SYNOPSIS

Issue Date: 17 May 2012

Document No.: EDMS-ERI-43620295:1.0

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.: 42160443-PAI-2003

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging, Dose-Loading Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-42160443 as Adjunctive Therapy in Subjects With Inadequately Controlled, Moderate to Severe, Chronic Low Back Pain.

EudraCT Number: 2009-009857-17

NCT No.: NCT00973024

Clinical Registry No.: CR016468

Coordinating Investigator: Dr. Joseph S. Gimbel, MD - Arizona Research Center, [redacted], USA

Study Center(s): The study was conducted in 3 countries: Belgium (2 sites), Canada (16 sites), and the USA (44 sites).

Publication (Reference): None

Study Period: Date of first subject enrolled (informed consent): 10 September 2009 to date of last observation for last subject: 20 May 2011. An unblinded analysis occurred on 10 August 2010 (at the end of the double-blind efficacy phase, for the pre-specified primary efficacy analysis) and the database lock occurred on 20 June 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 in agreement with the FDA.

Phase of Development: 2b

Objectives:

Primary Objectives:

The primary objectives of this study were to evaluate the analgesic effect size over 12 weeks of several doses and dosage regimens of fulranumab compared with placebo in subjects with moderate to severe, chronic, low back pain (LBP) that was not adequately controlled by standard pain therapy, and to evaluate the safety and tolerability of multiple subcutaneous (SC) doses of fulranumab in this population.

Secondary Objectives:

The key secondary objectives of this study were:

- To evaluate the efficacy of fulranumab compared with placebo as measured by back pain disability with subscales and total scores of the Oswestry Disability Index (ODI)
- To evaluate the efficacy of fulranumab compared with placebo as measured by the pain severity and pain interference subscales and total scores from the Brief Pain Inventory-Short Form (BPI-SF)

- To evaluate the efficacy of fulranumab compared with placebo as measured by the Patient Global Assessment (PGA).

Other secondary objectives were:

- To evaluate the pharmacokinetics (PK) of fulranumab after multiple dose administrations of fulranumab. A population PK approach was to be used to characterize the disposition characteristics of fulranumab in this study
- To evaluate the immunogenicity (antibodies to fulranumab) associated with fulranumab treatment
- To evaluate the long-term efficacy, safety, and tolerability of fulranumab in this subject population during the 92-week double-blind extension phase.

Methodology: This was a randomized, double-blind, placebo-controlled, dose-ranging with dose-loading study evaluating the analgesic efficacy, safety and tolerability of fulranumab at several doses and dosage regimens in subjects with moderate to severe, chronic, LBP that was not adequately controlled by standard pain therapy.

The study included a 3-week screening phase, a 12-week double-blind efficacy phase, a 92-week double-blind extension phase, and a 26-week post-treatment phase.

Number of Subjects (planned and analyzed): Approximately 360 subjects were planned to be enrolled with 72 subjects in each treatment group (4 fulranumab treatment groups and 1 placebo group). A total of 389 subjects were randomized and 385 subjects were dosed.

Diagnosis and Main Criteria for Inclusion: The study population was to be composed of men and women aged 18 to 80 years, inclusive, with moderate to severe, chronic, LBP that was not adequately controlled by standard pain therapy. Also, subjects were to be receiving a stable analgesic regimen consisting of nonsteroidal anti-inflammatory drugs or immediate-release opioids, for a minimum of 5 days each week for 4 weeks before screening, or long-acting opioids for 4 weeks before screening. An average pain score (on the numerical rating scale [NRS]) of ≥5 using twice daily pain scores recorded for pain related to LBP during 3 days before randomization was required.

Test Product, Dose and Mode of Administration, Batch No.: Fulranumab was a clear liquid administered by SC injection into the thigh: 1 mg every 4 weeks (1mgQ4wk), 3 mg every 4 weeks (3mgQ4wk), an initial 6 mg loading dose (LD) followed by 3 mg every 4 weeks (6mgLD+3mgQ4wk), or 10 mg every 4 weeks (10mgQ4wk). If a thigh injection was not possible, injections were administered in the abdomen (avoiding the area 2 inches around the navel).

Fulranumab was provided frozen in vials containing 1 mL of thawed solution (10 mg/mL). Doses were administered by volume (eg, 1 mg=0.1 mL, 3 mg=0.3 mL, 6 mg=0.6 mL, 10 mg=1 mL) after thawing. Lot number: D09PB7684.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was administered every 4 weeks as a clear liquid after thawing by SC injection into the thigh, at volumes that matched the fulranumab treatment volumes. If a thigh injection was not possible, injections were administered in the abdomen (avoiding the area 2 inches around the navel). Lot number: D09PF7691.

