**Janssen Research & Development, L.L.C.**

**Advisory Committee Briefing Document**

# Briefing Book for 12 March 2012 Arthritis Advisory Committee Meeting

**JNJ-42160443 (fulranumab)**

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## Abbreviations

| Abbreviation | Description of Abbreviated Term |
|---|---|
| AVN | avascular necrosis |
| BID | twice daily |
| BOCF | baseline observation carried forward |
| CI | confidence interval |
| COMB | combined value |
| DMC | data monitoring committee |
| DMOAD | disease modifying osteoarthritis agents |
| DPN | diabetic painful neuropathy |
| GI | gastrointestinal |
| IA | intra-articular |
| ITT | intent-to-treat |
| JOCO OA | Johnston County Osteoarthritis Project |
| LBP | lower back pain |
| LOCF | last observation carried forward |
| LS | least square |
| MRI | magnetic resonance imaging |
| NGF | nerve growth factor |
| NPSI | Neuropathic Pain Symptom Inventory |
| NRS | numerical rating scale |
| NSAID | nonsteroidal anti-inflammatory drug |
| OA | osteoarthritis |
| OAI | Osteoarthritis Initiative |
| ON | osteonecrosis |
| OARSI | Osteoarthritis Research Society International |
| PGA | Physician Global Assessment |
| PHN | postherpetic neuralgia |
| PTN | post-traumatic/post-surgical neuropathic pain |
| Qxwk | every x weeks |
| RPOA | rapidly progressive osteoarthritis |
| SMQ | Standardized MedDRA Query |
| SOF | Study of Osteoporotic Fractures |
| US | United States |
| WOMAC | Western Ontario and McMaster Universities Arthritis Index |

1. EXECUTIVE SUMMARY

# 1. EXECUTIVE SUMMARY

Chronic pain affects at least 116 million adults in the United States (US), resulting in an annual cost of $560 to $635 billion in direct expenses and lost productivity.[1] Chronic pain often persists after the resolution of the original illness or injury, causing changes in the nervous system that worsen over time. Often the underlying cause cannot be identified and chronic pain becomes a disease in itself. For many patients, treatment of pain is inadequate in part due to the limitations in the availability of effective treatments and inadequate patient and clinician knowledge about the best ways to manage pain.[1]

The osteoarthritis (OA) population is a large portion of this chronic pain population. The National Arthritis Data Workgroup of the National Institute of Health estimates that there are about 27 million adults with clinical OA.[2] First-line treatments (eg, nonsteroidal anti-inflammatory drugs [NSAIDs] or acetaminophen) do not always provide sufficient efficacy and are contraindicated in some patients. Patients with moderate to severe pain and functional impairment due to OA who are not sufficiently treated by first-line analgesics have limited treatment options. Currently available second-line treatment options are limited by efficacy and safety/tolerability issues. Opioids are often used as second-line pain therapy in patients with moderate to severe pain due to OA; however, opioids have modest efficacy, particularly regarding functional improvement and are associated with poor tolerability and the possibility of abuse.[3,4,5] These limitations result in the reluctance of physicians to prescribe opioids and the frequent lack of patient acceptance of treatment, which limit the use of opioids as a long-term analgesic option. Intra-articular (IA) therapies (corticosteroids, hyaluronic acid) also have limited efficacy and are associated with a risk of infection and other complications.[6,7]

**Fulranumab Clinical Studies**

Fulranumab, a novel anti-nerve growth factor (anti-NGF) monoclonal antibody drug, is being studied for the treatment of moderate to severe chronic pain when injected subcutaneously.

To date, 9 clinical studies of fulranumab have been initiated, including 2 Phase 1/1b studies and 7 Phase 2 studies. The 2 Phase 1/1b studies include a single-dose, dose escalation study in healthy subjects and a multiple-dose, dose-escalation study in subjects with OA knee pain. The 7 Phase 2 studies enrolled subjects with various pain conditions, including cancer-related pain (PAI-2001), OA pain (PAI-2004 Add-on; PAI-2006 Monotherapy), lower back pain (LBP; PAI-2003), post-herpetic neuralgia and post-traumatic/post-surgical neuropathic pain (PHN/PTN; NPP-2001), diabetic neuropathy (NPP-2002), and interstitial cystitis (PAI-2005).

Efficacy Data:

Two studies (PAI-2004 OA Add-on and PAI-2006 OA Monotherapy) provide the most useful information to date on the efficacy and safety of fulranumab in subjects with OA pain. The available data from these clinical studies suggest that fulranumab may provide clinically meaningful efficacy for improvement in pain and functional impairment when used in addition to a standard of care including first-line analgesics and/or opioids (PAI-2004 OA Add-on). The maximum effect of fulranumab in reducing OA pain has been observed with an intermediate dose (3mg every 4 weeks [3mgQ4wk]) in the dose range tested. A further dose increase does not appear to provide greater efficacy in subjects with OA pain (PAI-2004 OA Add-on). In the OA monotherapy study (PAI-2006), there was a high placebo effect, and neither fulranumab dose (3mgQ4wk nor 9mgQ4wk) demonstrated greater efficacy compared to placebo. However, a comparison against oxycodone CR in this study demonstrated that fulranumab had a greater effect in reducing pain and improving functional impairment compared to oxycodone CR in patients with moderate to severe OA pain. Fulranumab demonstrated clinically meaningful efficacy for improvement in pain and functional impairment in subjects with moderate to severe pain due to DPN whose pain was not sufficiently treated with standard of care (NPP-2002 DPN).

Safety and Tolerability:

Fulranumab was well tolerated in subjects with moderate to severe OA pain (PAI 2004 and PAI-2006) and in subjects with non-OA pain conditions, including moderate to severe pain due to DPN (NPP-2002), whose pain was not sufficiently treated with standard of care. The direct comparison against oxycodone CR in PAI-2006 (OA Monotherapy) demonstrated that fulranumab was better tolerated compared to oxycodone CR in subjects with moderate to severe OA pain. In historical comparisons with published data, fulranumab showed better tolerability compared to opioids, in particular, lower rates in gastrointestinal (GI) adverse events and better completion rates, which may improve compliance.[3] Recognizing the limitations of unadjusted cross-study comparisons, results from the historical comparison are similar to the findings in PAI-2006 (OA Monotherapy).

**AVN and RPOA**

Avascular necrosis (AVN) and rapidly progressive osteoarthritis (RPOA) were identified as specific safety concerns by the FDA in clinical studies of anti-NGF monoclonal antibodies and were initially detected in subjects who underwent joint replacement surgery. AVN involves extensive necrosis with a vascular etiology. In the clinical environment, the term osteonecrosis (ON) is sometimes used as a diagnostic term

interchangeably with AVN. ON is also used to describe histological findings of bone death from any cause. A focal pathological finding of osteonecrotic bone is not an uncommon finding in patients with severe OA and is distinct from AVN. To further investigate this occurrence, a thorough evaluation of the nonclinical safety data for fulranumab has been conducted. Bone and cartilage have not been identified as targets of fulranumab toxicity in the nonclinical safety data and, therefore, from these data, no link between fulranumab and ON can be established at this time. An evaluation of the clinical database for fulranumab was also undertaken.

RPOA is part of the spectrum of OA progression and can occur in the absence of anti-NGF drugs. In a subset of patients, OA progresses at a much faster rate, with marked joint space narrowing (eg, >2 mm per year) with and without osteolysis occurring in less than 1 to 2 years.[8,9,10,11,12] The incidence rate of RPOA in the general OA population has not been well described in the literature. In multiple retrospective case studies of patients with OA undergoing joint replacement surgery, RPOA has been frequently seen (1.9% to 18.2%).[13,14,15] Factors that have been suggested as associated with an increase risk of RPOA include advanced age, excess motor activity/heavy labor, obesity, female gender, minimal osteophyte formation, and NSAID use.[9,14,16,17]

**Joint Replacements in Fulranumab Clinical Studies**

As of 08 July 2011, 88 of 1,353 subjects treated in the 9 Phase 1/1b and Phase 2 studies of fulranumab had at least 1 joint replacement. Of the 1,353 subjects, 983 were treated with fulranumab, 303 with placebo, and 50 with oxycodone CR; treatment assignments remain blinded for 17 subjects in the cancer-related pain study (PAI-2001). Differences in the number of subjects randomized to each treatment group reflect asymmetric randomization ratios and differences in the study designs. Of the 88 subjects with joint replacement, there were 76 subjects treated with fulranumab, 11 with placebo, and 1 with oxycodone CR.

Most (75/88) of the subjects with joint replacement(s) were treated in studies in subjects with moderate to severe OA pain (2006145; PAI-2004, and PAI-2006). In PAI-2004 (OA Add-on), the study contributing most of the joint replacements, the incidence rate was 139 per 1000 person-years with fulranumab treatment (all dose groups combined) and 98 per 1000 person-years with placebo treatment.

In the fulranumab program, joint replacements occurred both on treatment and after study drug was discontinued. Further investigation is required to understand the rate of occurrence of joint replacement in relation to fulranumab treatment. The abrupt cessation of treatment due to the clinical hold makes interpretation of the current data difficult.

Possible explanations for the occurrence of joint replacements after the discontinuation of treatment include: 1) subjects deferred joint replacement surgery while on therapy due to adequate pain relief; 2) subjects had resumption of pain following discontinuation of fulranumab therapy and sought joint replacement; and 3) subjects had joint deterioration during study therapy, which resulted in joint replacement after the cessation of study therapy. Monitoring of joint replacement in a setting of ongoing treatment in future fulranumab studies will be conducted to provide more definitive information.

**Adjudication of Joint Replacements and Significant Joint-Related AEs in Fulranumab Clinical Studies**

All joint replacement cases and significant joint-related AEs (ie, AEs possibly related to joint destruction in subjects who did not have joint replacement) in the fulranumab studies reported as of 08 July 2011 were adjudicated by a panel of independent clinical experts (orthopedic surgeons, rheumatologists, and a radiologist) who have clinical experience in the diagnosis and management of patients with ON or RPOA. The experts used agreed upon criteria for the diagnosis of ON and RPOA and were blinded to randomized treatment assignment. The purpose of the adjudication was to determine if any joint replacement cases represented ON or RPOA**.** None of the cases were adjudicated as primary ON. All 17 joint replacement cases initially reported as ON were adjudicated as being consistent with RPOA (9 joints), normal progression of OA (7 joints), or insufficient information for a diagnosis (1 joint). One additional case initially reported as ON was adjudicated as normal progression of OA; joint replacement information was received after the case was adjudicated.

A safety signal for RPOA, identified as an event of concern by the FDA in the clinical hold letter, was detected in 18 joint replacements in 17 subjects. In PAI-2004 (Add-on OA), 15 (involving 16 joints) of 388 subjects treated with fulranumab had RPOA (3.9%; 95% confidence interval [CI], 2.2%-6.3%) compared with none of the 78 subjects in the placebo group 95% CI, 0-3.7%). In each of 2 non-OA pain studies, NPP-2001 (PHN/PTN) and PAI-2003 (LBP), 1 subject in the fulranumab group and no subjects in the placebo group had RPOA. Due to the small number of RPOA cases per treatment group, a dose effect for RPOA cannot be evaluated.

All joints diagnosed with RPOA in the fulranumab clinical studies occurred in subjects for whom a history of OA could be documented by radiographic image and/or symptomatology. Since OA studies only documented the presence of OA in an index joint (a hip or knee) and non-OA pain studies did not document the presence of OA in any joint at study entry, ascertainment of the complete OA history of subjects in the replaced joints was done retrospectively after the FDA notified the sponsor of the safety

concern. Subjects in the fulranumab OA studies who developed RPOA appeared to have somewhat higher baseline pain scores compared with joint replacement subjects without RPOA or non-joint replacement subjects.

**Risk Management for Future Fulranumab Studies in OA**

All but one joint diagnosed with RPOA in the fulranumab program occurred in subjects who were receiving a combination of NSAIDs and fulranumab. Based upon the available data from studies of another anti-NGF antibody (tanezumab), the sponsor proposes to limit concomitant chronic NSAID use in future fulranumab studies.

At present, there is insufficient evidence in the fulranumab clinical studies to determine whether RPOA is a dose-related phenomenon. In future fulranumab studies, doses will be selected based on the efficacy and tolerability profile.

The sponsor proposes to institute 2 new modifications in future fulranumab clinical studies in OA pain to lower the incidence of RPOA. Based upon findings from tanezumab trials and corroborated in the fulranumab data, it is expected that prohibiting concomitant chronic NSAID use and excluding higher fulranumab doses (6 mg and 10 mg) in future OA trials will substantially reduce the incidence of RPOA.

In order to assess the effectiveness of these measures and to detect a safety signal early in the study, the sponsor proposes to monitor joint safety by establishing measures to identify cases of RPOA (utilizing surveillance with standardized X-rays at predefined intervals as well as additional X-rays for joint-related AEs; establishing an independent adjudication committee to evaluate and render a diagnosis for all joint replacements and other joint-related AEs in a blinded fashion, and establishing an independent DMC to assess joint safety in an unblinded fashion). Depending upon findings, individual cases may be identified for additional follow-up; potentially resulting in earlier recognition of RPOA and allowing earlier and potentially less complex joint replacement surgery. An independent, unblinded DMC will monitor the cumulative benefit/risk profile of fulranumab and advise the sponsor of safety issues that may necessitate the termination of specific treatment groups in studies or termination of studies.

Based on the current clinical data, literature review, and results of the adjudication of joint replacement cases, the sponsor proposes that the risk management strategy will address the FDA's safety concerns and appropriately manage risk in further studies. As such, the potential benefits of fulranumab for treating pain in patients who may not have an alternative analgesic treatment option or for whom alternative treatments carry substantial risks (see Section 3), warrant the continued development of fulranumab to

further characterize its benefit-risk ratio in the treatment of OA pain and other chronic pain conditions. Additionally, fulranumab may provide potential benefits for improving functional impairment in patients with OA pain and may potentially delay or prevent joint replacement in some patients.

# 2. REGULATORY HISTORY

## 2. REGULATORY HISTORY

On 23 December 2010, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP), in a teleconference communicated to Johnson & Johnson Pharmaceutical Research & Development L.L.C (now Janssen Research and Development, L.L.C) that all studies being conducted under Investigational New Drug Application (IND) 100,485 for JNJ-42160443 (fulranumab, fully human anti-NGF monoclonal antibody) were being placed on full clinical hold and treatment must be stopped. In a 11 January 2011 written communication, FDA stated that these treatments must be stopped because "…anti-Nerve Growth Factor (anti-NGF) agents such as fulranumab have resulted in unexpected cases of joint destruction presumably due to avascular necrosis (AVN) (and/or) rapidly progressive osteoarthritis (RPOA) at a rate that was inexplicably high compared to what is expected in the population as a whole."

