SYNOPSIS

Issue Date: 04 July 2012

Name of Sponsor/Company	Janssen Research & Development, LLC
Name of Finished Product	To be determined
Name of Active Ingredient(s)	JNJ-42160443 (fulranumab)

Protocol No.: 42160443NPP2001

Title of Study: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-42160443 in Subjects With Postherpetic Neuralgia and Post-Traumatic Neuralgia, Followed by a Double-Blind Safety Extension and an Open-Label Safety Extension.

EudraCT Number: 2008-007478-39

NCT No.: NCT00964990

Clinical Registry No.: CR016474

Principal Investigator(s): Dr. Michael Drass, MD

Study Center(s): Belgium (3 sites), Spain (2 sites), and USA (31 sites)

Publication (Reference): None

Study Period: 27 August 2009 to 11 July 2011, Database Lock: 30 September 2011, after the end of the post-treatment phase, spontaneous reporting of joint replacements and collection of associated reporting was ongoing until 11 November 2011 as requested by the FDA.

Phase of Development: 2

Objectives:

Primary Objectives

- To evaluate the analgesic efficacy of fulranumab (1, 3, and 10 mg; administered as a single, subcutaneous injection every 28 days) in reducing average pain intensity in subjects with postherpetic neuralgia
- To evaluate the safety and tolerability of multiple doses of fulranumab (1, 3, and 10 mg), when administered as a single, subcutaneous injection every 28 days to subjects with postherpetic neuralgia for up to 2 years.

Secondary Objectives

- To evaluate the analgesic efficacy of fulranumab (10 mg; administered as a single, subcutaneous injection every 28 days) in reducing average pain intensity in subjects with post-traumatic neuralgia
- To evaluate the safety and tolerability of multiple doses of fulranumab (10 mg) when administered as a single, subcutaneous injection every 28 days to subjects with post-traumatic neuralgia for up to 2 years

- To evaluate the efficacy of fulranumab with respect to alternative pain endpoints (eg, evening assessment of pain at its worst in the last 24 hours, neuropathic pain symptoms, pain severity, and pain-related interference with activities, Patient Global Impression of Change)
- To evaluate the pharmacokinetics (PK) of fulranumab following multiple dose administrations
- To evaluate the immunogenicity (antibodies to fulranumab) associated with fulranumab treatment.

Exploratory Objectives

- To explore PK-efficacy relationships
- To explore the efficacy of fulranumab with respect to the most bothersome symptom from Neuropathic Pain Symptom Inventory (NPSI)
- To explore the impact of fulranumab treatment on functional health status (including physical and social functioning) and well-being, dimensions of sleep, fatigue, and neuropathic pain-related interference with activities
- To explore the impact of fulranumab treatment on brush evoked allodynia.

Methodology: This was a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy, safety, and tolerability of fulranumab in subjects with neuropathic pain, followed by a double-blind safety extension and an open-label safety extension.

The study consisted of 5 sequential phases: Screening (within 28 days prior to the first dose of study drug), a 12-week double-blind efficacy, a 40-week double-blind safety extension, a 52-week open-label safety extension, and a 26-week post-treatment/follow-up (to occur 26 weeks after the last dose of study drug).

Number of Subjects (planned and analyzed): Planned: Approximately 200 subjects with neuropathic pain diagnoses of postherpetic neuralgia (PHN) (n = 150) or post-traumatic neuralgia (n = 50 subjects) were planned to be enrolled. Analyzed: A total of 200 enrolled subjects were planned in the study. Of the 200 subjects, 111 subjects (65 subjects in PHN group and 46 subjects in the PTN group) in ITT population and 84 subjects (51 subjects in PHN and 33 subjects in the PTN group) in per protocol 12 weeks population were enrolled. In the DB efficacy phase, 49 subjects in the PHN group and 34 subjects in the PTN group completed the study. In the DB extension phase, 14 subjects completed the study.

Diagnosis and Main Criteria for Inclusion: The study population was to be composed of men and women aged between 18 and 80 years of age (inclusive), with neuropathic pain diagnoses of PHN (n=150) or post-traumatic neuralgia (n=50) who were intolerable to, not willing to use, or were not adequately controlled by standard of care. Subject randomization was stratified according to diagnostic groups (PHN or post-traumatic neuralgia) and current pain medication use (subjects who were currently using or subjects who were not currently using permitted pain medication).