Duration of Treatment: The planned duration of the study was approximately 133 weeks (3-week screening phase, 12-week double-blind efficacy phase, 92-week double-blind extension phase, and 26-week post-treatment phase). However, due to a negative efficacy outcome from the double-blind efficacy phase, the sponsor decided to stop treatment and communicated this action to investigators in a "dear investagator letter" dated 28 October 2010.

Criteria for Evaluation: Efficacy assessments included the NRS (0 to 10) for LBP-related pain, ODI, BPI-SF, PGA, rescue medication use, daily sleep interference assessments, Short Form-36 (SF-36), Health Survey, Medical Outcomes Study (MOS), Sleep Scale, Work Productivity Questionnaire (WPQ), and Safety, Tolerability, and Efficacy Preview (STEP) Interview. Safety assessments included adverse events (AEs), injection site evaluations, pregnancy testing, clinical laboratory tests, electrocardiogram (ECG), vital signs, physical examination, neurological assessments (including the abbreviated neurological examination, Total Neuropathy Score-Nurse [TNSn], Mini Mental State Examination [MMSE]), and the Beck Depression Inventory Second Edition (BDI-II). In addition, examination of joint safety was instituted that included imaging (X-ray, magnetic resonance imaging, ultrasound, and historical data pertaining to the joint replacement) and histology of tissue specimens. Blood samples were collected for evaluation of serum fulranumab concentrations, biomarkers, immunogenicity, and pharmacogenomics (from subjects who consented separately to the pharmacogenomic component of the study).

Statistical Methods: Assuming a standard deviation (SD) of 2.5 for each treatment group, a treatment difference versus placebo of 1.4 for the change from baseline to the end of the 12-week double-blind efficacy phase in the average pain intensity score, and assuming a 20% withdrawal rate, a sample size of 72 subjects for each of the fulranumab and placebo treatment groups would have 84% power to detect the assumed treatment difference, using a type I error rate of 0.05 and a 2-sided, 2-sample t-test. The total sample size to be considered was 360 subjects (72 subjects in each of the 4 fulranumab treatment groups and also in the placebo group).

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

The primary efficacy endpoint was the change from baseline to the end of the 12-week double-blind efficacy phase in the average LBP-related pain intensity score. The primary efficacy endpoint was based on the Last Observation Carried Forward (LOCF) imputation method. Sensitivity analyses were also performed based on Baseline Observation Carried Forward (BOCF) values and using a mixed effects repeated measures model (MMRM) of observed cases

The primary efficacy endpoint was analyzed based on analysis of covariance (ANCOVA) with treatment, baseline average pain score, baseline opioid use (use/nonuse) as factors, and baseline body weight group (<85 kg or ≥ 85 kg) as covariates. The primary efficacy evaluation compared each treatment group with placebo using a step-down procedure, in the following order: 1) 10mgQ4wk, 2) an initial 6-mg LD followed by 3mgQ4wk, 3) 3mgQ4wk, and 4) 1mgQ4wk. Treatment comparisons between each treatment group of fulranumab and placebo were tested at a 2 sided, 0.05 level of significance for each step. A comparison versus placebo was considered for the fulranumab treatment group only if all previous treatment comparisons from the predetermined sequence were statistically significant.

The primary efficacy evaluation, the average LBP-related pain intensity score at the end of the 12-week double-blind efficacy phase, was analyzed after all the subjects completed or were withdrawn from the 12-week double-blind efficacy phase. A pre-specified unblinding plan was followed to ensure maintenance of the blinding of subjects and of the study site staff.

Descriptive statistics were provided for the efficacy, safety, and PK data. Descriptive statistics on continuous measurements included mean, SD, median, and range, while categorical data were summarized using frequency counts and percentages. The incidence of subjects reporting treatment-emergent adverse events (TEAEs) were tabulated by system-organ class (SOC) and preferred terms. Clinically significant changes in clinical laboratory tests, physical and neurologic examinations, vital signs, 12-lead ECGs, BDI-II results, and neurologic evaluations (TNSn, MMSE) were also summarized.

Biomarker and pharmacogenomics analysis will be reported separately.

RESULTS:

STUDY POPULATION:

A total of 389 subjects with moderate to severe LBP not adequately controlled by standard pain therapy were randomized to the 5 treatment groups, and 385 subjects received at least 1 injection of the study drug: 76 in the placebo, 77 in the 1mgQ4wk, 77 in the 3mgQ4wk, 78 in the 6mgLD+3mgQ4wk, and 77 in the 10mgQ4wk group. Most of the subjects (330 of 389) completed the double-blind efficacy phase in each treatment group (79% to 88%); the percentage of subjects who discontinued this phase was low (12% to 21%). A total of 317 subjects entered the double-blind extension phase with approximately comparable numbers of subjects in each treatment group (61 to 67). The majority of subjects (72%) in this phase discontinued treatment due to sponsor's decision. There were slightly more women (54%) than men (46%), most racially White (84.4%), with a median age of approximately 53 years, and median body mass index (BMI) of 28.7 kg/m^2 (range: 14 to 51).