As a first step in lifting the full clinical hold, on 28 March 2011, the sponsor submitted a complete response requesting that the cancer pain protocol, 42160443-PAI-2001: "A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ42160443 as Adjunctive Therapy in Subjects With Cancer-Related Pain, Followed by an Open Label Extension Phase", be allowed to continue and to limit enrollment only to subjects with a limited life expectancy (ie, terminally ill subjects) with cancer-related pain. On 02 May 2011, FDA modified the full clinical hold to a partial clinical hold permitting only study 42160443-PAI-2001 in cancer-related pain to resume.

In addition, FDA informed the sponsor that it would convene an advisory committee meeting to assess the FDA identified risks and determine whether clinical development of the anti-NGF antibody class should continue. The Arthritis Advisory Committee meeting has been scheduled for 12 March 2012, and this briefing book is submitted to address the specific issues identified in the above referenced 23 December 2010 and 11 January 2011 FDA communications, plans for managing the identified risks, and rationale for continued development of fulranumab.

# 3. CURRENT TREATMENT OPTIONS FOR THE MANAGEMENT OF OA PAIN AND FUNCTIONAL IMPAIRMENT AND OTHER CHRONIC PAIN CONDITIONS

## 3.1. Osteoarthritis and the Management of OA Pain and Function Impairment

### Osteoarthritis

OA is a disease of the synovial joint secondary to a process that is attempting to contain a mechanically induced problem in the joint. It is best defined as the failed repair of joint damage that has been caused by excessive or aberrant mechanical stress (defined as force/unit area) on joint tissues.[18]

Because OA is the failure of an organ (the synovial joint), any of the tissues of that organ may be the first to fail – the articular cartilage, subchondral bone, ligaments, menisci (when present), periarticular muscles, peripheral nerves, or synovium. OA should not be considered to be a degenerative disease insofar as the cells of the cartilage and bone are normal and, if the high levels of intra-articular (IA) stress are reduced, can restore the damaged tissue to normal.

Thus, all cases of OA are due fundamentally to abnormal IA stress on the habitually loaded areas of the joint surface. It is not malalignment per se that is the cause of OA; it is the effect of the malalignment in concentrating the stress.

Research has suggested that lowering the abnormal mechanical stress can result in healing of an OA joint.[18,19] Notably, to date, healing or reversal of OA changes in the joint can be brought about only by mechanical means; drugs have not been shown to accomplish healing of OA or to delay progression of structural joint damage.

### Current Treatment Options for the Management of OA Pain and Function Impairment

The Institute of Medicine commissioned the Committee on Advancing Pain Research, Care and Education to assess the impact of pain in the US, the state of the science, and to make recommendations to advance the field.[1] In their report released on 29 June 2011, the committee concluded that "The magnitude of pain suffered by individuals and the associated costs constitute a crisis for America, both human and economic... [and that it] requires a cultural transformation in the way pain is perceived and managed on both the personal and societal levels." The Committee estimated that common chronic pain affects at least 116 million adults in the US, resulting in an annual cost of $560 to $635 billion in direct expenses and lost productivity. This estimate excludes institutionalized individuals (nursing homes, prisons, etc.), military personnel, children under 18 years of age,

personal caregivers, lost productivity of workers <24 and >65 years old, and emotional costs. Additionally, the report states that pain "contributes greatly to national rates of morbidity, mortality, and disability…. and is rising in prevalence."

The OA population is a significant portion of this chronic pain population. The National Arthritis Data Workgroup of the National Institute of Health estimates that there are about 27 million adults with clinical OA.[2] A recent internet survey, using a sample that is representative of the US population, estimates that chronic pain is experienced by about one-third of the population, is increasing with aging, and is most commonly attributed to LBP followed by OA pain.[20] With the surge of active "baby boomers" and consequent increased burden on medical and social services, the number of inadequately treated patients with chronic pain will increase over the next 2 decades.

Patients with moderate to severe pain and functional impairment due to OA have limited treatment options. Current treatment options, including NSAIDs, acetaminophen, and opioids, each have their own limitations. First-line treatment options (eg, NSAIDs, acetaminophen, and aspirin) do not always provide sufficient efficacy and are contraindicated in some patients due to side effects. Currently, available second-line treatment options (ie, opioids) are limited by poor efficacy and by safety/tolerability issues. Benefits associated with the use of opioids as a long-term analgesic option are limited by frequent side effects, including nausea (30%), constipation (23%), dizziness (20%), somnolence (18%), and vomiting (13%).[21] Fulranumab is intended for treating patients with OA pain who are not sufficiently treated with or are intolerant to current treatment options.

Current First-Line Treatment Options

Although first-line therapies are safe and effective for many patients, specific adverse events have been reported with these therapies. NSAIDs are associated with increased risk of clinically significant GI adverse events (eg, GI bleeding) and cardiovascular adverse events (eg, myocardial infarction and hypertension).[22] Results of a recent meta-analysis suggest an increased risk of ischemic stroke with rofecoxib and diclofenac; with a varying effect on the risk of ischemic stroke with other NSAIDs.[23]

Additionally, the long-term efficacy of NSAIDs in some patients is not optimal. In elderly patients, NSAIDs have limited efficacy and are poorly tolerated.[24] NSAIDs have also been associated with increasing the rate of OA progression.[25,26] The maximal efficacy of oral NSAIDs over 1 to 4 weeks reported in a meta-analysis was a "minimal perceptible improvement" against placebo.[24] Long-term NSAID efficacy at the end of a 2-year study showed that only 49% of patients reported they were better, 31% were

worse.[27] The long-term balance of efficacy and tolerability manifested as NSAID discontinuation rates at the end of a 1-year study showed that only 15% to 20% of patients with OA remained on the same NSAID.[28] Long-term use (>6 months) of both selective and non-selective oral NSAIDs is associated with similar elevated risk of gastrointestinal ulcer complications.[29,30]

Concomitant use of aspirin, even at low cardioprotective doses, doubles the incidence of GI bleeding and is an indication for gastroprotective therapy.[31,32]

The efficacy of topical NSAIDs is variable among studies. Topical NSAID therapy has the same safety risks as oral preparations.[33]

Acetaminophen has been associated with hepatotoxicity when used above recommended dosing regimens. Additionally, many patients may be unaware that numerous over the counter medications contain acetaminophen, thus increasing the chance of exceeding recommended daily dosing.[34]

The efficacy of both acetaminophen and NSAIDs for the treatment of moderate to severe OA pain is far from satisfactory whether looking at short- or long-term use. In a recent review of the literature by the Osteoarthritis Research Society International (OARSI) the efficacy of acetaminophen in relieving OA pain was reported, at best, to be similar to that of NSAIDs; however, in many studies, the efficacy of acetaminophen was inferior to that of NSAIDs. In addition, acetaminophen had no significant effect on stiffness or functional impairment in patients with symptomatic knee OA.[33]

Current Second and Third-Line Treatment Options

The efficacy of opioids for the treatment of OA pain is variable with some data showing that only strong opioids were significantly more effective than acetaminophen or NSAIDs.[33] Additionally, opioids do not show robust efficacy in terms of improving functional activity.[4] Opioid-related side effects particularly GI and central nervous system side effects are common, especially in the initial weeks of treatment, and have been reported to lead to cessation of therapy in 1 of 12 patients in the community setting[5] and up to 67% treatment discontinuation in controlled clinical trials.[3] Opioid tolerance can also reduce the efficacy of chronic opioid use when dose strength is reduced in an effort to make side effects more tolerable. Likewise opioid dependency and addiction are additional risks of chronic opioid use. Thus, despite its increasing use to treat chronic OA pain, chronic opioid use carries multiple risks.

Surveys of OA patients awaiting joint replacement surgery show a significant number of patients are not on any medications, most likely due to poor efficacy or, more importantly, poor tolerability of current treatment options.[35,36]

Other Treatment Options

As many patients are not satisfied with current pharmacological analgesic therapies due to lack of efficacy and/or poor tolerability, a number of them undergo more invasive treatment options or resort to alternative therapies with limited efficacy. The options prior to joint replacement surgery are limited.

Invasive treatment options such as IA injections of steroids or hyaluronic acid have limited efficacy and can be associated with safety concerns. The efficacy of IA hyaluronic acid injections to relieve hip OA pain has been reported to be no better than placebo.[6] Data on IA hyaluronic acid injections for painful knee OA are contradictory.[37,38] Additionally, reports of post-injection "pain flares" after IA hyaluronic acid injection have been reported to be as high as 27%.[7]

Intra-articular steroid injection for treatment of knee pain secondary to OA shows efficacy for only 1 week compared to placebo in a systematic review of prospective randomized control trials, but appears to be safe with no instances of infection or acute flares reported in a 2-year placebo-controlled study of every 3-month IA injections.[39,40] However, another publication looking at joint sepsis after knee injection reports incidences ranging from 1 in 3,000 to 1 in 5,000.[41] Data regarding complications of IA hip injection are not as thorough. Case reports of septic hip[42,43] and hip ON occurring after a single or multiple IA steroid injections[44] have been reported.[45]

Nonpharmacologic measures aimed at unloading the OA joint have been shown to be effective in patients with OA pain. These include education of the patient in the principles of joint protection, weight reduction in obese or overweight patients, strengthening of periarticular muscles, proper footwear, and the use of orthotics, a cane or a brace.[33]

Other therapies used by OA patients, such as glucosamine sulphate, chondroitin sulphate or topical agents, are largely ineffective or provide only short-term pain relief.[24]

### 3.2. Management of Other Chronic Pain Conditions

Currently available treatments have limited effectiveness for most people with severe chronic pain.[1] Analgesic treatment options (eg, acetaminophen, NSAIDs, corticosteroids, and opioids) for chronic pain conditions (ie, neuropathic, interstitial cystitis, cancer, and

low back pain) are limited by poor tolerability and less than optimal efficacy (see Section 3.1).

Neuropathic pain is estimated to afflict millions of people worldwide, with DPN being one of the most common types of neuropathic pain. Although several novel analgesic drugs have recently become available, the pharmacologic treatment of painful diabetic neuropathy remains an unmet medical need. It has been shown that the majority of patients with DPN achieve incomplete pain relief with currently available therapies.[46,47,48] In addition, individual tolerability remains a major challenge for treatment[49]; because DPN patients often have multiple co-morbidities, treatment is limited by the risk of potential adverse effects, possible drug interactions, and contraindications.[50]

# 4. NONCLINICAL PROGRAM

Fulranumab has been extensively evaluated in repeat dose toxicology studies up to 6 months in duration. The cynomolgus monkey was selected for these assessments as this species has been shown to be pharmacologically relevant, a requirement for biopharmaceutical toxicology testing in animals. Fulranumab is not pharmacologically active in rodents. Following chronic repeat, high dose subcutaneous or intravenous administration in normal healthy monkeys, no adverse effects were observed in the 6-week, 13-week or 26-week repeat-dose studies at the highest dosages tested (no-observed-adverse-effect-level 100, 150 and 150 mg/kg/week, respectively). High exposures to fulranumab were achieved in these studies relative to clinical exposure at 10 mg every 4 weeks (>2000 x human maximum plasma concentration and area under the curve. Assessments in these studies included histopathology evaluation of bone (rib) and femur (articular surface of the distal end). No evidence of bone or cartilage related toxicity was observed in these studies. No animal models of OA have been conducted with fulranumab because these models are in rodent species and fulranumab is not pharmacologically active in rodents. Although a great deal of research has been conducted on the biological effects of NGF, a clear link between NGF reduction/inhibition and ON or RPOA has not been reported in the published literature and therefore, the role of NGF, if any, in ON or RPOA is unknown.

An embryo-fetal development/pre-postnatal development study is ongoing with fulranumab. In this study, pregnant cynomolgus monkeys were subcutaneously dosed with 10 or 50 mg/kg/week starting on gestation Day 20. The pregnant dams in each dosage group were divided into 2 subgroups with some fetuses obtained by Cesarean section at gestation Days 140 to143 for direct evaluation of teratogenic potential and the second group allowed to proceed to natural delivery; offspring were necropsied at approximately 12 months of age. Neurohistopathology evaluation indicates an effect on the developing nervous system in fetuses and offspring. Further characterization is in progress. Additionally, 2 offspring in each dosage group where mothers were administered fulranumab, but not in the vehicle control group, experienced bone fractures. A relationship to in utero exposure to fulranumab cannot be excluded and therefore, this represents a potential developmental effect of in utero exposure to fulranumab. No bone fractures were observed in the pregnant mothers or in any young or adult monkeys dosed in other toxicology study with similar or higher dose levels of fulranumab. Therefore, these findings are considered to represent potential developmental effects related to in utero exposure to fulranumab and not related to direct toxicity in adult.

The in-life portion of a 15-week toxicology study to evaluate the potential effects of fulranumab on fertility in adult cynomolgus monkeys has completed and the histopathology evaluation is in progress. Monkeys in this study were dosed subcutaneously at 0, 10 or 50 mg/kg/week. Besides the fertility assessments, an evaluation of bone and cartilage was included in this study. The right knee of all monkeys on study were taken at necropsy and evaluated histologically. Bone, articular and growth plate cartilage, bone marrow, joint capsule and synovial membrane of both femur and tibia have been examined. No abnormal histopathological findings on bone or cartilage in adult cynomolgus monkeys were observed following 15 weeks of treatment with fulranumab.

## 5. CLINICAL PROGRAM

Fulranumab (JNJ-42160443) is a fully human, recombinant, monoclonal antibody (IgG2) with a specific capacity to neutralize the biologic actions of human NGF. Nerve growth factor plays an important role in the generation of pain and hyperalgesia in several acute and chronic pain states,[51] and anti-NGF therapy was associated with significant improvement in chronic pain in OA.[52] Therefore, anti-NGF therapy may be effective in the treatment of pain resulting from chronic OA as well as other chronic pain states.