Test Product, Dose and Mode of Administration, Batch No.: Fulranumab was provided as a sterile, frozen solution in glass vials. Each vial contained fulranumab at a concentration of 10 mg/mL. Fulranumab was formulated in 10 mM sodium acetate, 9.25% sucrose, and 0.004% polysorbate 20 at pH 5.2 and contained no preservatives. Upon thawing, the liquid was a clear liquid, practically free of particles. Active (fulranumab) of Lot D09PB7684 and D09PF7689 with expiry dates of 30 June 2011 and 20 January 2011 respectively were administered.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo for fulranumab was supplied as a sterile solution (approximately 1 mL fill volume) in glass vials. The placebo was clear and had

a solution composition of 10 mM sodium acetate, 9.25% sucrose, and 0.004% polysorbate 20 at pH 5.2. Placebo of Lot D09PF7691 with expiry date of 20 January 2011 was administered.

Duration of Treatment: The study duration (ie, start of screening phase through completion of follow-up phase) for a subject who participated in the 12-week double-blind efficacy phase was approximately 38 weeks; in the double-blind efficacy phase and the double-blind safety extension phase was approximately 78 weeks; and in the double-blind efficacy phase, the double-blind safety extension phase, and the open-label safety extension phase was approximately 130 weeks.

Criteria for Evaluation:

Primary:

- The primary efficacy evaluation was the daily evening assessment of average pain intensity over the last 24 hours using an 11-point numerical rating scale (NRS), where 0 = no pain and 10 = pain as bad as you can imagine
- The primary efficacy endpoint was the mean of the daily evening assessment of average pain intensity over 24 hours for the last 7 days of the double-blind efficacy phase minus the mean from the 7-day baseline period (prior to the first dose of study drug).

Secondary:

- Change from baseline in the mean of daily evening assessment of pain at its worst in the last 24 hours for the last 7 days of the double-blind efficacy phase
- Change from baseline in monthly Brief Pain Inventory (average pain intensity subscale score and average pain interference subscale score) during the double-blind efficacy phase
- Change from baseline in monthly Neuropathic Pain Symptom Inventory during the double-blind efficacy phase (NPSI Total and Subscores)
- Monthly Patient Global Impression of Change (PGIC).

Exploratory:

- Change from baseline in the mean daily evening assessment of the most bothersome symptom from NPSI (1-NPSI item; identified from baseline NPSI assessment) for the last 7 days of the double-blind efficacy phase
- Change from baseline in monthly (1 and 3) functional health status and well being as measured by 8 subscales (including physical and social functioning) of the Short Form-36 Health Survey (SF-36) during the double-blind efficacy phase
- Change from baseline in the mean of daily assessment of sleep interference for the last 7 days of the double-blind efficacy phase
- Change from baseline in MOS-Sleep (sleep dimensions including latency, maintenance, awakenings, quality, and pain interference) at the end of the double-blind efficacy phase
- Change from baseline in monthly Patient Global Impression of Severity (PGIS) during the double-blind efficacy phase
- Change from baseline in area and intensity of brush-evoked allodynia at the end of the double-blind efficacy phase
- Change from baseline in usual level of fatigue at the end of double-blind efficacy phase

- Change from baseline in activity limitations at the end of double-blind efficacy phase.

Statistical Methods:

Sample Size Determination

The primary efficacy endpoint was the change in the 7-day mean of average daily evening assessment of pain intensity over the last 24 hours (measured daily on an 11-point NRS), calculated as the mean of the last 7 days in the double-blind efficacy phase minus the mean of the 7-day baseline period.

Sample size calculation for the dose-response analysis was performed using the MCP-Mod package in R. With 150 subjects randomized (45 for placebo and 10 mg and 30 for 1 and 3 mg), the power of the MCP-Mod procedure to establish a dose-response relationship is ≥75% at a 1-sided 5% significance level under the assumption that the variance was 2.4 and the maximum effect was 1.25, and ≥60% if the underlying difference was 1.0 point (thought to be minimally clinically meaningful). If an interim analysis was required to be conducted when 80 subjects completed the double-blind efficacy phase, the power of the MCP-Mod procedure to establish a dose-response relationship was to be ≥50% at a 1-sided 5% significance level under the same assumptions.

With respect to the exploratory comparison of 10 mg vs placebo in the PTN diagnostic group, assuming a two sided alpha=0.1 test with 25 subjects per group, there was 56% power to detect a true underlying difference of 1.25 points.

Primary Efficacy Analyses

All subjects who were randomly assigned to treatment in the double-blind efficacy phase and had received at least one dose of fulranumab or placebo were included in the intent-to-treat population for the efficacy analysis.

Within the PHN group, the dose-response of the primary efficacy endpoint were evaluated using the MCP-Mod procedure to test a positive overall treatment effect (dose-response relationship), followed by 3 pairwise comparisons of each individual dosage groups against placebo to estimate the treatment magnitude for each dosage level.

