SYNOPSIS

Issue Date: 26 June 2012

Document No.: EDMS-ERI-26955749:1.0

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

Protocol No.: 42160443-PAI-2004

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-42160443 as Adjunctive Therapy in Subjects With Moderate to Severe Knee or Hip Pain From Osteoarthritis

EudraCT Number: 2009-009856-19

NCT No.: NCT00973141

Clinical Registry No.: CR016471

Coordinating Investigator(s): Marc Afilalo, M.D, MCFP (EM), FACEP, CSPQ, FRCP(C); ED-AMR, [redacted], Canada

Study Centers: 4 countries: Canada (18 sites), Korea (4 sites), Poland (5 sites) and USA (61 sites).

Publication (Reference): none

Study Period: Date of first subject enrolled (informed consent): 08 September 2009 - to date of last observation for last subject: 30 June 2011; Unblinded analyzes occurred on 10 August 2010 and 25 March 2011, and the database lock occurred on 30 August 2011. As requested by the Food and Drug Administration (FDA), spontaneous reporting of joint replacements and collection of associated reports after the end of the post-treatment phase was ongoing until 11 November 2011.

Phase of Development: Phase 2

Objectives:

Primary Objectives

The primary objectives of the 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, knee or hip pain from osteoarthritis (OA) 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 average pain intensity scores at the end of Weeks 4 and 8 and over the entire double-blind efficacy phase
- To evaluate the efficacy of fulranumab compared with placebo, as measured by the pain, stiffness, and function subscales of the Western Ontario and McMaster Osteoarthritis Index 3.1(WOMAC™ 3.1)
- To evaluate the efficacy of fulranumab compared with placebo as measured by the pain severity and pain interference subscales of 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

- To evaluate the pharmacokinetics of fulranumab after multiple dose administrations of fulranumab. A population pharmacokinetic (PK) approach will 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 in subjects with moderate to severe, chronic knee or hip pain from OA 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 26-week post-treatment phase.

Number of Subjects (planned and analyzed): Approximately 420 subjects were planned to be enrolled with 70 subjects in each treatment group. A total of 468 were randomized and 466 were analyzed.

Diagnosis and Main Criteria for Inclusion: The study population was to be composed of men and women aged 40 to 80 years, inclusive, with moderate to severe, chronic, knee or hip pain from OA 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 (NSAIDs) or immediate-release opioids, for a minimum of 5 days each week for the 4 weeks before screening, and/or long-acting opioids for the 4 weeks before screening. An average pain score (Numerical Rating Scale [NRS]) of ≥5 using twice daily pain scores recorded for pain related to osteoarthritis during the 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 after thawing of the solution: 1 mg every 4 weeks, 3 mg every 8 weeks, 3 mg every 4 weeks, 6 mg every 8 weeks and 10 mg every 8 weeks. If a thigh injection was not possible, injections were administered into the anterior abdominal wall (avoiding the area 2 inches around the navel).

Fulranumab was provided frozen in vials containing 1 mL (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. Batch number: D09PB7684

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

Duration of Treatment: The planned study duration 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 that was 22 weeks in duration). Treatment was stopped due to an FDA requested clinical hold on 23 December 2010.

Criteria for Evaluation: Efficacy assessments included the numerical rating scale (0-10) for OA-related pain (NRS), WOMAC 3.1, BPI-SF, PGA, SF-36 Health Survey, MOS Sleep Scale, and sleep interference assessment; Safety assessments included adverse events, clinical laboratory tests, vital signs, ECGs, neurological assessments (including the brief neurological examination, TNSn, MMSE), the BDI®–II,

injection site evaluation, pregnancy testing, and physical examination. In addition, examination of joint safety was instituted that included collection of consultation, surgical, imaging (X-ray, MRI, ultrasound), and pathology reports associated with joint related adverse events. Blood samples were collected for examination of study drug serum concentrations, (pharmacokinetics), biomarkers, immunogenicity, and pharmacogenomics (if consented separately).

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 70 subjects for each of the fulranumab and placebo treatment groups would have 83.5% 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 was to be considered 420 subjects (70 subjects in each of the 5 fulranumab treatment groups and also in the placebo group).

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

The primary efficacy endpoint was the change from baseline to the end of the 12-week double-blind efficacy phase in the average OA-related pain intensity score.

The primary efficacy endpoint was analyzed based on analysis of covariance (ANCOVA) with treatment as a factor, baseline average pain score, baseline opioid use (use/nonuse), 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) 10 mg every 8 weeks, 2) 6 mg every 8 weeks, 3) 3 mg every 4 weeks, 4) 3 mg every 8 weeks, and 5) 1 mg every 4 weeks. 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 a fulranumab treatment group only if all previous treatment comparisons from the predetermined sequence were statistically significant.

The primary efficacy evaluation, the average OA-related pain intensity score at the end of the 12-week double-blind efficacy phase, was analyzed after all subjects completed or withdrew from the 12-week double-blind efficacy phase. To explore the efficacy and safety results related to dosing every 4 versus 8 weeks, additional analyses were performed at the time of the database lock with data from those subjects who also completed 16 weeks of double-blind treatment. A pre-specified unblinding plan was followed to ensure maintenance of the blinding of the 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. Summaries of 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 provided.

RESULTS:

STUDY POPULATION:

A total of 468 subjects with moderate to severe chronic pain of osteoarthritis that was not adequately controlled by the standard of care, from Canada, Korea, Poland, or the USA, were enrolled in a total of 88 sites. These subjects were randomized to 1 of 6 treatment groups: 78 in the placebo, 78 in the

1mgQ4wk, 77 in the 3mgQ8wk, 79 in the 3mgQ4wk, 78 in the 6mgQ8wk, and 78 in the 10mgQ8wk group.

