |
| Baseline BMI (mean [SD]) (kg/m$^2$) | 30.6 (6.96) | 28.5 (5.99) | 28.2 (4.89) | 27.8 (5.44) | 26.6 (4.86) | 23.2 (—) | 27.4 (4.85) |
| Current pain medication use (n [%]) | | | | | | | |
|   No | 11 (55.0) | 7 (53.8) | 7 (53.8) | 10 (52.6) | 6 (27.3) | 1 (100) | 5 (21.7) |
|   Yes | 9 (45.0) | 6 (46.2) | 6 (46.2) | 9 (47.4) | 16 (72.7) | 0 | 18 (78.3) |

    At baseline, the patients were required to have at least 6 months of PHN or PTN.
    BMI indicates body mass index; n, number of patients in each group; N, number of patients; PHN, postherpetic neuralgia; PTN, posttraumatic neuralgia.

(30% responder rate, 50% responder rate, Table S1, Supplemental Digital Content 1, http://links.lww.com/CJP/A363). Approximately half of the PHN (55% for both placebo and fulranumab groups) and PTN (43% for placebo and 48% for the fulranumab 10 mg Q4 wk group) patients reported their status as "not changed" as measured

**TABLE 2.** Change From Baseline to Week 12 in the Average Pain Intensity Score (Last Observation Carried Forward), Intent-to-Treat Analysis Set

| | PHN | | | | PTN | |
| --- | --- | --- | --- | --- | --- | --- |
| | Placebo (N = 20) | Fulranumab 1 mg Q4 wk (N = 13) | Fulranumab 3 mg Q4 wk (N = 13) | Fulranumab 10 mg Q4 wk (N = 19) | Placebo (N = 22) | Fulranumab 10 mg Q4 wk (N = 23) |
| Pain on average past 24 h | | | | | | |
|   Baseline (mean [SD]) | 6.8 (0.90) | 7.0 (1.41) | 6.5 (0.89) | 6.7 (1.20) | 6.6 (1.10) | 7.3 (1.37) |
|   Change from baseline (mean [SD]) | −0.9 (1.61) | −1.4 (1.49) | −1.1 (2.17) | −1.0 (1.72) | −1.5 (1.99) | −0.9 (1.85) |
|   P (minus placebo)*† | | 0.50 | 0.81 | 0.86 | | 0.25 |
|   Difference of LSM (SE) | | −0.4 (0.63) | −0.2 (0.63) | −0.1 (0.57) | | 0.7 (0.60) |
|   95% CI | | (−1.69; 0.84) | (−1.43; 1.11) | (−1.24; 1.04) | | (−0.52; 1.92) |

    *P-values and least squares means from ANCOVA model with treatment, baseline current pain medication as factors, and baseline average pain score as covariate.
    †Nominal unadjusted P-values are presented.
    CI indicates confidence interval; LSM, least square means; N, number of patients; PHN, postherpetic neuralgia; PTN, posttraumatic neuralgia.

**TABLE 3.** Change From Baseline to the End of the First 4, 8, and 12 Weeks in the Average Pain Intensity Score (Baseline Observation Carried Forward), Intent-to-Treat Analysis Set