Fulranumab is being developed for subjects with moderate to severe chronic pain. To date, 9 clinical studies of fulranumab have been initiated, including 2 Phase 1/1b studies and 7 Phase 2 studies. Study 20040195 was a Phase 1 single-dose, dose escalation study with IV and SC administration in healthy subjects, and Study 20060145 was a Phase 1b multiple-dose, dose-escalation study using subcutaneous administration in subjects with OA knee pain. Both studies had been completed at the time of the clinical hold. The 7 Phase 2 studies enrolled subjects with various pain conditions, including cancer-related pain (PAI-2001), OA pain (PAI-2004 OA Add-on, PAI-2006 Monotherapy), LBP (PAI-2003), PHN/PTN (NPP-2001), DPN (NPP-2002), and interstitial cystitis (PAI-2005) and have a 12- to 16-week, double-blind efficacy phase, except the cancer-related pain study. Studies PAI-2003, PAI-2004, NPP-2001, and NPP-2002 also have 1- to 2-year, double-blind extension phases to examine long-term safety of fulranumab. In 2 of these studies (NPP-2001 and NPP-2002), the double-blind extension phase is followed by a 1-year, open-label safety extension phase. Study PAI-2001 (cancer-related pain) has a 4-week double-blind efficacy phase followed by an open-label extension phase, and 12-week follow-up phase. The remaining studies (PAI-2005 and PAI-2006) do not have extension phases. All Phase 2 studies, with the exception of PAI-2001 (cancer-related pain), have a 26-week post-treatment phase. All Phase 2 studies were ongoing at the time of the clinical hold. All Phase 2 studies ongoing at the time of the clinical hold have been terminated with the exception of PAI-2001 (cancer-related pain). A summary of the study designs for the 9 clinical studies is provided in Attachment 1.

At the time of the full clinical hold, the double-blind efficacy phases in 2 studies, PAI-2004 (OA Add-on) and PAI-2003 (LBP), had been completed. In both studies, fulranumab or placebo was added to the current analgesic treatment regimen in subjects not adequately treated by standard of care, including first-line analgesics and/or opioids. All dosing in PAI-2003 (LBP) was stopped by the sponsor in November 2010 due to lack of efficacy at the dose of fulranumab investigated. In addition, approximately two-thirds of the 300 subjects planned for PAI-2006 (OA Monotherapy) were enrolled and only

96 of these subjects were randomized early enough to have completed the first 12 weeks of the double-blind efficacy phase. The analysis of study results for PAI-2006 was performed, as planned in the amended protocol, on the data collected as of 28 December 2010.

Two studies (PAI-2004 OA Add-on and PAI-2006 OA Monotherapy) provide the most useful information to date on the efficacy and safety of fulranumab in subjects with OA pain. The results from the Phase 2 studies are described in further detail below.

A cut-off date of 08 July 2011 was chosen for the discussion of joint replacement cases in the fulranumab clinical studies as this date corresponds with the cut–off date for the analysis of adjudicated joint replacements cases in Section 5.6.

## 5.1. Exposure

At the time of the full clinical hold (23 December 2010), 1,353 subjects had been treated in 9 clinical studies. A total of 983 subjects were treated with fulranumab in 2 completed Phase 1/1b (20040195 [healthy subjects], 20060145 [OA]) and 6 terminated Phase 2 studies (PAI-2004 [OA Add-on], PAI-2003 [LBP], and PAI-2006 [OA Monotherapy], PAI-2005 [interstitial cystitis], NPP-2001 [PHN/PTN], and NPP-2002 [DPN]). In one ongoing Phase 2 study (PAI-2001; cancer pain) data remain blinded. As per protocol, all subjects were to be followed for 6 months after the last dose of study drug. The 6-month follow-up phase was completed in all studies as of July 2011.

The fulranumab Phase 2 clinical studies varied in the duration of exposure and observation time, study design (add-on and monotherapy), and subject populations (OA pain and non-OA pain). The exposure and observation times for each study are presented in Table 1. The exposure time for each subject was defined as the number of days between the first dose to the last dose (exposure time (days) = last dose date – first dose date + 1), and the observation time for each subject was defined as the number of days between the first dose to the last study visit (observation time (days) = last study visit date – first dose date +1). Observation time includes time that subjects were both on and off treatment. The total person-years of exposure (or observation) were calculated as the total days of exposure (or observation) for all subjects divided by 365.25.

Among the Phase 2 studies, PAI-2004 (OA Add-on) provides the greatest duration of fulranumab exposure (276.4 person-years; average exposure for each subject of 260 days or 8.7 months) in subjects with OA pain. The durations of exposure and observation were longer in PAI-2004 than in PAI-2006. The duration of observation was 454.5 person-years (average observation for each subject of 427.9 days or 1.2 years) in

PAI-2004 (OA Add-on) vs 52.6 person-years (average exposure for each subject of 196.1 days or 0.5 years) in PAI-2006. These 2 studies provide the most useful information on the use of fulranumab in subjects with OA pain.

**Table 1:** Exposure and Observation Time in the 6 Phase 2 Fulranumab Studies

| | Placebo | | | Fulranumab | | |
|---|---|---|---|---|---|---|
| | N | Exposure Years[a] | Observation Years[b] | N | Exposure Years[a] | Observation Years[b] |
| **OA Pain Studies** | | | | | | |
| PAI-2004 (OA Add-on) | 78 | 47.2 | 81.8 | 388 | 276.4 | 454.5 |
| PAI-2006 (OA Monotherapy)[c] | 48 | 12.2 | 27.8 | 98 | 24.3 | 52.6 |
| **Non-OA Pain Studies[d]** | | | | | | |
| PAI-2003 (LBP) | 76 | 43.3 | 75 | 309 | 183 | 311.4 |
| PAI-2005 (Interstitial bladder) | 17 | 2.4 | 9.3 | 14 | 1.8 | 8.2 |
| NPP-2002 (DPN) | 24 | 8.2 | 20.4 | 53 | 22 | 46.2 |
| NPP-2001 (PHN/PTN) | 42 | 14.7 | 31.7 | 69 | 25.9 | 54.1 |
| **Total** | 285 | 128.1 | 246.1 | 931 | 533.3 | 927 |

DPN=diabetic painful neuropathy; LBP=low back pain; OA=osteoarthritis; PHN/PTN=post-herpetic neuralgia and post traumatic/post-surgical neuropathic pain.

[a] Exposure Years = the time from the first dose to the last dose.

[b] Observation Years = the time from the first dose to the end of the study, including post-treatment phases.

[c] For 50 subjects treated with oxycodone CR in PAI-2006, the exposure and observation times were 8.7 exposure years and 25.1 observation years.

[d] Treatment assignments remain blinded in the ongoing study in cancer-related pain (PAI-2001); therefore data for PAI-2001 are not included in this table.

The duration of observation in PAI-2004 (OA Add-on) was calculated from the date of the first dose to the date of the last disposition record or 08 July 2011, whichever occurred later) (Table 2). As of 08 July 2011, the duration of observation was longer in the fulranumab dose groups (88.0 to 95.8 person-years) than in the placebo group (81.9 person-years).

**Table 2:** Duration of Observation in PAI-2004 (OA Add-on) as of 08July 2011, Approximately 6 Months After Clinical Hold

| | Placebo (N=78) | Fulranumab 1mgQ4wk (N=77) | Fulranumab 3mgQ8wk (N=76) | Fulranumab 3mgQ4wk (N=79) | Fulranumab 6mgQ8wk (N=78) | Fulranumab 10mgQ8wk (N=78) |
|---|---|---|---|---|---|---|
| **Observation days[a] (as of 08 July 2011)** | | | | | | |
| N | 78 | 77 | 76 | 79 | 78 | 78 |
| Mean | 383.7 | 454.6 | 433.8 | 434.7 | 413.0 | 411.9 |
| SD | 161.79 | 128.74 | 125.59 | 131.58 | 133.27 | 141.35 |
| Median | 460.0 | 488.0 | 483.5 | 484.0 | 463.5 | 452.0 |
| Minimum | 29 | 51 | 100 | 85 | 51 | 31 |
| Maximum | 640 | 646 | 603 | 627 | 609 | 625 |
| Total observation (subject years) | 81.9 | 95.8 | 90.3 | 94.0 | 88.2 | 88.0 |

OA=osteoarthritis; Qxwk=every x weeks.

[a] date of the first dose to date of the last disposition record or 08 July 2011, whichever occurred later

The duration of observation was calculated as of 20 January 2011, 28 days after the clinical hold was put in place and a time that reflects when all subjects had not received study drug for at least 28 days (see Section 5.5.1.2 for further discussion). As of 20 January 2011, the duration of observation ranged from 71.5 to 75.4 person-years among the fulranumab dose groups and 66.3 person-years in the placebo group (Table 3). The shorter duration of observation in the placebo group compared with the fulranumab dose groups at both time points (as of 08 July 2011 and 20 January 2011) is consistent with the lower completion rate in the double-blind efficacy phase in the placebo group (86%) compared with the fulranumab dose groups (88% to 94%).

**Table 3:** Duration of Observation in PAI-2004 (OA Add-on) as of 20 January 2011, 28 Days After Clinical Hold

| | Placebo (N=78) | Fulranumab 1mgQ4wk (N=77) | Fulranumab 3mgQ8wk (N=76) | Fulranumab 3mgQ4wk (N=79) | Fulranumab 6mgQ8wk (N=78) | Fulranumab 10mgQ8wk (N=78) |
|---|---|---|---|---|---|---|
| **Observation days[a] (as of 20 Jan 2011)** | | | | | | |
| N | 78 | 77 | 76 | 79 | 78 | 78 |
| Mean | 310.7 | 354.3 | 346.2 | 348.7 | 337.9 | 334.6 |
| SD | 108.06 | 85.71 | 75.75 | 82.33 | 86.69 | 90.28 |
| Median | 337.0 | 357.0 | 350.0 | 350.0 | 353.0 | 345.0 |
| Minimum | 29 | 51 | 100 | 85 | 51 | 31 |
| Maximum | 472 | 477 | 473 | 492 | 477 | 490 |
| Total Observation (subject years) | 66.3 | 74.7 | 72.0 | 75.4 | 72.2 | 71.5 |

OA=osteoarthritis; Qxwk=every x weeks.

[a] date of the first dose to date of the last disposition record or 20 Jan 2011, whichever occurred later

## 5.2. Efficacy Data

### 5.2.1. Fulranumab Studies in OA Pain

The available data from the clinical studies suggest that fulranumab may provide clinically meaningful efficacy for improvement in pain and a reduction in functional impairment in subjects with moderate to severe pain due to OA (PAI-2004 OA Add-on). In the range tested, the maximum effect of fulranumab has been observed with 3mgQ4wk; further dose increase did not appear to provide greater efficacy. Based on historical comparisons with published data, fulranumab showed better efficacy and improved functional impairment compared to opioids.[3] Although there was a high placebo effect in PAI-2006 (OA Monotherapy), the direct comparison against oxycodone CR suggested that fulranumab may have a larger effect size in improving pain and function compared to opioids in subjects with moderate to severe OA pain.

**PAI-2004 (OA Add-on)**

In Study PAI-2004, 466 subjects with moderate to severe, chronic, OA knee or hip pain not adequately controlled by standard pain therapy (n=78 placebo; n=77 fulranumab 1mgQ4wk; n=76 fulranumab 3mgQ8wk; n=79 fulranumab 3mgQ4wk; n=78 fulranumab 6mgQ8wk; n=78 fulranumab 10mgQ8wk) received at least 1 injection of study medication and were included in the intent-to-treat (ITT) analysis set. Among these subjects, 57.5% were women, 85% were white, 32% were taking opioids at baseline, 60% were in the weight group of ≥85 kg, and 77% had knee as the target joint. The median age was 61 years (36% were ≥65 years of age) (Attachment 2). Subjects were required to have a Kellgren-Lawrence score of ≥2. At screening, 43%, 40%, and 17% of subjects had Kellgren-Lawrence scores of 2, 3, and 4, respectively (Attachment 17). The demographic and baseline characteristics were generally balanced across treatment groups. Median average pain scores at baseline based on an 11-point numerical rating scale [NRS] ranged from 6.5 to 7.0 (Attachment 4), and median WOMAC pain scores ranged from 6.1 to 6.5 across the treatment groups (Attachment 5). Most of the subjects (75%) had severe baseline pain (≥6.0) based on the 11-point NRS (Attachment 3). Most of the subjects (85%) were taking NSAIDs prior to and during the study (Attachment 6), and 32% were taking opioids (Attachment 2).

Fulranumab was well tolerated with higher treatment completion rates compared with placebo. Among all randomized subjects, 88% to 94% of fulranumab-treated subjects completed the double-blind efficacy phase compared with 86% on placebo (Attachment 7). Most subjects (82% to 90% in the fulranumab dose groups and 76% in the placebo group) received 4 injections of study drug during the first 16 weeks of the study. The most common reasons for treatment discontinuation were lack of efficacy

(5%) and subject withdrew consent (6%) among placebo-treated subjects and other reasons and subject withdrew consent (each 3%) among fulranumab-treated subjects.

The primary efficacy endpoint was the change from baseline in the average pain score based on an 11-point NRS in the last recorded 7 days of the 12-week double-blind efficacy phase. The primary analysis set for efficacy was an intent-to-treat analysis set (all randomized subjects with at least one injection).

The maximum effect was observed with an intermediate dose (3mgQ4wk). There were statistically significantly greater pain reductions based on the NRS scores in the fulranumab 3mgQ4wk (-1.3), 6mgQ8wk (-0.8), and 10mgQ8wk (-0.8) treatment groups compared to placebo at Week 12 using a last observation carried forward (LOCF) endpoint (Table 4). Results of a sensitivity analysis based on the baseline observation carried forward (BOCF) imputation method were consistent with the primary LOCF analysis. Similar findings were observed for the change from baseline in the Patient Global Assessment (PGA). All but the lowest fulranumab treatment group (1mgQ4wk) were statistically significantly better than placebo in reducing pain based on the Western Ontario and McMaster Universities Arthritis Index (WOMAC) subscale of pain, and all fulranumab treatment groups were statistically significantly better than placebo in improving physical function and stiffness based on the respective WOMAC subscales.

Results for the NRS pain scores at Week 12 and Week 16 and WOMAC pain and function subscale scores at Week 12 are provided in Attachment 4, Attachment 5, and Attachment 8, respectively. Results of PGA at Week 12 are provided in Attachment 9.