Each individual active dose group were compared to placebo using the 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. No multiplicity adjustment for the 3 pairwise comparisons was planned. For the 10 mg vs. placebo comparison, the treatment by diagnostic group interaction was to be tested, and if found to be non-significant, the diagnostic groups were to be combined.

Subgroup analyses of the primary endpoint were done within the current pain medication use (yes/no) stratification groups.

Sample Size Re-estimation

Due to uncertainty regarding the shape of the dose response curve, sample size re-estimation was to be undertaken for the PHN diagnostic group when enrollment was nearing completion, at which time it was expected that at least 50% of the PHN subjects were completed the double blind efficacy phase. The exact timing of this sample size re-estimation was a function of the enrollment and completion rates. An independent statistical group was to perform the unblinded sample size re-estimation. The statistical group followed a pre-specified analysis plan that was developed in collaboration with the study team. In addition, procedures were developed to ensure the blinding of the subject level data for parties outside of the independent statistical group. If the sample size was increased, the potential for increased Type 1 error was acknowledged, and results were to be interpreted with appropriate caution. In addition, the sample

size for the post-traumatic neuralgia diagnostic group was to be re-estimated just prior to the completion of enrollment or any time thereafter.

Other Analyses

Analyses of the secondary and exploratory endpoints that were collected daily followed a similar approach to that used for the primary endpoint.

Descriptive statistics was provided with respect to the double-blind efficacy phase as well as the safety extension phase for selected demographics, safety, PK, and efficacy data. Descriptive statistics on continuous measurements included means, medians, standard deviations, and ranges, while categorical data were summarized using frequency counts and percentages. The number and percentage of subjects reporting treatment-emergent adverse events were tabulated by system organ class and preferred term. Summaries of clinically significant changes in physical examinations, neurologic examinations, injection site evaluations, clinical laboratory evaluations, 12-lead ECGs, vital signs, and neurologic evaluations (TNSn and MMSE) results was also to be provided.

If data permit, the relationships between fulranumab serum concentrations and efficacy or safety response were to be analyzed graphically. If an efficacy or safety effect was observed, a suitable PK/efficacy or PK/safety model was to be applied to explore the exposure-response relationship.

The association with treatment emergent sensory symptoms with other baseline factors such as fasting glucose levels, body mass index, age, cholesterol level, triglyceride level, and ethnic group was also to be explored.

RESULTS:

STUDY POPULATION:

A total of 111 subjects (65 subjects for the assessment of neuropathic pain [PHN] and 46 subjects were enrolled for the assessment of post-traumatic neuralgia [PTN]) were enrolled in the study. The planned enrollment was 200 subjects, and was not reached because of the clinical hold.

Double-Blind Efficacy Phase:

PHN: Of the 65 subjects in the ITT group, a total of 49 subjects (75%) completed the DB efficacy phase and 16 (25%) subjects were withdrawn. The highest percentage of subjects [5 subjects (26%)] withdrawn was from the 10mgQ4wk group. The major reason for withdrawal was subject choice. Other reason was due to the sponsor discontinuation of the study. Discontinuation due to adverse event was 1 subject each in the 3mgQ4wk and 10mgQ4wk groups.

Demographics and baseline characteristics, across treatment groups had slightly more women (52.3%) than men (47.7%), most racially white (86.2%), with a median age of approximately 70 yrs, median weight of 76.3 kg, median BMI of 28.1 kg/m^2 (range: 18 to 46), with a majority of subjects $\geq$ 65 yrs (70.8%).

The median treatment exposure over the double-blind efficacy phase was similar across all treatment groups: approximately 83.0 to 84.5 days.

PTN: Of the 46 subjects in the ITT group, a total of 34 subjects (74%) completed the DB efficacy phase and 12 (26%) subjects were withdrawn. The highest percentage of subjects (7 subjects [32%]) withdrawn was from the placebo group. The major reason for withdrawal was due to the sponsor discontinuation of the study. The second major reason was subject choice.

Demographics and baseline characteristics, across treatment groups had more women (60.9%) than men (39.1%), most racially white (91.3%), with a median age of approximately 49 yrs, median weight of 79.4 kg, median BMI of 26.3 kg/m^2 (range: 18 to 37), with a majority of subjects < 65 yrs (82.6%).

The median treatment exposure over the double-blind efficacy phase was similar across all treatment groups: approximately 84.0 to 86.0 days.

Double-Blind Extension Phase:

Of the 73 subjects, 14 (19%) subjects completed the DB extension phase and 59 (81%) subjects were withdrawn. The highest percentage of subjects (25 [83%] subjects) was withdrawn from the placebo group. The second highest percentage of subjects (24 [86%] subjects) was withdrawn from the 10mgQ4wk group. The major reason for withdrawal was due to the sponsor discontinuation of the study.