| | | PHN | | | | PTN | | |
|---|---|---|---|---|---|---|---|---|
| | N | LSM (SE) | Difference in LSM (95% CI) vs. Placebo | *P*\*† | N | LSM (SE) | Difference in LSM (95% CI) vs. Placebo | *P* |
| Week 4 | | | | | | | | |
| Pain on average past 24 h | | | | | | | | |
| Placebo | 16 | −1.206 (0.31) | — | — | 17 | −1.262 (0.45) | — | — |
| Fulranumab 1 mgQ4 wk | 10 | −0.563 (0.40) | 0.64 (−0.36, 1.65) | 0.21 | — | — | — | — |
| Fulranumab 3 mgQ4 wk | 10 | −0.809 (0.40) | 0.40 (−0.62, 1.41) | 0.43 | — | — | — | — |
| Fulranumab 10 mgQ4 wk | 15 | −0.094 (0.32) | 1.11 (0.21, 2.01) | 0.02 | 15 | −1.040 (0.51) | 0.22 (−1.11, 1.56) | 0.74 |
| Week 8 | | | | | | | | |
| Pain on average past 24 h | | | | | | | | |
| Placebo | 16 | −1.069 (0.37) | — | — | 17 | −1.495 (0.46) | — | — |
| Fulranumab 1 mgQ4 wk | 10 | −1.182 (0.47) | −0.11 (−1.31, 1.09) | 0.85 | — | — | — | — |
| Fulranumab 3 mgQ4 wk | 10 | −0.986 (0.47) | 0.08 (−1.13, 1.29) | 0.89 | — | — | — | — |
| Fulranumab 10 mgQ4 wk | 15 | −0.758 (0.38) | 0.31 (−0.76, 1.38) | 0.56 | 15 | −1.230 (0.52) | 0.27 (−1.10, 1.63) | 0.69 |
| Week 12 | | | | | | | | |
| Pain on average past 24 h | | | | | | | | |
| Placebo | 16 | −1.011 (0.43) | — | — | 17 | −1.802 (0.51) | — | — |
| Fulranumab 1 mgQ4 wk | 10 | −1.416 (0.54) | −0.40 (−1.79, 0.98) | 0.56 | — | — | — | — |
| Fulranumab 3 mgQ4 wk | 10 | −0.837 (0.54) | 0.17 (−1.22, 1.56) | 0.80 | — | — | — | — |
| Fulranumab 10 mgQ4 wk | 15 | −0.810 (0.44) | 0.20 (−1.03, 1.43) | 0.75 | 15 | −1.472 (0.57) | 0.33 (−1.17, 1.83) | 0.66 |

\**P*-values and LSM from ANCOVA model with treatment, baseline, current pain medication as factors, and baseline average pain score as covariate.
†Nominal unadjusted *P*-values are presented.
CI indicates confidence interval; LSM, least square means; N, number of patients; PHN, postherpetic neuralgia; PTN, posttraumatic neuralgia.

by PGIC. Most of the remaining patients reported improvement in their status (Table S2, Supplemental Digital Content 2, http://links.lww.com/CJP/A364).

## Pharmacokinetic Results

Mean trough serum fulranumab concentrations increased in an approximately dose-proportional or slightly greater than dose-proportional manner at doses and dosing regimens ranging from 1 mgQ4 wk to 10 mgQ4 wk (data not shown). Steady-state serum fulranumab concentrations were generally achieved by week 17 to week 21 following 4-weeks maintenance dosing. Mean trough serum fulranumab concentrations were generally maintained at steady state through week 53, when treated with 4-week maintenance dosing. Serum fulranumab concentrations did not appear to be impacted by the concurrent use of other pain medications or by the type of pain (PHN or PTN). A relationship between serum fulranumab concentrations and clinical efficacy was not observed.

## Immunogenicity Results

Two (2.9%) patients in the fulranumab treatment groups developed antibodies to fulranumab by the end of the study (data not shown). Overall, antibody responses to fulranumab showed low titers (1:10 and 1:40). None of the antibodies developed were able to neutralize the biological effects of fulranumab in vitro.

## Safety Results

Overall, fulranumab at all doses was generally well-tolerated. In the PHN population, the overall percentage of patients with TEAEs was similar between placebo (80%) and fulranumab 10 mgQ4 wk group (79%) and the other 2 treatment groups (62% each). In the PTN population, the overall percentage of patients with TEAEs was comparable

in the placebo (86%) and 10 mgQ4 wk (78%) groups (Table 5). Osteoarthritis was the only TEAE in the PHN population with a > 10% difference in the incidence rate between the 10 mgQ4 wk group and placebo, whereas in the PTN population, both sinusitis and carpal tunnel syndrome occurred with a > 10% incidence difference between the 10 mgQ4 wk group and placebo.

The overall percentage of neurological-related TEAEs was similar across all the treatments groups. Most frequently reported neurological-related TEAEs were hypoesthesia (placebo: 1 [2%] patient; 3 mgQ4 wk: 1 [7%] patient; 10 mgQ4 wk: 3 [7%] patients), carpal tunnel syndrome (10 mgQ4 wk: 3 [7%] patients), peripheral neuropathy (1 mgQ4 wk: 1 [8%] patient; 10 mgQ4 wk: 1 [2%] patient), and paresthesia (placebo: 4 [10%] patients; 3 mgQ4 wk: 1 [7%] patient; 10 mgQ4 wk: 1 [2%] patient); events were largely mild to moderate in severity. No patients in fulranumab group and 14% of the patients in placebo group discontinued the treatment due to neurological-related TEAEs. There was no case of serious neurological-related TEAE that led to treatment discontinuation. Neurological TEAEs leading to a neurological consultation were noted in 1 patient each in placebo (paresthesia) and 10 mgQ4 wk (carpal tunnel syndrome and paresthesia) groups.