**Table 4:** Change From Baseline to the End of Double-Blind Efficacy Phase in the Average Pain Intensity, WOMAC, and Patient Global Assessment – Intent-to-Treat Analysis Set (PAI-2004 OA Add-on)

| | Fulranumab 1mgQ4wk (n=77) | Fulranumab 3mgQ8wk (n=76) | Fulranumab 3mgQ4wk (n=79) | Fulranumab 6mgQ8wk (n=78) | Fulranumab 10mgQ8wk (n=78) |
|---|---|---|---|---|---|
| **Week 12 LOCF** | | | | | |
| **Average Pain Score (11-point NRS)** | | | | | |
| Baseline Mean (SD) | 6.9 (1.49) | 6.7 (1.19) | 6.6 (1.07) | 6.8 (1.08) | 6.9 (1.14) |
| Change from Baseline | | | | | |
| LS Mean (SE) vs placebo | -0.5 (0.36) | -0.6 (0.36) | -1.3 (0.36) | -0.8 (0.36) | -0.8 (0.36) |
| p-value[a,b] | 0.133 | 0.108 | <0.001 | 0.030 | 0.030 |
| **WOMAC Subscale of Pain** | | | | | |
| Baseline Mean (SD) | 6.3 (1.84) | 6.4 (1.46) | 6.1 (1.48) | 6.3 (1.58) | 6.4 (1.42) |
| Change from Baseline | | | | | |
| LS Mean (SE) vs placebo | -0.5 (0.36) | -0.8 (0.36) | -1.2 (0.36) | -0.8 (0.36) | -0.9 (0.36) |
| p-value[a] | 0.175 | 0.020 | <0.001 | 0.034 | 0.013 |
| **WOMAC Subscale of Physical Function** | | | | | |
| Baseline Mean (SD) | 6.2 (2.02) | 6.5 (1.35) | 6.2 (1.58) | 6.2 (1.77) | 6.4 (1.51) |
| Change from Baseline | | | | | |
| LS Mean (SE) vs placebo | -0.7 (0.36) | -0.9 (0.36) | -1.3 (0.36) | -0.8 (0.36) | -1.3 (0.36) |
| p-value[a] | 0.048 | 0.009 | <0.001 | 0.019 | <0.001 |
| **Patient Global Assessment** | | | | | |
| Baseline Mean (SD) | 6.9 (1.82) | 6.9 (1.41) | 6.8 (1.29) | 7.0 (1.33) | 7.1 (1.42) |
| Change from Baseline | | | | | |
| LS Mean (SE) vs placebo | -0.3 (0.39) | -0.6 (0.39) | -1.2 (0.39) | -0.8 (0.39) | -0.8 (0.39) |
| p-value[a] | 0.409 | 0.105 | 0.002 | 0.032 | 0.041 |

ANCOVA=analysis of covariance; LOCF=last observation carried forward; NRS=Numerical Rating Scale; Qxwk=every x weeks; SE=standard error; WOMAC=Western Ontario and McMaster Universities Arthritis Index

Negative values indicate lower pain rating scores compared to baseline score

[a] Test for no difference between treatments from ANCOVA model with factor(s) treatment group, baseline score, baseline opioid use (use, non-use), baseline body weight group (<85 kg, ≥85 kg) (type III SS).

[b] unadjusted p-value.

## Comparison of Fulranumab in PAI-2004 with Opioids in Published Literature

A comparison of the WOMAC pain and physical function subscale effect size at Week 12 for fulranumab in Study PAI-2004 (OA Add-on) (Figure 1) and multiple opioids (tapentadol CR 100 to 250 mg twice daily [BID] and oxycodone CR 20 to 50 mg BID) in a randomized, placebo-controlled study with a similar OA population and study design (Figure 2)[3] suggests that fulranumab may be superior to opioids in improving pain and function in patients with OA pain. Subjects in both studies were required to have an average baseline pain intensity score of ≥5 during the 3 days before randomization using an 11-point NRS. In both studies, the majority of subjects were women (58% in PAI-2004 and 59% to 63% in the historical study) and most were white (85% and 72% to 79%, respectively). The mean ages of subjects in the 2 studies were similar (61 years in PAI-2004 and 58 years in the historical study); the majority of subjects in both studies

were younger than 65 years (64% and 72% to 77%, respectively). In both studies, a mixed-model repeated measures analysis was used, and the WOMAC pain and physical function subscales scores were based upon a scale of 0 to 10.

**Figure 1:** Fulranumab LS Mean Difference (SE) Minus Placebo in WOMAC Pain and Function Scores at Week 12 in PAI-2004 (OA Add-on)

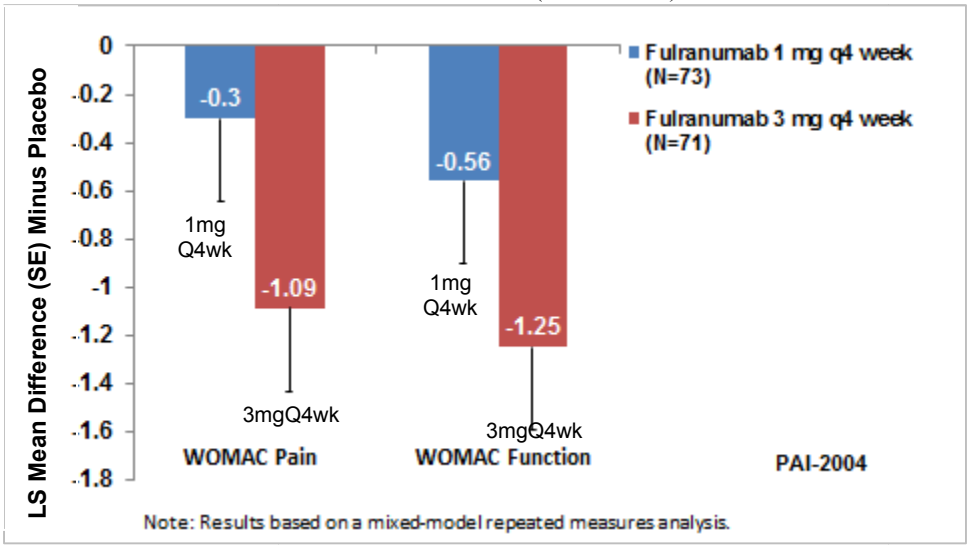
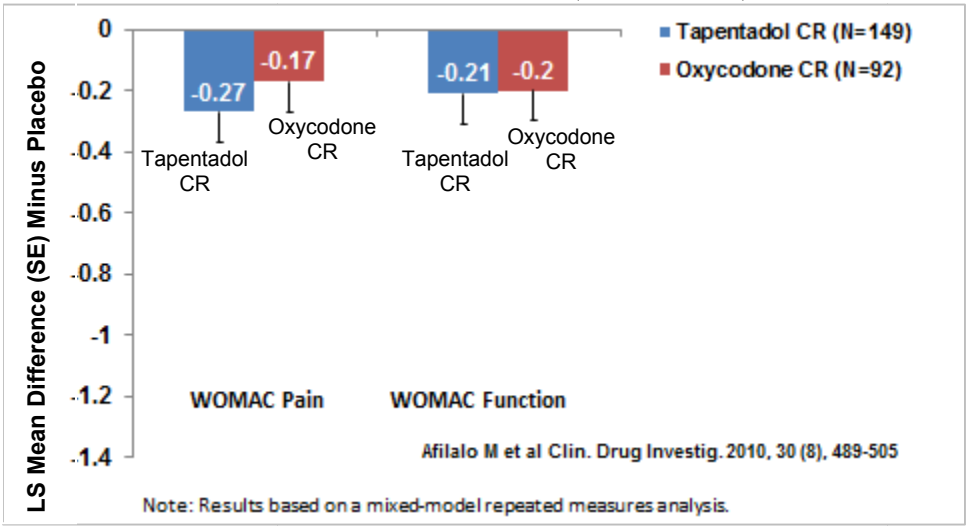



**Figure 2:** Tapentadol CR and Oxycodone CR LS Mean Differences (SE) Minus Placebo in WOMAC Pain and Function Scores at Week 12 (Historical Data)




## PAI-2006 (OA Monotherapy)

PAI-2006 is a monotherapy study, which included washout of all pain medications before baseline and included an active control (oral oxycodone CR 20 to 50 mg BID, controlled individual dose adjustment). In this double-dummy design study, subjects received fulranumab or placebo study drug by subcutaneous injection and placebo or oxycodone CR as oral study drug. The fulranumab doses were selected based on the

results of other fulranumab studies and were within the range of the expected therapeutic dose.

Approximately two-thirds (196) of the 300 subjects planned for this study were enrolled and 96 subjects were randomized early enough to have completed the first 12 weeks of the double-blind efficacy phase before the study drug was stopped due to the clinical hold (Attachment 10). An analysis was conducted on the data available (data cut-off by 28 December 2010).

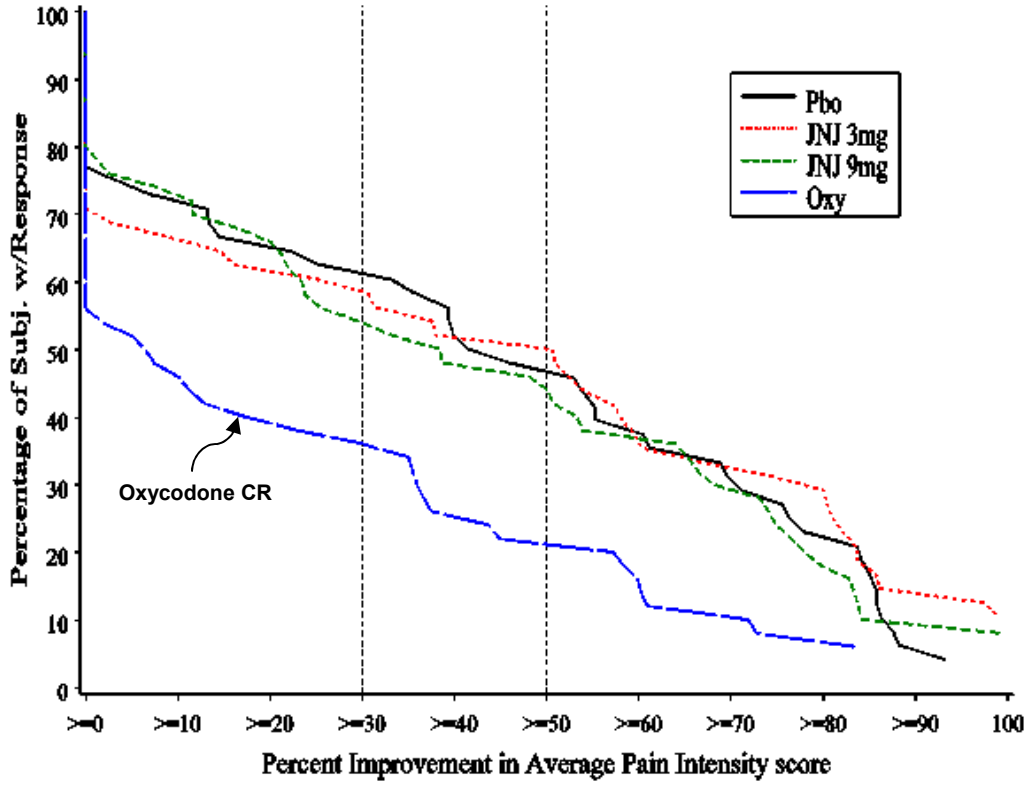
A total of 196 subjects with moderate to severe, chronic knee pain from OA that was not adequately controlled by standard pharmacologic therapy or who could not tolerate standard therapy (n=48 placebo; n=48 fulranumab 3mgQ4wk; n=50 fulranumab 9mgQ4wk; n=50 oral oxycodone CR 20 to 50 mg BID) received at least 1 injection of study drug (fulranumab or placebo) and were included in the ITT population (Attachment 10). Subjects were required to have a Kellgren-Lawrence score of ≥2. Among these subjects, 56% were women and 76% were white. Median age was 58 years (28% were ≥65 years of age). The demographic and baseline characteristics were generally balanced across treatment groups (Attachment 11). Median average pain scores at baseline based on an 11-point NRS ranged from 6.8 to 7.1, and median WOMAC pain scores ranged from 6.8 to 7.0 across the treatment groups.

Among all randomized subjects included in the interim analysis, 39 (20%) subjects had completed the 16-week double-blind treatment phase, 50 (26%) had withdrawn from the double-blind treatment phase, and 107 (55%) were ongoing (Attachment 12). Completion rates for the 16-week double-blind treatment phase were greater for the subjects in fulranumab 3mgQ4wk and 9mgQ4wk groups (25% and 20%, respectively) compared with oxycodone CR (10%), and similar to that for subjects in the placebo group (25%). Fewer subjects in the fulranumab 3mgQ4wk and 9mgQ4wk groups had withdrawn from the study due to lack of efficacy (4% and 0%, respectively) compared with subjects treated with oxycodone CR (6%).

The primary efficacy endpoint for the interim analysis was the responder rate curve based on the percent improvement from baseline to the end of the first 12 weeks of double-blind phase or to 28 December 2010 (whichever was earlier) in the average OA-related pain intensity scores. A modified imputation strategy (pre-specified in statistical analysis plan prior to unblinding) was used for the primary endpoint that incorporated data from all randomized subjects and took into account the impact of censoring due to the clinical hold. Both placebo and fulranumab (at both doses) showed significantly improved pain relief in the responder analysis, compared to oxycodone CR,

but neither dose of fulranumab separated from placebo (Figure 3; Table 5). The high placebo response makes it difficult to determine in this study if fulranumab was efficacious. However, the results demonstrate the limited efficacy (Attachment 13) and poor tolerability of opioids in treating subjects with OA pain relative to placebo or fulranumab.

**Figure 3:** Distribution of Pain Responder Rates at the End of the First 12 Weeks of Double-Blind Efficacy Phase – Intent-to-Treat Analysis (PAI-2006 OA Monotherapy)




Subjects who discontinued were classified as non-responders, i.e. had a response rate of 0.
Placebo N=48, JNJ 3mg N=48, JNJ 9mg N=50, Oxy N=50

**Table 5:** Comparison Versus Oxycodone and Placebo of the Distributions of Pain Responder Rates at the End of the First 12 Weeks of Double-Blind Phase – Logrank - Intent-to-Treat Analysis Set (PAI-2006 OA Monotherapy)

| Time Interval: Week 12 (COMB) Parameter | Placebo | Fulranumab 3mgQ4wk | Fulranumab 9mgQ4wk | Oxycodone CR BID |
|---|---|---|---|---|
| NUMBER OF SUBJECTS | 48 | 48 | 50 | 50 |
| P-value (vs. Placebo) | | 0.7394 | 0.8431 | 0.0021 |
| P-value (vs. Oxycodone CR BID) | | 0.0082 | 0.0122 | |

BID=twice daily; COMB=combined value; CR=controlled release; OA=osteoarthritis; Qxwk=every x weeks
Comparison is based on Logrank test.