Most of the subjects (423 of 468) completed the double-blind efficacy phase in each treatment group (86% to 94%) leading to a low percentage of subjects who discontinued treatment in this phase (6 % to 14%) with a higher percentage of subjects in the placebo group compared with the fulranumab groups. Of the subjects who discontinued, the reason of lack of efficacy was highest in the placebo group (5%). Discontinuation due to adverse event was generally low (0% to 4%) in all treatment groups. A total of 401 subjects entered the double-blind extension phase, with approximately comparable numbers of subjects in each treatment group (59 to 70). The majority of subjects discontinued due to sponsor's decision because the fulranumab project was placed on clinical hold by the FDA on 23 December 2010. A total of 405 subjects entered the post-treatment phase (from either the double-blind efficacy phase or the double-blind extension phase) with approximately equal numbers of subjects from each treatment group (63 to 72). Most subjects completed this phase.

Demographics and baseline characteristics, across treatment groups, were generally balanced with slightly more women (57.5%) than men (42.5%), most were racially white (approximately 85.4%), with a median age of approximately 61 yrs of age, with a majority of subjects younger than 65 yrs (63.9%), with a median body mass index of 31.1 kg/m^2 (range: 19 to 70).

The median treatment exposure over the double-blind phases was similar across all treatment groups: approximately 12 to 13 months with 3 of those months during the double-blind efficacy phase. The remaining exposure during the extension phase was to be 96 weeks in duration but was curtailed due to the clinical hold.

EFFICACY RESULTS

There was a consistent improvement in pain with 3mgQ4wk and 10mgQ8wk fulranumab compared with placebo across the primary and secondary efficacy variables with adjunctive pain treatment at the 12-week endpoint and the changes were statistically significant compared with placebo with either LOCF or BOCF analyses. Patient reported outcomes also showed improvement in physical function and sleep for these treatment groups.

There was a consistent pattern of statistically significant improvement compared with placebo for other pain associated measures with 3mgQ4wk and 10mgQ8wk fulranumab (ie, NRS 50% responder rate, WOMAC pain subscale, PGA, BPI-SF pain interference and pain intensity subscales, and SF-36 bodily pain). In addition, there was also an improvement in function between all fulranumab treatment groups compared with placebo on the WOMAC physical function and stiffness subscales. Functional improvement was also shown with 3mgQ4wk and 10mgQ8wk fulranumab on the SF-36 vitality subscale.

An improvement in sleep was shown on the sleep interference measure (3mgQ8wk, 3mgQ4wk, and 10mgQ8wk fulranumab); MOS sleep scales of sleep adequacy and sleep problems index I (all fulrnaumab groups) with improvements in the sleep adequacy, sleep problem index I and II subscales with 3mgQ4wk as early as Week 9; sleep index II (6mgQ8wk and 10mgQ8wk); and sleep shortness of breath or headache in the 3mgQ4wk group. Other related efficacy measures of OMERACT-OARSI responders and rescue medication were consistent with the positive efficacy described above. Similar patterns of statistical significance were observed with the baseline observation carried forward (BOCF) analyses that were indicative of the robustness of the last observation carried forward (LOCF) analysis results.

CLINICAL PHARMACOLOGY RESULTS:

Pharmacokinetics

- Mean trough serum fulranumab concentrations increased in an approximately dose-proportional or slightly greater than dose-proportional manner across the treatment regimens.
- Steady state serum fulranumab concentrations were generally achieved by the Week 17 visit.
- Mean trough serum fulranumab concentrations were generally maintained at steady state through the Week 57 visit.
- There was no evidence of accumulation in serum fulranumab concentrations over time.
- Serum fulranumab concentrations were lower in subjects with higher body weight.

Immunogenicity

- Only 2 (0.5%) subjects developed antibodies to fulranumab through the end of the study. These antibody responses to fulranumab had low titers (≤ 1:160) and did not reduce serum fulranumab concentrations.
- None of the antibodies developed were able to neutralize the biological effects of fulranumab in vitro.

SAFETY RESULTS:

- Fulranumab was well tolerated with a low percentage of subjects who discontinued due to adverse events throughout the study.
- Subjects in the fulranumab group were more likely to report adverse events in the musculoskeletal and connective tissue disorders or nervous system disorders SOCs compared with those in the placebo group. During the combined double-blind treatment phase, the overall percentage of subjects with adverse events was similar among the treatment groups. The most common events were arthralgia, osteoarthritis, pain in extremity, paraesthesia, headache, upper respiratory tract infection, and nasopharyngitis.
- Serious adverse were in a lower percentage of subjects during the double-blind phases compared to the post-treatment phase. This pattern was driven in the post-treatment phase by a greater reporting frequency for joint replacements/arthroplasty during this phase. No deaths occurred.
- There were no clinically relevant changes in laboratory tests, vital signs, or ECGs values among the treatment groups. There was no evidence of glucose intolerance.
- There were no events of clinical interest that were considered related to fulranumab treatment by the IDMC that required stopping treatment for a group or for the study.
- Injection site reactions were mild or moderate.
- There was no evidence of antibody formation that was associated with adverse events.

STUDY LIMITATIONS:

Study drug treatment was terminated after all subjects completed the double-blind efficacy phase and during the double-blind extension phase due to safety concerns of anti-NGF agents.

CONCLUSIONS:

In subjects with moderate to severe chronic pain of osteoarthritis that is not adequately treated with current standard of care, fulranumab at doses of 3mgQ4wk and 10mgQ8wk as adjunctive treatment showed an improvement in pain and pain related assessments during a 12-week double-blind period compared with placebo. In addition, there was also an improvement in physical function and sleep.

Fulranumab was generally well tolerated compared with placebo.

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