During the combined DB efficacy and extension phases, 7 patients experienced serious TEAEs (placebo: 2 [10%] patients; 1 mgQ4 wk: 1 [8%] patient; 10 mgQ4 wk: 4 [21%] patients) in the PHN population, whereas 5 patients experienced serious TEAEs (placebo: 2 [9%] patients and 10 mgQ4 wk: 3 [13%] patients) in the PTN population. Moderate bradycardia was reported in 1 patient (2%) in the 10 mgQ4 wk group, whereas hypotension and orthostatic hypotension were reported in 1 patient (2%) each in the 10 mgQ4 wk group, which were mild to moderate in severity.

**TABLE 4.** Change From Baseline to Week 12 in Worst Pain Intensity, Brief Pain Inventory-Short Form (Treatment Relief Subscale), and Neuropathic Pain Symptom Inventory Score (Total Subscale) (Last Observation Carried Forward), Intent-to-Treat Analysis Set

| | PHN | | | | PTN | |
|---|---|---|---|---|---|---|
| | **Placebo** **(N = 20)** | **Fulranumab** **1 mg Q4 wk** **(N = 13)** | **Fulranumab** **3 mg Q4 wk** **(N = 13)** | **Fulranumab** **10 mg Q4 wk** **(N = 19)** | **Placebo** **(N = 22)** | **Fulranumab** **10 mg Q4 wk** **(N = 23)** |
| Worst pain intensity | | | | | | |
| Baseline (mean [SD]) | 7.6 (0.97) | 7.9 (1.17) | 7.4 (0.83) | 7.9 (1.05) | 7.7 (1.14) | 8.0 (1.13) |
| Change from baseline (mean [SD]) | −0.9 (1.59) | −1.6 (1.63) | −0.9 (2.01) | −1.2 (1.57) | −1.5 (1.89) | −0.9 (1.98) |
| *P* (minus placebo)*† | | 0.21 | 0.99 | 0.49 | | 0.29 |
| Difference of LSM | | −0.8 (0.61) | 0.0 (0.61) | −0.4 (0.55) | | 0.6 (0.59) |
| 95% CI | | (−1.99; 0.44) | (−1.21; 1.22) | (−1.48; 0.71) | | (−0.55; 1.82) |
| Brief pain inventory-short form (treatment relief) | | | | | | |
| Baseline (mean [SD]) | 18.5 (21.34) | 26.7 (29.95) | 18.5 (25.12) | 23.2 (25.18) | 22.9 (23.27) | 20.9 (23.72) |
| Change from baseline (mean [SD]) | 8.5 (29.78) | 5.8 (33.70) | −8.5 (23.75) | 2.1 (21.49) | 14.8 (28.04) | 4.8 (27.78) |
| *P* (minus placebo)*† | | 0.70 | 0.04 | 0.64 | | 0.19 |
| Difference of LSM | | 3.4 (8.60) | −17.1 (8.30) | −3.6 (7.48) | | −10.8 (8.09) |
| 95% CI | | (−13.86; 20.56) | (−33.76; −0.54) | (−18.54; 11.42) | | (−27.15; 5.57) |
| Neuropathic pain symptom inventory (total subscale) | | | | | | |
| Baseline (mean [SD]) | 46.4 (20.37) | 36.5 (16.73) | 41.3 (18.26) | 41.7 (20.24) | 46.4 (19.56) | 47.6 (18.48) |
| Change from baseline (mean [SD]) | −9.2 (18.92) | −14.1 (17.13) | −8.4 (12.86) | −7.5 (11.53) | −8.4 (16.38) | −6.0 (16.22) |
| *P* (minus placebo)*† | | 0.09 | 0.82 | 0.99 | | 0.61 |
| Difference of LSM | | −8.8 (5.09) | −1.1 (4.91) | −0.1 (4.42) | | 2.6 (4.93) |
| 95% CI | | (−18.96; 1.43) | (−10.96; 8.71) | (−8.91; 8.78) | | (−7.41; 12.53) |

*P-values and LSM from ANCOVA model with treatment, baseline current pain medication as factors, and baseline average pain score as covariate.
†Nominal unadjusted P-values are presented.
CI indicates confidence interval; LSM, least square means; N, number of patients; PHN, postherpetic neuralgia; PTN, posttraumatic neuralgia.