### 5.2.2. Fulranumab Studies in Other Chronic Pain Conditions

**NPP-2002 (DPN)**

In Study NPP-2002, 77 subjects with neuropathic pain associated with DPN that was not adequately controlled by standard of care (n=24 placebo; n=16 fulranumab 1mgQ4wk; n=14 fulranumab 3mgQ4wk; n=23 fulranumab 10mgQ4wk) received at least 1 injection of study drug and were included in the ITT analysis set. Among these subjects, 44% were women and 82% were white. The median age was 60 years (30% were ≥65 years of age). Approximately one half of the subjects (51%) were receiving concomitant medication for neuropathic pain at the Screening visit. The demographic and baseline characteristics were generally balanced across treatment groups. There was limited use of NSAIDs not being taken for cardiac prophylaxis in this study (29%).

Fulranumab was well tolerated with higher completion rates compared with placebo; 79% to 87% of fulranumab-treated subjects completed the 12-week double-blind efficacy phase compared with 75% on placebo. Most subjects (75% to 87% in the fulranumab dose groups and 79% in the placebo group) received 3 injections of study drug during the first 12 weeks of the study. The most common reasons for discontinuation from the 12-week double-blind efficacy phase were sponsor discontinued study (17%) among placebo-treated subjects and sponsor discontinued study and lost-to-follow-up (each 4%) among fulranumab-treated subjects.

The primary efficacy endpoint was the mean of the daily evening assessment of average pain intensity based on an 11-point NRS at the end of the 12-week double-blind phase. The primary analysis set for efficacy was an ITT analysis set (all randomized subjects with at least 1 injection). Despite early termination of enrollment, a positive linear dose response in the improvement of pain intensity in response to fulranumab treatment (primary endpoint) was achieved. Although the study was not powered to show pair wise efficacy of any dose versus placebo, the highest dose, 10mgQ4wk demonstrated statistically superior efficacy compared to placebo at the end of the 12-week double-blind efficacy phase on multiple endpoints. The LS mean changes from baseline for the ITT population using the LOCF imputation method were -1.4, -1.3, -2.0, and -2.6 for placebo, 1mgQ4wk, 3mgQ4wk, and 10mgQ4wk groups, respectively. LS mean changes from baseline using the BOCF imputation method were similar (-1.0, -1.3, -2.2, and -2.3 for the placebo, 1mgQ4wk, 3mgQ4wk, and 10mgQ4wk groups, respectively). These mean changes that increase with dose are consistent with the linear dose-response (primary endpoint).

A statistically significant difference in the LS means between the 10mgQ4wk and placebo group was observed with respect to change from baseline in average pain intensity using either the LOCF (p=0.040) or the BOCF imputation method (p=0.027), despite the fact this study was terminated.

The responder rates for subjects with ≥30% improvement were 21%, 44%, 43%, and 61% subjects in the placebo, fulranumab 1mgQ4wk, fulranumab 3mgQ4wk, and fulranumab 10mgQ4wk groups, respectively.

Results from the Neuropathic Pain Symptom Inventory (NPSI) assessment suggested that fulranumab treatment may specifically improve the symptoms of neuropathic pain prominent in the DPN population. A dose response in the LS mean changes from baseline for NPSI scores was observed. Additionally, the analysis of change from baseline in the assessment of the most bothersome symptom from the NPSI showed the greatest improvement in the 10mgQ4wk group.

**NPP-2001 (PHN/PTN)**

In Study NPP-2001, 111 subjects with PHN or PTN received at least 1 injection of study drug and were included in the ITT analysis set (The planned enrollment was 200 subjects). Of the 65 subjects in the PHN population (n=20 placebo; n=13 fulranumab 1mgQ4wk; n=13 fulranumab 3mgQ4wk; n=19 fulranumab 9mgQ4wk), 52% were women, 86% were white, and the median age was 70 years. Of the 46 subjects in the PTN population (n=22 placebo; n=1 fulranumab 3mgQ4wk; n=23 fulranumab 9mgQ4wk), 61% were women, 91% were white, and the median age was 49 years. The demographic and baseline characteristics were generally balanced across treatment groups.

In the PHN population, of the 65 subjects who entered the double-blind efficacy phase, there were 49 (75%) that completed and 16 (25%) who withdrew from this phase. In the PTN population, of the 46 subjects who entered the double-blind efficacy phase, a total of 34 (74%) completed and 12 (26%) subjects withdrew from this phase.

The primary efficacy evaluation was the once-daily average pain intensity assessment over the last 24 hours. The study did not reveal significant efficacy findings on primary or secondary endpoints. The magnitude of effect seen was less than what was anticipated, however, the clinical hold reduced the power significantly, from a per-protocol estimate of ≥74% to detect a dose response to an estimate of ≥39%, with a sample size of approximately 51.

**PAI-2003 (LBP)**

In Study PAI-2003, 385 subjects with moderate to severe, chronic LBP pain not adequately controlled by standard pain therapy (n=76 placebo; n=77 fulranumab 1mgQ4wk; n=77 fulranumab 3mgQ4wk; n=78 fulranumab 6mg loading dose (LD)+3mgQ4wk; n=77 fulranumab 10mgQ4wk) received at least 1 injection of study medication and were included in the ITT population. Among these subjects, 54% were women and 84% were white. Median age was 53 years (18% were ≥65 years of age). The demographic and baseline characteristics were generally balanced across treatment groups.

Among all treated subjects, 85% completed the double-blind efficacy phase. Most subjects (81.6% in the placebo group and 87.1% in the fulranumab group) received 3 injections of study drug.

The primary efficacy endpoint was the change from baseline in the average pain score based on an 11-point NRS in the last recorded 7 days of the 12-week double-blind efficacy phase. There was no statistically significant difference between the fulranumab 10 mg group and the placebo group (p=0.647). According to the step-down method, the procedure was stopped at this comparison with the conclusion that no fulranumab group versus placebo comparison was statistically significant.

**PAI-2005 (Interstitial Cystitis and/or Painful Bladder Symptoms)**

In Study PAI-2005, 31 subjects with interstitial cystitis and/or painful bladder syndrome were enrolled in the study (n=17 placebo and n=14 fulranumab 9mgQ4wk) received at least 1 injection of study drug and were included in the ITT population. Of these subjects, 84% were women, 94% were white, and the median age was 49 years. Among all treated subjects, 24 (77%) completed and 7 (23%) withdrew. No subjects discontinued due to adverse events, as attributed by the investigator. Most subjects (88% in the placebo group and 71% in the fulranumab 9mgQ4wk group) had all 3 planned injections of study drug.

The primary objective of this study was to explore the efficacy of fulranumab compared to placebo using the change from baseline at 12 weeks in the mean of the average pain intensity and to assess the safety and tolerability of this treatment in subjects with moderate to severe chronic pain from interstitial cystitis and/or painful bladder syndrome. Due to the small sample size and termination of the study, no inferential statistical analyses were performed.

The mean decrease in NRS average pain score was comparable in the 2 treatment groups (-1.2 for placebo and -1.4 for fulranumab 9mgQ4wk). Comparable results were observed

for the ITT and per-protocol analysis sets. Fulranumab 9mgQ4wk showed numerically better results than placebo for the Pelvic Pain and Urgency/Frequency Questionnaire total score, Patient Perception of Bladder Condition score, O'Leary-Sant Interstitial Cystitis Symptom Index total score, and Global Response Assessment. However, due to the small sample size attributable to termination of the study, no firm conclusions can be drawn regarding these results.

**Phase 2 Efficacy Conclusions:**

- The available results of the fulranumab studies have suggested clinically meaningful efficacy for improvement in pain and functional impairment in subjects with moderate to severe pain due to OA (PAI-2004 OA Add-on). The maximum effect of fulranumab has been observed with an intermediate dose (3mgQ4wk) in the dose range tested; further dose increase did not appear to provide greater efficacy.
- Opioids are often used as second-line pain therapy in patients with moderate to severe pain due to OA. Based on historical comparisons with published data, fulranumab showed better efficacy and improved functional impairment compared to opioids.[3] Although there was a high placebo effect in PAI-2006 (OA Monotherapy) compared to PAI-2004, the direct comparison against oxycodone CR in PAI-2006 suggested that fulranumab may have a larger effect size in improving pain and function compared to opioids in patients with moderate to severe OA pain.
- Fulranumab demonstrated clinically meaningful efficacy for improvement in pain and functional impairment in subjects with moderate to severe pain due to DPN whose pain was not sufficiently treated with standard of care (NPP-2002 DPN). A positive linear dose response in the improvement of pain intensity at the end of the double-blind efficacy phase in response to fulranumab treatment (the primary endpoint) was observed despite less than full enrollment due to the termination of the study. A statistically significant difference in the LS means between the 10mgQ4wk and placebo groups was attained using both the LOCF and BOCF imputation methods.

## 5.3. Safety and Tolerability Data

### 5.3.1. Fulranumab Studies in OA Pain

Fulranumab was well tolerated based on completion rates in the double-blind efficacy phases. The direct comparison against oxycodone CR in the OA monotherapy study demonstrated that fulranumab was better tolerated compared to oxycodone CR in subjects with moderate to severe OA pain (PAI-2006). Based on historical comparisons with published data, fulranumab showed better tolerability compared to opioids, in particular lower rates in GI adverse events and better completion rates, which may improve compliance.[3] Recognizing the limitations of unadjusted cross-study comparisons, results from the historical comparison are similar to the findings in the PAI-2006 (OA Monotherapy).

**PAI-2004 (OA Add-on)**

All adverse events reported in PAI-2004 as of 08 July 2011 were summarized. This includes all safety data accrued through all study phases. The percentages of subjects with treatment-emergent adverse events (TEAEs) were similar among subjects treated with fulranumab (86% to 95%) and subjects treated with placebo (88%). The most common (>10% of all fulranumab subjects) adverse events for fulranumab-treated subjects were arthralgia (21% versus 15% for placebo), osteoarthritis (18% versus 14% for placebo), paresthesias (13% versus 5%), and upper respiratory tract infections (13% versus 5% for placebo) (Attachment 14).

A search of the clinical database was conducted to identify subjects with TEAEs included in the broad scope of the peripheral neuropathy Standardized MedDRA Query (SMQ). Treatment-emergent adverse events included in the broad scope of the peripheral neuropathy SMQ were reported for 21% for subjects treated with fulranumab and 14% for subjects treated with placebo.

Serious adverse events were reported for 17% of subjects treated with placebo and 25% of subjects treated with fulranumab. Adverse events resulting in study drug discontinuation were reported for 12% of subjects treated with fulranumab and 5% of subjects treated with placebo.

Based on historical comparison with published data, fulranumab showed better tolerability compared to opioids.[3] The study drug discontinuation rate due to TEAEs following fulranumab treatment in PAI-2004 was 12%. This rate of discontinuation was much lower than the discontinuation rates due to TEAEs in placebo-controlled studies of using opioids to treat pain secondary to OA (42.7% reported for oxycodone CR; 27% reported for tramadol ER).[3,53]

**PAI-2006 (OA Monotherapy)**

The percentages of subjects with TEAEs reported as of 08 July 2011 were similar among subjects treated with placebo, fulranumab 9mgQ4wk, and oxycodone CR (80% to 84%) and lower among subjects treated with fulranumab 3mgQ4wk (65%). PAI-2006 was actively enrolling at the time of clinical hold, with subjects in both double-blind efficacy and post-treatment follow-up phases. The most common adverse events for fulranumab-treated subjects (≥10%) were headache (14% versus 10% for placebo) and nasopharyngitis (11% versus 10% for placebo). Gastrointestinal disorders of nausea and constipation, and nervous system disorders of dizziness and somnolence were reported more frequently among subjects treated with oxycodone CR (22% to 32%) than among subjects treated with any dose of fulranumab (5% to 9%).

Serious adverse events were reported for 2% of subjects treated with fulranumab, 4% of subjects treated with placebo, and 4% of subject treated with oxycodone CR.

Fewer subjects in the fulranumab 3mgQ4wk and 9mgQ4wk groups had withdrawn from the study due to adverse events (10% and 0%, respectively) compared with subjects treated with oxycodone CR (24%). A greater proportion of subjects in the oxycodone CR group discontinued treatment because of GI disorders of nausea and vomiting (6% to 10%) compared to subjects treated with fulranumab (0%). In addition, more subjects in the oxycodone CR group discontinued oral treatment because of nervous system disorders of dizziness (4%), somnolence (6%), and fatigue (4%) than subjects treated with fulranumab (0% to 1%).

### 5.3.2. Fulranumab Studies in Other Chronic Pain Conditions

**NPP-2002 (DPN)**

Based on treatment completion rates, fulranumab was well tolerated in subjects with moderate to severe pain due to DPN whose pain was not sufficiently treated with standard of care.

The percentages of subjects with TEAEs during the combined double-blind efficacy and extension phases were similar among subjects treated with fulranumab (81% to 86%) and subjects treated with placebo (75%). The most common TEAEs (≥ 5 fulranumab-treated subjects) were arthralgia (11% versus 13% for placebo), diarrhea (9% versus 8% for placebo), and peripheral edema (11% versus 0% for placebo).

After database lock, findings compatible with Charcot of the foot was assessed for one subject (Subject 500267) with DPN (Attachment 15). The subject received 2 doses of fulranumab 1mgQ4wk. Diabetes is the most common cause of Charcot arthropathy.[54] Radiological changes associated with Charcot neuroosteoarthropathy have been reported in up to 13% of patients with diabetic neuropathy.[54,55]

Serious adverse events were reported for 8 (15%) subjects treated with fulranumab (both doses combined) and no subject in the placebo group. No deaths were reported in the study. Treatment was discontinued for 2 (4%) subjects treated with fulranumab (both doses combined) and no subjects in the placebo group.

There were 9 (17%) subjects in the combined fulranumab group and 2 (8%) subject in the placebo group with at least 1 TEAE that was included in broad scope of the peripheral neuropathy SMQ.

**NPP-2001 (PHN/PTN)**

The overall incidence of AEs and serious adverse events appeared to be similar between treatment groups in PHN and PTN subjects. Because of the small sample sizes and the occurrence of many individual AEs in only 1 or 2 subjects per treatment group, it is difficult to identify treatment effects.

Serious adverse events were reported 11% of fulranumab-treated subjects and 10% of placebo-treated subjects in the PHN cohort and for 13% of fulranumab-treated subjects and 9% of placebo-treated subjects in the PTN cohort. Adverse events resulting in study drug discontinuation were reported for 9% of fulranumab-treated subjects and none of the placebo-treated subjects in the PHN cohort and for 4% of fulranumab-treated subjects and 14% of placebo-treated subjects in the PTN cohort.