EFFICACY RESULTS:

This study failed to achieve the primary objective to demonstrate that fulranumab was significantly better than placebo as measured by the change in average pain intensity at the end of the 12-week double-blind efficacy phase. The observed placebo-corrected change in average pain intensity for fulranumab treatment groups ranged from 0.0 to -0.2 (change in an 11-point NRS scale, negative numbers favoring fulranumab).

There was no observed dose-response in the primary endpoint among the fulranumab treatment groups. There was a trend in increasing change in average pain intensity at the end of the double-blind efficacy phase with increasing dose of fulranumab in the subset of subjects using concurrent opioids. Improvement was greater in the <85 kg subgroup across all fulranumab groups compared to the ≥85 kg subgroup. There were no statistically significant changes 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 double-blind efficacy phase. Results based on the BOCF and MMRM analyses were consistent with the LOCF analysis.

There were no consistent statistically significant changes across the fulranumab treatment groups from baseline to endpoint compared to placebo as measured by responder analysis (overall responder curves, 30% responder rates, 50% responder rates), change in the ODI, BPI-SF subscales, PGA, SF-36 norm-based subscale scores, WPQ Lost Time Equivalents (LTEs) for paid work and daily activities. There were no notable changes from baseline observed in the NRS for pain not related to LBP. No statistically significant change from baseline to the end of the double-blind efficacy phase in the average daily dose of rescue medication was observed. The 6mgLD+3mgQ4wk and 10mgQ4wk fulranumab treatment groups recorded the lowest median percentage of days on rescue medication in 12 weeks.

CLINICAL PHARMACOLOGY RESULTS:

Pharmacokinetics:

- Mean trough serum fulranumab concentrations increased in an approximately dose-proportional or greater than dose-proportional manner across the fulranumab treatment groups.
- Steady-state serum fulranumab concentrations were generally achieved by Week 17 following Q4wk maintenance dosing. Mean trough serum fulranumab concentrations were generally maintained at steady state through Week 37 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 were impacted by body weight, there were generally lower concentrations observed in subjects with higher body weight.

Immunogenicity

- Only 4 subjects in the fulranumab treatment groups developed antibodies to fulranumab through the end of the study.
- Antibody responses to fulranumab were low titers (1:20 to 1:320).
- None of the antibodies developed were able to neutralize the biological effects of fulranumab *in vitro*.
- Based on the data from 4 subjects who were positive for antibodies to fulranumab, the development of antibodies to fulranumab did not reduce serum fulranumab concentrations.

The results generated from a population PK analysis will be reported separately.

SAFETY RESULTS:

With the inclusion of all phases (ie, double-blind phase and post-treatment phase included), the overall percentage of subjects with AEs was similar between the treatment groups (76% to 90%). The most frequently reported AEs with fulranumab were in the infections and infestations, musculoskeletal and connective tissue disorders, nervous system disorders, and gastrointestinal disorders SOCs. The most common adverse events in these SOC's during the combined double-blind phases were upper respiratory tract infection, nasopharyngitis, sinusitis, arthralgia, back pain, pain in extremities, paraesthesia, and headache, and hypoaesthesis.

A single death occurred during the study in the fulranumab 10mgQ4wk treatment group due to the serious adverse events (SAEs) of pneumonia streptococcal and lung neoplasm malignant. This event was not considered to be related to study drug treatment.

During the combined phases of the study, there were 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, there was a low incidence of SAEs and TEAEs leading to discontinuation. There was no treatment-related pattern for these events.

There were few events of interest (bradycardia-, hypotension-, neurological and motor-related AEs, renal failure, and hepatic failure as per protocol). All events of interest were reviewed by the IDMC. There was no IDMC recommendation to stop a dose group or the study based on the review of the events of interest and the stopping rules defined in the protocol.

There were no clinically relevant differences in vital signs or ECGs values among the treatment groups. There was no evidence of glucose intolerance.

Most injection site reactions were either absent or mild during the combined double-blind phases.

STUDY LIMITATIONS:

The critical limitation of this study was the negative efficacy outcome that was unanticipated.

CONCLUSION(S):

In subjects with moderate to severe, chronic LBP insufficiently controlled by standard pain therapy, fulranumab failed to demonstrate analgesic activity as adjunctive treatment during a 12-week double-blind efficacy phase compared with placebo. Fulranumab was generally well tolerated when compared with placebo.

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed Product. Some information in this posting may differ from the approved labeling for the Product. Please refer to the full prescribing information for indications and proper use of the product.