There were no TEAEs indicative of hepatic or acute renal failure during the study. No clinically significant changes from baseline in total neuropathy score-nurse and MMSE were observed. Five joint replacements occurred during the study, 2 in the placebo and 3 in the fulranumab 10 mg Q4 wk groups. All cases of joint replacement were reviewed by the independent adjudication committee (IAC). Four of the joint replacement cases were determined by the IAC to be from normal progression of osteoarthritis; 1 case in the fulranumab 10 mg Q4 wk group was determined to be RPOA. None of the joint replacement cases were assessed by the IAC to be either osteonecrosis or RPOA with features of osteonecrosis. The single case adjudicated as RPOA occurred in a patient on fulranumab using regular concurrent nonsteroidal anti-inflammatory drugs, and who had a prior history of osteoarthritis in the affected joint before joint replacement. The majority of the joint replacements (n = 3) 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 relationship.

Injection-site evaluations (investigator-assessed, after each injection) of mild rating were noted across all the groups. No clinically significant changes in laboratory parameters, vital signs, or ECGs were noted in any patient during the study. There were no deaths in the study.

## DISCUSSION

NGF plays an important role in the generation of pain and hyperalgesia in several acute and chronic pain states through the sensitization of nociceptive neurons.[23,24] A new class of analgesic drugs, the anti-NGFs, is a potential option in treatment of conditions where the current therapeutics are deemed ineffective. This paper reports the safety and analgesic efficacy of fulranumab, an anti-NGF compound, in the treatment of PHN and PTN. No significant reduction was achieved in either neuropathic populations versus placebo in average daily pain score at both time points (week 4 or week 8) of the 12-week DB efficacy phase (except for PHN patients at week 4 [P = 0.02] in the 10 mg group).

This study was planned to generate long-term data on fulranumab treatment in the PTN and PHN patient population. However, the planned enrollment of 200 patients was not achieved due to the clinical hold, resulting in enrollment of only 111 patients, which is a limitation of this study. Approximately 75% of PHN and PTN patients were

**TABLE 5.** Treatment-emergent Adverse Events Occurring in At Least 10% of Patients for Combined Double-blind Efficacy and Double-blind Safety Extension Periods, Intent-to-Treat Analysis Set

| | PHN (n [%]) | | | | PTN (n [%]) | | |
|---|---|---|---|---|---|---|---|
| **TEAEs** | **Placebo (N = 20)** | **Fulranumab 1 mg Q4 wk (N = 13)** | **Fulranumab 3 mg Q4 wk (N = 13)** | **Fulranumab 10 mg Q4 wk (N = 19)** | **Placebo (N = 22)** | **Fulranumab 3 mg Q4 wk (N = 1)** | **Fulranumab 10 mg Q4 wk (N = 23)** |
| Total no. patients with TEAEs | 16 (80) | 8 (62) | 8 (62) | 15 (79) | 19 (86) | 1 (100) | 18 (78) |
| Sinusitis | 2 (10) | — | — | 1 (5) | 1 (5) | 1 (100) | 4 (17) |
| Ear infection | — | — | — | — | — | 1 (100) | — |
| Staphylococcal infection | — | — | — | — | — | 1 (100) | — |
| Headache | 2 (10) | — | 3 (23) | 1 (5) | 2 (9) | — | 3 (13) |
| Herpes zoster | 1 (5) | — | 2 (15) | 0 | — | — | — |
| Arthralgia | 4 (20) | — | 1 (8) | 4 (21) | 3 (14) | — | 1 (4) |
| Osteoarthritis | 1 (5) | — | — | 4 (21) | — | — | — |
| Nasopharyngitis | 3 (15) | — | — | 1 (5) | 3 (14) | — | 1 (4) |
| Upper respiratory tract infection | 3 (15) | — | — | 1 (5) | — | — | — |
| Paresthesia | — | — | — | — | 3 (14) | — | 1 (4) |
| Pain in extremity | 2 (10) | 3 (23) | — | 1 (5) | 3 (14) | — | — |
| Carpal tunnel syndrome | — | — | — | — | — | — | 3 (13) |
| Back pain | 2 (10) | 1 (8) | 1 (8) | 2 (11) | — | — | — |
| Edema peripheral | 1 (5) | 1 (8) | 0 | 2 (11) | — | — | — |
| Diarrhea | 2 (10) | — | — | 2 (11) | — | — | — |
| Hip arthroplasty | 1 (5) | — | — | 2 (11) | — | — | — |
| Anemia | — | — | 1 (8) | 2 (11) | — | — | — |
| Influenza | — | — | — | 2 (11) | — | — | — |
| Urinary tract infection | — | — | — | 2 (11) | — | — | — |
| Muscle spasms | 2 (10) | — | 1 (8) | — | — | — | — |
| Musculoskeletal pain | 2 (10) | — | — | 1 (5) | — | — | — |
| Contusion | 2 (10) | — | — | 1 (5) | — | — | — |
| Rash | 2 (10) | — | — | — | — | — | — |
| Anxiety | 2 (10) | — | — | — | — | — | — |