**PAI-2003 (LBP)**

The percentage of subjects with TEAEs were higher among subjects treated with fulranumab 3mgQ4wk, 6mgLD+3mgQ4wk and 10mgQ4wk (83% to 90%) than for subjects treated with placebo (76%) or fulranumab 1mgQ4wk (77%). The most common (≥10% of all fulranumab subjects) adverse events for fulranumab-treated subjects were upper respiratory tract infection (15% versus 8% for placebo), back pain (15% versus 16% for placebo), arthralgia (14% versus 12%), pain in extremity (11% versus 8% for placebo), paraesthesia (14% versus 8% for placebo), headache (12% versus 8% for placebo), hypoaesthesia (12% versus 7% for placebo), and diarrhea (12% versus 4% for placebo).

Treatment-emergent adverse events included in the broad scope of the peripheral neuropathy SMQ were reported for 22% of subjects treated with fulranumab and 13% of subjects treated with placebo.

Serious adverse events were reported for 9% of subjects treated with fulranumab and 11% of subjects treated with placebo. Adverse events resulting in study drug discontinuation were reported for 7% of subjects treated with fulranumab and 7% of subjects treated with placebo.

**PAI-2005 (Interstitial Cystitis and/or Painful Bladder Symptoms)**

The most common TEAEs during the double-blind phase reported in the fulranumab 9mgQ4wk group were diarrhea (21% [3/14] vs. 12% [2/17] for placebo), urinary tract infection (14% [2/14] vs. 12% [2/17] for placebo), and carpal tunnel syndrome (14% [2/14] vs. 0% for placebo). One serious adverse event (kidney infection) occurred in the

placebo group. No subjects died during the study, and no subjects discontinued due to adverse events, as attributed by the investigator.

**PAI-2001 (Cancer Pain)**

Serious adverse events were reported for 8 of 17 subjects treated in the Phase 2 study in cancer pain; 6 subjects died. Treatment assignments remain blinded in this ongoing study.

**Safety and Tolerability Conclusions:**

- Fulranumab was well tolerated in subjects with moderate to severe OA pain (PAI-2004 and PAI-2006) and in subjects with non-OA pain conditions, including moderate to severe pain due to DPN (NPP-2002), whose pain was not sufficiently treated with standard of care.
- Based on the direct comparison in the OA monotherapy study (PAI-2006) and the historical comparison with published data, fulranumab showed better tolerability compared to opioids.[3]

## 5.4. Osteonecrosis and RPOA

### 5.4.1. Osteonecrosis

The FDA has identified AVN as a specific safety concern for the anti-NGF class presumably based on the observation that in some joint replacement cases of subjects enrolled in anti-NGF clinical programs, X-ray or pathology findings provided by the clinical study sites were reported as being consistent with a diagnosis of ON or AVN.

To investigate this finding, a thorough evaluation of the nonclinical safety data for fulranumab has been conducted (Section 4). Bone and cartilage have not been identified as targets of toxicity and therefore, no link between fulranumab and ON can be established based on nonclinical data.[56]

All cases of joint replacement, including all those previously reported as ON or AVN, were adjudicated by a panel of independent clinicians who are experts in the diagnosis of ON and AVN and who were blinded to treatment assignment. All joint replacement cases originally reported as being ON or AVN were adjudicated as normal progression of OA or RPOA (Section 5.6).

By definition, ON means the death of bone, however “osteonecrosis is not a specific entity but the final pathway of several conditions leading to bone death”.[57] The terms AVN and ON have often been used interchangeably to describe bone necrosis. The literature on ON and AVN is often confusing in the use of these 2 terms. Most authors are generally consistent with the following: “avascular necrosis is often used improperly to designate any bone lesion that contains some histological evidence of necrosis or that is misinterpreted as exhibiting imaging features of AVN. …Bone tissue necrosis is a

nonspecific abnormality that can occur whenever a disease process causes major cell stress. Thus, some degree of bone necrosis can be seen in severe OA. …AVN, in contrast, is defined as massive necrosis of bone and bone marrow as the only or …predominant abnormality".[58] Thus, the term AVN should not be used to describe a focal bone necrosis.

Other authors also assert that "Osteonecrosis of the femoral head may take two forms….Primary osteonecrosis of the anterior superior part of the femoral head may be demonstrated by its characteristic appearance on magnetic resonance imaging (MRI) and radiographs…..focal subarticular ON has been reported as a secondary event in the femoral heads surgically removed with a clinical diagnosis of osteoarthritis."[59] These authors go on to state that "primary ON…is a late occurrence that follows collapse of the articular cortex….osteonecrotic bone may be found in an area unaffected by arthritis….secondary ON occurs in areas of bone already affected by arthritis or fracture".

In summary, bone necrosis can be seen on pathology as an event secondary to the normal progression of OA or RPOA. Primary ON including AVN may be distinguished by experts from the secondary ON observed in subjects with advanced OA based on a review of imaging and pathology data.

In the general population, the incidence of ON as the prominent abnormality, is low. The American Academy of Orthopedic Surgeons' website states that in the United States "It is estimated that doctors see about 10,000 to 20,000 new cases of ON each year". However this is misleading. In fact, ON is a common finding in patients with advanced OA. Secondary ON in OA has been reported in 8% to 38% of pathology specimens of excised femoral heads from multiple cases series of advanced OA patients.[60,61,62,63] The incidence of knee ON based on limited data is thought to be 1/10 that of hip ON.[64]

The Study of Osteoporotic Fractures (SOF) is a community-based study of 7,930 women, 65 years or older. Eligible subjects had a baseline pelvis radiograph (cross-sectional or longitudinal) and a follow-up assessment for hip replacement. Subjects were included without regard to radiographic hip OA status at baseline. At the request of the sponsor, additional analyses were conducted by Dr. Michael Nevitt, an SOF principal investigator, to provide information on the prevalence and incidence of radiologic hip ON.[65] Subjects were required to have radiologic hip OA at baseline to be included in the ON analyses. The radiologic criteria used for the diagnosis of ON were: increased sclerosis of the femoral head, wedge shaped, with and without central lucencies, with and without femoral head deformity/collapse and with and without secondary degenerative change. Radiologists reviewed the X-rays to determine if the radiographic findings were

consistent with a radiologic diagnosis of ON. Two readers jointly reviewed all cases scored as having ON to reach consensus. In this study, the baseline prevalence of ON was 2.05% (25/1222) when all patients regardless of OA severity were included. The prevalence of ON was higher in subjects with Croft grades of 3 (7%; 18/245) and 4 (57%; 4/7), as well as in subjects with hip pain on most days of a month in the past year (3.89%; 20/514) and those who used NSAIDs 5-7 days per week (4.13%; 10/242). Patients recruited in the SOF were followed, on average, for 8.3 years. The cumulative incidence of new ON cases after 8.3 years was 2.21% (19/859) and, similar to the prevalence results, was generally higher in subjects with greater Croft grade, hip pain, and NSAID use.[65]

Hence in the advanced OA population that participated in the fulranumab clinical program, it is not unexpected to see X-ray and pathology reports consistent with a diagnosis of ON.

**Conclusions**:

- In nonclinical studies, bone and cartilage have not been identified as target organs of toxicity for fulranumab.
- In the general population, the incidence of radiologic ON in hip OA is low.
- Focal bone necrosis is often seen in pathology specimens of excised hips in patients with advanced OA.
- All joint replacement cases reported as ON based on X-ray or pathology reports provided by the clinical study sites were adjudicated by independent experts as being part of the normal progression of OA or RPOA.

### 5.4.2. OA Progression and RPOA

**OA Progression**

The methods and criteria used in assessing OA progression have varied among the studies reported in the published literature. Progression of OA is usually measured radiologically; however, neither radiological grading (ie, Kellgren-Lawrence or Croft grades) nor quantitative measures necessarily correlate with symptoms. In addition, quantitative assessments of joint space narrowing in knee OA can differ based on the radiological imaging methods used (eg, standard anteroposterior view, fixed flexion, weight bearing, supine).[66] Standardized views of the knee such as the fixed flexion method, which are conducive to use in multicenter trials and have been used in epidemiologic studies such as the Osteoarthritis Initiative (OAI) and Johnston County Osteoarthritis Project (JOCO OA) studies, have limited ability to quantify small changes in joint space width and have poor reproducibility due to lack of alignment of the medial

tibial plateau with central beam X-ray.[66,67] The variability in radiological methodology, the training of radiological readers as well as the number of readers can all contribute to variability in radiological measurements.[68]

There is a wide range in the rate at which OA progresses in any population. Some patients will have stable disease for many years. Symptomatic OA patients tend to have a faster rate of disease progression than asymptomatic patients based on community-based observational studies of OA patients.[69]

Risk Factors for OA Progression

A number of risk factors have been associated with the progression of knee OA: baseline Kellgren-Lawrence grade,[70] baseline joint space width,[71] meniscal pathology,[72,73] bone edema,[73] patellofemoral OA,[71] female gender,[75] joint pain,[52] mechanical loading of the joint.[76] For malalignment (varus, valgus), obesity,[76,77] and low vitamin D serum levels[78,79,80], there are conflicting data.

The risk factors associated with hip OA progression are congenital hip joint abnormality, hip dysplasia, older age, female gender, severity of radiologic disease (JSN, bone edema, etc.), atrophic bone response, supralateral femoral head displacement.[9,69,81,82] At the request of the sponsor, additional analyses of the SOF data were conducted by Dr. Nevitt to provide information on the risk factors for OA progression.[83] Hip OA progression was defined as an increase of ≥1 in Croft grade, a decrease in minimum joint space narrowing of ≥0.5 mm or an increase in total osteophyte score of ≥2. In this study with an average follow-up of 8.3 years, the risk of radiographic progression of hip OA increased for subjects with a history of hip replacement in the contralateral hip, OA in both hips, higher baseline Croft scores, NSAID use of 5 to 7 days per week, and the presence of femoral osteophytes ≥2.

Regular use of NSAIDs has also been associated with the acceleration of OA progression. Numerous studies including case series and randomized studies support a possible relationship between indomethacin use and OA.[84] A large community-based study demonstrated an association of OA progression and the regular use of diclofenac,[85] but not with the occasional diclofenac use or the use of other NSAIDS, such as ibuprofen and naproxen. The risk of OA progression may vary with the specific NSAID used, as well as the dose and duration of the NSAID used. NSAID use will be monitored in future fulranumab clinical studies.

The progression (which may be rapid in some cases) of existing OA, as a consequence of increased loading of the OA joint by a patient who has been treated with an effective analgesic, has been designated, "analgesic arthropathy".[86]

The possibility that an effective analgesic may accelerate existing OA is supported by preclinical data[88] and biomechanical studies of NSAIDs in patients with OA of the knee.[76] This is consistent with a potential mechanical mechanism for anti-NGF antibodies to accelerate OA progression.

**RPOA**

In a subset of patients, OA progresses at a much faster rate, with significant joint space narrowing (eg, >2 mm per year) with or without osteolysis occurring in less than 1 year.[8] This has been described in the literature as rapidly progressing/progressive OA (RPOA) (also as rapidly destructive arthropathy [RDA] and other terms) and is a recognized condition that occurs in the absence of anti-NGF drug use.

RPOA has been reported in multiple case series of subjects with advanced OA. RPOA was first described by Forestier in 1957[74] and was further characterized in 2 independent case series in 1970.[89] More recent case series also referred to this phenomenon as rapidly destructive OA.[13,14,90]

The absence of reported RPOA in studies of OA pain is misleading. Most pain studies do not systematically collect joint X-rays at intervals frequent enough and with standardized procedures sensitive enough to detect RPOA. Many pain studies also do not systematically collect, analyze, and report joint surgery as safety events because they are considered as planned hospitalizations and are not considered serious adverse events.

Information on the incidence of RPOA is available from studies in which X-rays are collected routinely in studies of disease modifying OA agents (DMOAD), some of which also use joint replacement as a study endpoint.

The incidence of hip RPOA was evaluated in a prospective, longitudinal, double-blind, placebo-controlled study of diacerein, a DMOAD that may modify the progression of OA. Subjects in this study were at least 50 years old and had primary hip OA with significant baseline pain levels (ie, daily hip pain for at least 3 months). In this study, 6% (28/463) of subjects exhibited RPOA (ie, ≥2 mm joint space narrowing during a 2-year period).[9,10]

In contrast, the results of a 30-month, double-blind, placebo-controlled study designed to evaluate the effects of doxycycline on the rate and linearity of JSN provide information

on the incidence of knee RPOA. Subjects in this study were obese women, ages 45 to 64 years, with unilateral radiographic knee OA. Only 9 of 431 (2.1%) randomized subjects exhibited RPOA (ie, ≥2 mm joint space narrowing during a 16-month period).[11,12]

The lower incidence of RPOA reported in the doxycycline study compared with that reported in double-blind, placebo-controlled diacerein study may be attributed in part to differences in subject recruitment and differences in the joints (hip versus knee) studied. Subjects recruited in the double-blind, placebo-controlled diacerein study had significant symptomatic baseline pain and sought medical treatment from a rheumatologist; these subjects are similar to the subjects enrolled in the fulranumab OA studies. In the doxycycline study, subjects were recruited regardless of baseline pain symptoms. Comparisons of RPOA rates in fulranumab studies with those reported in the studies with no minimal baseline pain level, like the doxycycline study, are misleading.

The incidence of RPOA from selected case series reported in the published literature ranged from 1.9% to 18.2% for hip.[13,14,15] The wide variability is likely due to the differences in the study design, patient populations, imaging technique, and criteria used to assess RPOA.[91] The incidence rate of RPOA in the knee using standard radiographic methods has not been previously reported in the literature.

Additional characteristics associated with RPOA have been identified: minimal osteophyte formation, advanced age, excess motor activity/heavy labor, obesity, and female gender.[14,9]

In some patients, RPOA is observed in the absence of other well defined risk factors.[13,8] Little is known regarding the mechanisms involved in the pathophysiology of RPOA. Retrospective case series have suggested a relationship between joint overuse and obesity and RPOA of the hip[92] and between obesity and genu varum and RPOA of the knee.[93] Another case series suggest patients with atrophic OA may be at higher risk of RPOA.[13] A link between the inhibition of NGF and an acceleration of OA has not been previously reported in the literature.

### 5.4.3. Incidence of Joint Replacement

At the request of the sponsor, additional analyses of longitudinal, prospective cohort studies were conducted by Dr. Nevitt (OAI and SOF) and Dr. Joanne Jordan (JOCO OA) to provide information on the incidence of joint replacement.