PHN: The median treatment exposure over the double-blind extension phase was less in placebo group (135.5 days) as compared with the fulranumab treatment groups (204.0, 249.0, and 243.5 days).

PTN: The median treatment exposure over the double-blind extension phase was less in placebo group (122.0 days) as compared with the fulranumab treatment groups (278.0 and 204.5 days).

Post-Treatment Phase:

Of the 86 subjects who entered the post-treatment phase, 64 subjects completed the post-treatment phase and 22 subjects were withdrawn. The highest number of subjects (12 subjects) was withdrawn from the placebo group and the major reason for the withdrawal was due to subject choice.

Although the clinical hold of the fulranumab program required that study dosing be stopped, subjects were allowed to continue all other study procedures until he or she missed 3 doses, at which time the subject withdrew from the treatment phases and could enter the post-treatment phase.

EFFICACY RESULTS:

This study failed to achieve the primary objective to demonstrate that efficacy with fulranumab was significantly better than placebo as measured by the change in average pain intensity at Week 12 of the DB efficacy phase in subjects with a diagnosis of PHN.

There were no statistically significant changes observed in average pain intensity for any of the fulranumab treatment groups compared to placebo at either Week 4 or Week 8 of the 12-week DB efficacy phase except for the 10mgQ4wk treatment group at Week 4, where a statistically significant change in average pain intensity score was noted in the per protocol population for both BOCF and LOCF (p value of 0.017).

There were no statistically significant differences for any of the fulranumab treatment groups compared to placebo as measured by responder analysis (overall responder curves, 30% responder rate, 50% responder rate), most bothersome symptom from NPSI, allodynia assessment, PGIS, single item from BFI, and activity limitations questionnaire except for sleep assessments (MOS sleep assessment and sleep interference assessment) and SF-36 that had statistically significant improvement in the fulranumab 3mgQ4wk group.

There were no statistically significant differences in worst pain in the past 24 hours, NPSI (except for the 1mgQ4wk group in the burning spontaneous pain subscale with p-value of 0.004 in PHN subjects). A statistically significant improvement from baseline in treatment relief (p=0.043) was observed in the BPI-SF in PHN subjects (3 mgQ4wk).

The relationship between serum fulranumab concentrations and clinical efficacy were not observed. Based on the data from 2 subjects who were positive for antibodies to fulranumab, development of antibodies to fulranumab did not preclude clinical efficacy.

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 1mgQ4wk to 10mgQ4wk
- Steady-state serum fulranumab concentrations were generally achieved by Week 17 to Week 21 following Q4wk maintenance dosing. Mean trough serum fulranumab concentrations were generally maintained at steady state through Week 53 when treated with Q4wk maintenance dosing.
- There was no evidence of accumulation in serum fulranumab concentrations over time when given subcutaneously Q4wk
- Serum fulranumab concentrations did not appeared to be impacted by current use of pain medications or by type of pain (PHN or PTN).

ANTIBODIES TO FULRANUMAB SUMMARY

- Only 2 (2.9%) subjects in the active treatment groups developed antibodies to fulranumab through the end of the study
- Antibody responses to fulranumab were low titers (1:10 and 1:40, respectively)
- None of the antibodies developed were able to neutralize the biological effects of fulranumab *in vitro*.

SAFETY RESULTS:

During all the phases of the study, fulranumab was well tolerated with a low percentage of subjects with adverse events leading to discontinuation during all phases of the study. The safety profile showed no deaths and few serious adverse events during the double-blind phases. The rate of adverse events was higher in the infections and infestations, musculoskeletal and connective tissue, and general disorders and administration site conditions SOCs. The overall percentage of subjects with adverse events was higher in the placebo and 10mgQ4wk groups than in the other two groups for the combined DB efficacy and extension phase. The most frequent events were in the infections and infestations, musculoskeletal and connective tissue, and general disorders and administration site conditions SOCs. During the combined phases of the study, there were a few SAEs and a low incidence of TEAEs that led to discontinuation, with no apparent treatment group or dose relationship. During the double-blind efficacy phase for PHN and PTN, a low incidence of SAEs and TEAEs leading to discontinuation was observed. There were few adverse events of clinical interest (bradycardia, hypotension, neurological and motor related adverse events, renal failure, and hepatic failure per protocol) in the study.

STUDY LIMITATIONS:

The fulranumab program was placed on clinical hold by the FDA. When study treatment was terminated, approximately 50% of planned subjects were randomized.

CONCLUSIONS:

The study failed to show efficacy with fulranumab in subjects with either PHN or PTN, however, approximately 50% of planned subjects were randomized due to a clinical hold. Fulranumab was generally well tolerated compared with placebo.

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