Percentages calculated with the number of patients in each group as denominator and incidence is based on the number of patients experiencing at least 1 adverse event, not the number of events.

N indicates number of patients; n, patients reporting TEAEs; PHN, postherpetic neuralgia; PTN, posttraumatic neuralgia; TEAEs, treatment-emergent adverse events.

able to complete the 12-week DB efficacy phase and ∼66% of patients could enter DB extension phase. LOCF may not be the best method to use to measure the change from baseline in average pain intensity (primary endpoint) as an overly optimistic result may be obtained for the study drug. In our study, BOCF method was also used and the results were comparable. It is advised to explore other imputation strategies as part of the sensitivity analyses.

Similar to the primary efficacy results (analyzed by NRS scale), there were no significant differences observed for any of the fulranumab treatment groups compared with placebo as measured by responder analysis, most bothersome symptom from NPSI, PGIC, and BPI-SF, except a significant improvement from baseline in treatment pain relief subscale ($P = 0.04$) observed in the BPI-SF for PHN group (3 mg Q4 wk). The NPSI total score measures the overall pain intensity and is correlated to numerical pain scales, whereas individual subscales may assess distinct dimensions of neuropathic pain.[20] There were no significant differences in any of the subscales including burning spontaneous pain, pressing spontaneous pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia subscales (data not shown).

The NRS scale used to access the average pain intensity (primary efficacy endpoint), despite having practical advantages in terms of not requiring any physical materials and widespread acceptance in clinical practice, has its own limitations. The scores are subjective and can be influenced by many social, cognitive, and contextual factors. The variability seen between the efficacy results as measured by NRS and BPI treatment pain relief subscales may be explained by these factors. In addition, the sensitivity of pain relief and that of pain intensity have been reported to mostly correlate but are not always similar.[25]

Fulranumab has demonstrated significant analgesic activity in patients with pain associated with chronic osteoarthritis of the knee or hip and pain associated with painful diabetic neuropathy,[18,19] but failed to show analgesic activity in either of the neuropathic populations enrolled in this study. The reasons for differences observed

in the responses to fulranumab in different patient populations are not well-understood. In this study, the PHN and PTN were monophasic in etiology (caused by an isolated insult like viral or traumatic). One hypothesis for the differential effect may be that NGF released from unhealthy axons causes pain by acting on intact axons or terminals. In painful diabetic neuropathy, which is chronic, there are both dying and intact axons, whereas in monophasic neuropathies the injured axons either die or heal, and pain may be less dependent on NGF. Another possible reason is that the patients included in the current study were particularly refractory to any drug therapy and had chronic and longer-lasting pain, although there is no evidence either way to support this possibility. Overall efficacy results for both PHN and PTN are consistent with an earlier study of a similar anti-NGF class treatment (tanezumab) used for PHN.[26] Serum fulranumab concentrations did not appear to be impacted by concurrent use of pain medications or by the type of neuropathic pain (PHN or PTN). As robust efficacy was not observed, it is difficult to assess correlation between serum fulranumab concentrations and clinical efficacy. The lack of correlation could be due to the lack of efficacy and may be buried in the noise of placebo effect.