A cohort of 4,796 patients from the OAI study was used to assess the risk of knee replacement.[94] The study population for this analysis:

- Was comprised of 3 sub-cohorts: the progression sub-cohort (n=1,390) included participants with both frequent knee symptoms in the past 12 months and radiographic knee OA; the incidence sub-cohort (n=3,284) included participants without frequent knee symptoms and ROA in the same knee at baseline, but with risk factors for developing knee OA; and the non-exposed control sub-cohort (n=122) included participants with no symptoms, no ROA, and no risk factors.
- Was followed for up to 4 years (mean: 3.86 years).

In this study, knee replacement rates for patients with baseline Kellgren-Lawrence scores of 3 and 4 were, on average, 1.7 and 7.25 per 100 person-years, respectively (Table 6). Among patients (n=1605) with baseline NRS pain scores ≥5 (on a scale of 0-10), knee replacement rates for patients with baseline Kellgren-Lawrence scores of 3 and 4 were, on average, 2.86 and 8.87 per 100 person-years, respectively. Statistically significant risk factors for joint replacement included age (≥65 years), body mass index (≥30 kg/m$^2$), and a higher baseline Kellgren-Lawrence score.

**Table 6:** Osteoarthritis Initiative Study: Baseline Kellgren-Lawrence Scores

| | All Patients (n=4,796) | | | | Baseline NRS Pain Score ≥5[a] (n=1,605) | | | |
|---|---|---|---|---|---|---|---|---|
| Baseline Kellgren-Lawrence Grade[b] | Number of Patients | Patients with Confirmed TKR | Patient-Years | Rate per 100 PY | Number of Patients | Patients with Confirmed TKR | Patient-Years | Rate per 100 PY |
| 1: Both Knees 0-1 | 2,162 | 4 | 8,151.3 | 0.05 | 533 | 3 | 1,906.6 | 0.16 |
| 2: Worse Knee 2 | 1,293 | 27 | 4,887.5 | 0.55 | 421 | 18 | 1,525.5 | 1.18 |
| 3: Worse Knee 3 | 1,011 | 61 | 3,583 | 1.7 | 449 | 44 | 1,539.7 | 2.86 |
| 4: Worse Knee 4 | 330 | 78 | 1075.9 | 7.25 | 202 | 56 | 631.6 | 8.87 |

NRS=numerical rating scale; PY = person-years; TKR = total knee replacement.
[a] Patients with pain severity in past 7 days ≥5 (0-10 NRS) in either knee.
[b] Kellgren-Lawrence score = worse of 2 knees, based on the assessment at the study site using fixed flexion method.

The JOCO OA study is a longitudinal, prospective observational study of approximately 3,100 patients, aged 45 years or older, with knee or hip OA.[95] In this study, knee replacement rates for patients with baseline Kellgren-Lawrence scores of 3 and 4 were, on average, 2.77 and 8.14 per 100 person-years, respectively (Table 7). Statistically significant risk factors for joint replacement included female gender, body mass index (≥30 kg/m$^2$), and a higher baseline Kellgren-Lawrence score. These findings are consistent with the data reported in the OAI study (Table 6).

Among subjects with hip OA, the number of subjects with higher baseline Kellgren-Lawrence (3 or 4) was small in this community-based study. Statistically significant risk factors for joint replacement included age (≥65 years), body mass index (≥30 kg/m$^2$), and a higher baseline Kellgren-Lawrence score (Table 7).

**Table 7:** Johnston County Osteoarthritis Project: Baseline Kellgren-Lawrence Scores

| | Patient with Knee OA (n=1,627) | | | | Patients with Hip OA (n=1,491) | | | |
|---|---|---|---|---|---|---|---|---|
| Baseline Kellgren-Lawrence Grade[a] | Number of Patients | Patients with Confirmed TKR | Patient-Years | Rate per 100 PY | Number of Patients | Patients with Confirmed THR | Patient-Years | Rate per 100 PY |
| 1: Both 0-1 | 1,319 | 9 | 7,802.62 | 0.12 | 910 | 5 | 5,330.79 | 0.09 |
| 2: Worse 2 | 189 | 10 | 1,130.21 | 0.88 | 522 | 5 | 3,163.92 | 0.16 |
| 3: Worse 3 | 89 | 14 | 505.00 | 2.77 | 39 | 0 | 257.67 | 0.00 |
| 4: Worse 4 | 30 | 12 | 147.50 | 8.14 | 18 | 3 | 117.67 | 2.55 |

OA=osteoarthritis; PY = person-years; TKR = total knee replacement.

[a] Kellgren-Lawrence score = worse of 2 knees or hips, based on the assessment at the study site using fixed flexion method.

In the SOF study, hip replacement rates for patients with baseline Croft scores[96] of 3 and 4 were, on average, 4.38 and 16.58 per 100 person-years, respectively (Table 8). Statistically significant risk factors for joint replacement included age and a higher baseline Croft score.[83]

**Table 8:** Study of Osteoporotic Fractures: Baseline Croft Scores

| | All Women (n=7,930) | | | |
|---|---|---|---|---|
| Baseline Croft Score[a] | Number of Patients | Patients with Confirmed Total Hip Replacement(s) | Person-Years | Rate per 100 Person-Years |
| 0-1 | 7,251 | 48 | 53,903 | 0.09 |
| 2 | 366 | 28 | 2,547.6 | 1.10 |
| 3 | 277 | 73 | 1,666.7 | 4.38 |
| 4 | 36 | 27 | 162.9 | 16.58 |

OA=osteoarthritis.

[a] Croft score of the worst hip based on the assessment at the study site using the following scale: 0 = normal: no definite features of OA; 1 = possible OA; only 1 definite OA feature present, typically either just an osteophyte alone or joint space narrowing alone; or possible OA features present; 2 = definite/mild OA: 2 definite OA features present; either both joint space narrowing and osteophytes present, or joint space narrowing plus 1 other feature (subchondral sclerosis, subchondral cyts) or osteophytes plus one of these other features; 3 = moderate-severe OA: at least 3 of the 4 OA features present; 4 = severe OA with deformity: at least 3 of the 4 OA features present plus femoral head deformity.

In a separate 3-year prospective longitudinal study (EULAR Study) in subjects with significant painful knee OA (>30 mm on a 100-mm visual analogue scale), 12% of subjects required knee replacement, of which, 8% occurred in the first year. The incidence of knee replacement was greater for patients with Kellgren-Lawrence scores of 3 or 4 (27%; 78/294) than for patients with Kellgren-Lawrence scores of 1 or 2 (7%; 16/237).[97]

Joint replacement is not an endpoint typically collected in many pain studies. However, randomized, placebo-controlled studies of disease modifying agents in painful OA, which used joint replacement as an endpoint, significant rates of joint replacement were demonstrated. For example, in one study of a disease modifying agent in subjects with

painful hip OA (ECHODIAH Study), the incidence of joint replacement was 36% (50/138) in the placebo group over a 3-year period.[98]

In the ERIDIAS study, in which avocado-soybean unsaponifiables avocado was studied over 3 years as a DMOAD in subjects with painful hip OA, 18.5% (74/399) of subjects required joint replacement.[99]

The difference in rates of joint replacements between community-based studies such as the OAI, SOF and JOCA studies compared to the EULAR, ERIDIAS and ECHODIAH studies is related to the difference in subject selection criteria. The EULAR, ERIDIAS and ECHODIAH studies selected patients with painful OA joint, whereas significant pain was not an entry criterion for the community-based studies. However, subgroup analyses of the OAI and SOF support a higher rate of joint replacement in subjects with significant baseline OA pain.

Although interpretation of differences among studies has limitations, the rate of joint replacement observed in the placebo group in PAI-2004 (10.0 per 100 patient-years; Table 12) suggested that subjects with late-stage OA were enrolled in PAI-2004. This is consistent with the enrollment criteria that subjects were required to have pain ≥5 (based on an 11-point NRS) to enter into PAI-2004.

**Conclusions**:

- RPOA is part of the spectrum of OA progression.
- The pathophysiology of RPOA is unknown.
- Chronic use of NSAIDs may decrease pain leading to increased loading of the diseased joint, which may result in more rapid OA progression.

## 5.5. Bone or Joint-Related Events

In addition to examining subjects with joint replacement in the fulranumab clinical studies (Section 5.5.1), the sponsor conducted a comprehensive search of the clinical database to identify subjects with fracture-related adverse events (Section 5.5.2.1) and possible joint-related adverse events (Section 5.5.2.2). The adjudicated findings for all joint replacements are described in Section 5.6.

### 5.5.1. Joint Replacements in Fulranumab Studies

The decision to perform a joint replacement is complicated and is influenced by many factors, such as adequate medical insurance, patient perceptions and preferences, and

local medical practice.[100] In the fulranumab program, joint replacements occurred both on treatment and after the study drug discontinuation.

As of 08 July 2011, 88 of 1,353 subjects treated in the 9 Phase 1/1b and Phase 2 studies of fulranumab had at least 1 joint replacement (Table 9); data for these subjects are described in this section.

Most (75/88) of the subjects with joint replacement(s) were treated in studies in subjects with moderate to severe OA pain (2004145, 1 subject; PAI-2004, 71 subjects; and PAI-2006, 3 subjects) (Table 9). This finding is expected as OA is a known risk factor for joint replacement surgery. Overall, in PAI-2004 (OA Add-on), the study contributing most of the joint replacement cases, joint replacements were reported at a rate of 139 per 1000 person-years in the fulranumab group (any dose) and 98 per 1000 person-years in the placebo group (Table 10).

The incidence rate of joint replacement was lower in the fulranumab clinical studies of non-OA pain conditions compared with the OA Add-on study, PAI-2004 for the fulranumab and placebo groups (Table 10). The lower incidence rate of joint replacement in clinical studies of non-OA pain conditions compared to PAI-2004 (OA Add-on) is expected as OA is not a criterion for entry in non-OA pain studies.

Among subjects enrolled in the 2 studies in moderate to severe OA pain, there was a lower rate of joint replacements in PAI-2006 (38 and 0 per 1000 person years for fulranumab and placebo groups, respectively) than in PAI-2004 (139 and 98 per 1000 person-years for fulranumab and placebo groups, respectively). The differences in the incidence rates in these 2 studies may be attributed to a number of reasons, including differences in the subject populations, study design (add-on vs monotherapy), duration of therapy (4 months versus 6 to 12 months), and follow-up in each study at the time of this report.

**Table 9:** Joint Replacement in Subjects in the Phase 1/1b and Phase 2 Fulranumab Clinical Studies (Reported as of 08 July 2011)

| Study Number | Pain Condition | Subjects Treated | Subjects with at Least One Joint Replacement n/N (%)[a] | | | |
|---|---|---|---|---|---|---|
| | | | Placebo | Fulranumab | Oxycodone CR | Total |
| **Phase 1/1b Completed Studies** | | | | | | |
| 20040195 | Healthy subjects | 46 | 0/12 | 0/34 | N/A | 0 |
| 20040145 | Knee OA | 24 | 0/6 | 1/18 (5.6) | N/A | 1 |
| **Phase 2 Terminated Studies With Unblinded Data** | | | | | | |
| PAI-2004 | Knee or hip OA | 466 | 8/78 (10.3) | 63/388 (16.2) | N/A | 71 |
| PAI-2003 | Low back pain | 385 | 1/76 (1.3) | 7/309 (2.3)[b] | N/A | 8[b] |
| PAI-2006 | Knee OA pain | 196 | 0/48 | 2/98 (2.0) | 1/50 (2.0) | 3 |
| PAI-2005 | Interstitial cystitis/painful bladder syndrome | 31 | 0/17 | 0/14 | N/A | 0 |
| NPP-2001 | Neuropathic pain[c] | 111 | 2/42 (4.8) | 3/69 (4.3) | N/A | 5 |
| NPP-2002 | Neuropathic pain[d] | 77 | 0/24 (0.0) | 0/53 (0.0) | N/A | 0 |
| **Phase 2 Ongoing Study With Blinded Data** | | | | | | |
| PAI-2001 | Cancer Pain | 17 | 0/blinded | 0/blinded | N/A | 0 |
| | All Studies | 1,353 | 11 | 76[b] | 1 | 88[b] |

CR=controlled release; N/A=not applicable; OA=osteoarthritis.

[a] n=number of subjects with at least one joint replacement; N=number of subjects who received at least 1 dose of study drug. Treatment assignments remain blinded in PAI-2001.

[b] One subject (Subject 131607) in PAI-2003 with surgery for a lumbar device failure is not counted in this table.

[c] Neuropathic pain diagnoses of post-herpetic neuralgia or post-traumatic/post-surgical neuropathic pain syndrome

[d] Diabetic painful neuropathy and small fiber neuropathy associated with impaired glucose tolerance.

**Table 10:** Joint Replacement in Subjects in the Phase 2 Fulranumab Clinical Studies (Reported as of 08 July 2011)

| Study Number[a] | Pain Condition | Subjects Treated | Subjects with at Least One Joint Replacement n/person year (Rate in 1000 person year)[b] | | |
|---|---|---|---|---|---|
| | | | Placebo | Fulranumab | Oxycodone CR |
| **Studies in OA Pain** | | | | | |
| PAI-2004 | Knee or hip OA | 466 | 8/81.8 (98) | 63/454.5 (139) | N/A |
| PAI-2006 | Knee OA pain | 196 | 0/27.8 (0) | 2/52.6 (38) | 1/25.1 (40) |
| **Studies in Other Chronic Pain Conditions** | | | | | |
| PAI-2003 | Low back pain | 385 | 1/75 (13) | 7/311.4 (22)[c] | N/A |
| NPP-2001 | Neuropathic pain[d] | 111 | 2/31.7 (63) | 3/54.1 (55) | N/A |

CR=controlled release; N/A=not applicable; OA=osteoarthritis

[a] No joint replacements were reported in PAI-2005 (interstitial cystitis/painful bladder symptoms) and NPP-2002 (DPN); PAI-2001 in cancer pain is ongoing and treatment assignments remain blinded.

[b] n=number of subjects with at least one joint replacement

[c] One subject (Subject 131607) in PAI-2003 with surgery for a lumbar device failure is not counted in this table; but is included in the adjudication findings.

[d] Neuropathic pain diagnoses of post-herpetic neuralgia or post-traumatic/post-surgical neuropathic pain syndrome

A summary of the number of subjects with joint replacement(s), by treatment group, reported as of 08 July 2011 in the Phase 2 studies with unblinded data is provided in Table 11. No subject had a joint replacement in PAI-2005 and NPP-2002. Based on the available information from the fulranumab clinical studies, a dose effect for joint replacement cannot be excluded.