Fulranumab was generally well-tolerated at all 3 doses evaluated in the study. During the combined DB phases (efficacy and extension safety), the overall rate of TEAEs was similar among placebo and fulranumab treatment groups. No apparent dose relationship was observed. No deaths were reported. During the DB efficacy phase for PHN and PTN, a low incidence of serious TEAEs and the TEAEs leading to discontinuation was observed. The majority of patients were withdrawn from the DB extension phase due to sponsor's decision to discontinue the study as a result of the FDA clinical hold. The most common neurological-related TEAEs were those related to hypoesthesia, carpal tunnel syndrome, peripheral neuropathy, and paresthesia. These findings are consistent with a study evaluating efficacy and safety of fulranumab in painful diabetic peripheral neuropathy patients wherein similar neurological-related TEAEs (neuropathic pain, neuropathy, paresthesia, and carpal tunnel syndrome) were reported.[19] Few TEAEs of clinical interest (bradycardia, hypotension, neurological, and motor-related TEAEs) were reported in this study, consistent with previous safety information on fulranumab.[18,19] No changes were noted on vital signs assessed (blood pressure, pulse rate measures, ECGs).

Events of RPOA and osteonecrosis resulting in rapid joint destruction leading to joint replacement surgery were identified as specific safety concerns by the FDA in clinical studies of anti-NGF drugs in development.[27] In 2010, FDA placed all anti-NGF therapies (including fulranumab) on clinical hold for all indications except cancer pain.[28] However, the clinical hold was lifted in 2012 with a recommendation for a close safety surveillance.[27] One case of RPOA leading to joint replacement was reported in this study, although 7 patients enrolled had a history of OA. No case of osteonecrosis was reported in the study. The safety findings observed in this study were consistent with previous studies of fulranumab[18,19] and other anti-NGFs in pain therapy such as tanezumab.[26]

Larger clinical studies involving more patients are needed to fully characterize the efficacy of fulranumab, ideally with an active comparator. In addition, clinical studies evaluating long-term safety and tolerability of this potentially new class of analgesic drug are required.

## CONCLUSIONS

This study failed to show that fulranumab at a dose up to 10 mg once every 4 weeks, compared with placebo, was efficacious in reducing pain in patients with PHN or PTN. There was some evidence of pain reduction only at the highest dose of fulranumab (10 mgQ4 wk) at the 4-week time point. The limitation of the study is the small sample size. Overall, fulranumab at all doses was generally well-tolerated in PHN and PTN patients in this study.

*Center, Lexington, KY, Petersen D, MD; Valley Medical Center, PLLC, Lewiston, ID, Radnovich R, DO; Injury Care Medical Center, Boise, ID, Rao HT, MD; The Neurological Institute, P.A., Charlotte, NC, Rapo SE, MD; Clinical Research Center of Cape Cod, Inc., Hyannis, MA, USA Rederich GJ, MD; Redondo Beach, CA, Schmidt LM, DO; Genova Clinical Research, Tucson, AZ, Schwartzman RJ, MD; Drexel University College of Medicine, Philadelphia PA, Shamim T, MD; Heartland Clinical Research, Inc., Omaha, NE, Steinberg JM, MD; Sunrise Clinical Research, Inc., Hollywood, FL, Tuchman M, MD; Palm Beach Neurological Center Advanced Research Consultants, Inc., Palm Beach Gardens, FL, Upender R, MD; HCCA Clinical Research Solutions, Tullahoma, TN, Weintraub JR, DO; Ann Arbor, MI, White A, MD; Port Orange, Fl, Wymer JP, MD, PhD; Upstate Clinical Research, LLC, Albany, NY, Beesley BA, MD, Upstate Clinical Research, LLC, Albany, NY, Young DG; MD Northern California Research, Sacramento, CA, Belgium: Hans G, MD, PhD;UZ Antwerpen, Edegem, Belgium, Morlion B, MD; UZ Leuven, Pellenberg, Belgium, Vanelderen P, MD; Ziekenhuis Oost-Limburg, Genk, Belgium, Spain: Guerrero A, MD; Hospital Clinico San Carlos, Madrid, Spain, Gomar C, MD, PhD; Hospital Clinic de Barcelona, Barcelona, Spain, de Andres JA, MD, PhD; Hospital General de Valencia, Valencia, Spain, Pêrez C, MD; Hospital de La Princesa, Madrid, Spain, Vincente-Fatela L MD, PhD; Hospital Doce de Octubre, Madrid, Spain (Note: some sites had coprimary investigators or the primary investigator changed during the course of the study).*

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