**Table 11:** Joint Replacement in Subjects in the Phase 2 Terminated Studies, by Treatment Group (Reported as of 08 July 2011)

| | Subjects with at Least 1 Joint Replacement n/N (%)[a] | | | |
|---|---|---|---|---|
| Randomized Treatment Group | PAI-2004 (OA Add-on) | PAI-2006 (OA Monotherapy) | PAI-2003 (LBP) | NPP-2001 (PHN/PTN) |
| Placebo | 8/78 (10.3) | 0/48 | 1/76 (1.3) | 2/42 (4.8) |
| Fulranumab dose group[b] | | | | |
| 1mgQ4wk | 9/77 (11.7) | NA | 2/77 (2.6) | 0/13 |
| 3mgQ8wk | 8/76 (10.5) | NA | NA | NA |
| 3mgQ4wk | 17/79 (21.5) | 0/48 | 1/77 (1.3) | 0/14 |
| 6mgLD+3mgQ4wk | NA | NA | 2/78 (2.6) | NA |
| 6mgQ8wk | 12/78 (15.4) | NA | NA | NA |
| 9mgQ4wk | NA | 2/50 (4.0) | NA | NA |
| 10mgQ8wk | 17/78 (21.8) | NA | NA | NA |
| 10mgQ4wk | NA | NA | 2/77 (2.6) | 3/42 (7.1) |
| **Total Fulranumab** | **63/388 (16.2)** | **2/98 (2.0)** | **7/309 (2.3)** | **3/69 (4.3)** |
| **Oxycodone CR** | **NA** | **1/50 (2.0)** | **NA** | **NA** |
| **Total (All Treatment Groups)** | **71/466** | **3/196** | **8/385** | **5/111** |

LD=loading dose; LBP=lower back pain; NA=not applicable; OA=osteoarthritis; PHN = postherpetic neuralgia; PTN=post-traumatic/post-surgical neuropathic pain; Qxwk=every x weeks.

[a] n=number of subjects with at least one joint replacement; N=Number of subjects who received at least 1 dose of study drug.

[b] Arranged in increasing order based upon initial dose.

In the fulranumab clinical studies, a diagnosis date (ie, the date when the decision was made to have a joint replacement) was available for 105 of the 115 joint replacement surgeries (Note: some subjects had >1 joint replacement surgery). Most (85%) joint replacement surgeries were performed within 4 months after the diagnosis date, and almost all (95%) joint replacement surgeries were performed within 6 months after the diagnosis date. Thus, a follow-up at 6 months after the last dose is considered sufficient to obtain information on joint replacement surgeries.

Between 08 July 2011 and 08 December 2011, ten subjects (involving 12 joints) had nonsolicited post-study joint replacements that were reported to the sponsor and had not been previously adjudicated. Of these, 6 subjects (involving 7 joints) provided informed consent for the collection of their joint replacement data and had sufficient radiologic images for adjudication; findings for these subjects are provided in Attachment 16.

#### 5.5.1.1. Comparison of Subjects With and Without Joint Replacement in PAI-2004 (OA Add-on)

A comparison of subjects with and without joint replacement surgeries reported as of 08 July 2011 in PAI-2004 (OA Add-on), by treatment group, is provided in the sections that follow. The numbers of fulranumab-treated subjects with at least 1 joint replacement surgery in the remaining fulranumab clinical studies were small (0 to 8 subjects/study).

**Demographic and Baseline Characteristics**

In both treatment groups, a greater proportion of subjects with joint replacements were women, ≥65 years of age, and had hip identified as the target joint compared with subjects with no joint replacement. In the fulranumab group, greater proportions of subjects with joint replacements had screening Kellgren-Lawrence scores of 3 or 4 compared with subjects with no joint replacement. In the fulranumab group, subjects with joint replacements tended to have higher baseline pain scores than subjects with no joint replacement. The small number of subjects with joint replacement (8 subjects) in the placebo group prevents meaningful comparisons.

Overall, subjects enrolled in PAI-2004 tended to have WOMAC pain scores on entry in the study that were similar to those reported in patients with lower limb OA who were scheduled for joint replacement surgery.[35,36]

Among the 5 fulranumab dose groups, there were no clear differences in the demographic and baseline characteristics for subjects with and without joint replacements (Attachment 17). There was a suggestion for a greater proportion of subjects with Kellgren-Lawrence scores of 3 or 4 among subjects with joint replacements than among subjects with no joint replacements.

**Prior /Concomitant Medication Usage**

Prior and concomitant NSAIDs and/or corticosteroid use may affect the rate of OA and ON occurrence.

NSAID Use

The majority of subjects (85%) in PAI-2004 were taking NSAIDs prior to and during the study as analgesic medications; thus, the effect of NSAID use on joint replacement cannot be determined in this study (Attachment 6).

Corticosteroids Use

In PAI-2004 (OA Add-on), subjects who took corticosteroids within 3 months prior to enrollment were excluded from the study, and the use of high-dose corticosteroids was

prohibited during the efficacy phase of the study. The effect of prior corticosteroid use on joint replacements cannot be determined due to the small number of subjects who took corticosteroids prior to the study entry (Attachment 18 and Attachment 19).

There was no indication of a higher incidence of corticosteroid use during the study (all phases combined) for subjects with joint replacements relative to those without joint replacements; however, conclusions are limited by the small number of subjects with joint replacements in each treatment group (Attachment 20).

**Pain and Function Relationship for Subjects With and Without Joint Replacement in PAI-2004 (OA Add-on)**

Mean changes from baseline over time in the double-blind efficacy and extension phases in the average pain intensity score, WOMAC pain subscale score, WOMAC physical function subscale score, Patient Global Assessment Score, SF-36 physical function scale score in PAI-2004 (OA Add-on) were examined for subjects with and without joint replacements. Descriptive statistics for the same efficacy variables for the change from baseline to last measurement and second to last measurement before joint replacement diagnosis were also computed for all subjects with joint replacement.

There was no clear pattern of increased activity or pain in subjects with and without joint replacements; however, conclusions are limited by the small number of subjects with joint replacement in each treatment group.

A qualitative review of pain intensity for subjects during treatment with study drug and after stopping the study drug did not show any consistent patterns that could predict a risk of developing RPOA.

**Fulranumab Serum Concentrations**

In PAI-2004 (OA Add-on), fulranumab serum concentrations through Week 81 in each treatment group were generally comparable for subjects with and without joint replacement. There was no evidence of higher systemic exposure to fulranumab in subjects with joint replacement compared to those without joint replacement within each treatment group.

#### 5.5.1.2. Rate of Joint Replacement in the Fulranumab Studies

The sponsor and the independent DMC have monitored the incidence of joint replacement in subjects in the fulranumab clinical studies. This monitoring includes the computation of the hazard ratio and incidence rate (per 1000 person-years) of joint replacements.

In the fulranumab clinical studies as of 08 July 2011, most (75/88) of the subjects with joint replacement(s) were treated in the 3 studies in moderate to severe pain due to OA, and most (71/75) of these subjects with OA pain were treated in PAI-2004 (OA Add-on) (Table 9). Due to the add-on design of studies PAI-2003 and PAI-2004, the incidence of the joint replacement in the placebo groups reflect the analgesic standard of care of the subjects enrolled in the studies.

In study PAI-2004 (OA Add-on), the study contributing most of the joint replacements, the median duration of exposure for fulranumab subjects was 40 weeks with 15% of subjects exposed for at least 52 weeks at the time of the clinical hold (23 December 2010). As of 08 July 2011, the incidence rate was 143 per 1000 person-years in the fulranumab group and 100 per 1000 person-years in the placebo group in PAI-2004 (OA Add-on) (Table 12). A Kaplan-Meier plot of the time to joint replacement is provided in Attachment 21. The incidence rate in the placebo group (100 per 1000 person-years,) is similar to the incidence rate reported for patients with severe OA with pain scores ≥5 in the OAI study (88.7 per 1000 person-years; Table 6) suggesting that the population in PAI-2004 is consistent with a population with severe, symptomatic OA.

**Incidence of Joint Replacement on Treatment and After Drug Discontinuation**

In the fulranumab program, joint replacements occurred both on treatment and after study drug discontinuation. Hazard rates may have been affected by the clinical hold (23 December 2010). Hazard ratios calculated as of 20 January 2011, 28 days after the clinical hold was put in place, reflect a time when all subjects had not received study drug for at least 28 days, the minimal injection interval (described in this section as "on treatment"), while hazard ratios calculated as of 08 July 2011, reflect counts of joint replacements at a time when exposure was expected to be reduced to concentrations that were not clinically relevant (ie, after drug discontinuation). Further, subjects who underwent joint replacement after 20 January 2011 were likely to have made the decision to have surgery with the knowledge that the trials had been discontinued due to the clinical hold and no active treatment was to be administered.

The overall hazard ratio for joint replacement for subjects treated with fulranumab versus placebo was greater after study drug discontinuation (ie, 08 July 2011, approximately 6 months after the clinical hold) (1.40; 90% CI, 0.76%-2.61%, Table 12) compared with the hazard ratio on treatment (ie, 20 January 2011, 28 days after the clinical hold) (0.90; 90% CI, 0.46%-1.78%, Table 13). Across all fulranumab dose groups, the incidence rate of joint replacement reported on treatment (20 January 2011) was not

significantly greater than that observed with placebo (Table 13). After study drug discontinuation (08 July 2011), the incidence of joint replacement increased in all fulranumab dose groups; however, in the 2 lowest fulranumab dose group (1mgQ4wk and 3mgQ8wk), the incidence was similar to that of placebo, and in the 3mgQ4wk, 6mgQ8wk, and 10mgQ8wk fulranumab dose groups it was greater than that of placebo.

**Table 12:** Joint Replacement Analysis in PAI-2004 (OA Add-on) Reported as of 08 July 2011, Approximately 6 Months After Clinical Hold (Time to Surgery)

| Randomized Treatment Group | No. of Subjects | No. of Subjects with at Least 1 JR | Hazard Ratio | 90% CI for Hazard Ratio | IR | IRR | 90% CI for IRR |
|---|---|---|---|---|---|---|---|
| Placebo | 78 | 8 | | | 100 | | |
| Fulranumab 1mgQ4wk | 77 | 9 | 0.84 | (0.38 - 1.88) | 96 | 0.95 | (0.43 - 2.12) |
| Fulranumab 3mgQ8wk | 76 | 8 | 0.87 | (0.38 - 1.98) | 91 | 0.90 | (0.4 - 2.05) |
| Fulranumab 3mgQ4wk | 79 | 17 | 1.84 | (0.91 - 3.72) | 189 | 1.89 | (0.93 - 3.82) |
| Fulranumab 6mgQ8wk | 78 | 12 | 1.38 | (0.65 - 2.93) | 141 | 1.41 | (0.66 - 2.98) |
| Fulranumab 10mgQ8wk | 78 | 17 | 2.08 | (1.03 - 4.22) | 206 | 2.05 | (1.01 - 4.15) |
| **Total Fulranumab** | **388** | **63** | 1.4 | (0.76 - 2.61) | **143** | 1.43 | (0.77 - 2.65) |
| **Total** | **466** | **71** | | | **137** | | |

CI=confidence interval; IR=Incidence rate per 1000 person-years; IRR=incidence rate ratio; JR=joint replacement; No.=number; OA=osteoarthritis; Qxwk=every x weeks.
Hazard ratio and IRR are computed for an active treatment group versus placebo based on all JR cases.

**Table 13:** Joint Replacement Analysis in PAI-2004 (OA Add-on) for Surgery Performed as of 20 January 2011, 28 Days After Clinical Hold (Time to Surgery)

| Randomized Treatment Group | No. of Subjects | No. of Subjects with at Least 1 JR | Hazard Ratio | 90% CI for Hazard Ratio | IR | IRR | 90% CI for IRR |
|---|---|---|---|---|---|---|---|
| Placebo | 78 | 7 | | | 107 | | |
| Fulranumab 1mgQ4wk | 77 | 4 | 0.47 | (0.17-1.33) | 54 | 0.50 | (0.18 - 1.41) |
| Fulranumab 3mgQ8wk | 76 | 3 | 0.38 | (0.12-1.19) | 42 | 0.39 | (0.13 - 1.21) |
| Fulranumab 3mgQ4wk | 79 | 9 | 1.13 | (0.49-2.6) | 124 | 1.15 | (0.5 - 2.64) |
| Fulranumab 6mgQ8wk | 78 | 8 | 1.05 | (0.45-2.46) | 114 | 1.06 | (0.45 - 2.48) |
| Fulranumab 10mgQ8wk | 78 | 12 | 1.59 | (0.73-3.47) | 174 | 1.62 | (0.74 - 3.54) |
| **Total Fulranumab** | **388** | **36** | 0.90 | (0.46-1.78) | **101** | 0.94 | (0.48 - 1.85) |
| **Total** | **466** | **43** | | | **102** | | |

CI=confidence interval; IR=Incidence rate per 1000 person-years; IRR=incidence rate ratio; JR=joint replacement; No.=number; OA=osteoarthritis, Qxwk=every x weeks.
Hazard ratio and IRR are computed for an active treatment group versus placebo based on all joint replacement cases.

The improvement in pain during the 16-week efficacy period was comparable across all fulranumab dose groups in PAI-2004 (OA Add-on) (Table 14). The majority of subjects (85%) continued into the extension phase with a median duration of double-blind treatment of 40 weeks. Improvements in pain and function, as measured by WOMAC, were maintained in the extension phase for subjects who continued to receive treatment.

**Table 14:** NRS Change From Baseline (LOCF) and Subjects Reporting Joint Replacement in PAI-2004 (OA Add-on)

| Treatment Group | N | LS Mean (SE) Week 16 NRS Change from Baseline, LOCF (p-value)[a,b] | Subjects with Reported Joint Replacement (Time to Surgery) | |
|---|---|---|---|---|
| | | | 08 July 2011 N (IR) | 20 January 2011 N (IR) |
| Placebo | 78 | -1.8 (0.26) (NA) | 8 (100) | 7 (107) |
| JNJ-42160443 1mgQ4wk | 77 | -2.7 (0.26) (0.026) | 9 (96) | 4 (54) |
| JNJ-42160443 3mgQ8wk | 76 | -2.4 (0.27) (0.138) | 8 (91) | 3 (42) |
| JNJ-42160443 3mgQ4wk | 79 | -3.2 (0.26) (<0.001) | 17 (189) | 9 (124) |
| JNJ-42160443 6mgQ8wk | 78 | -2.5 (0.27) (0.069) | 12 (141) | 8 (114) |
| JNJ-42160443 10mgQ8wk | 78 | -2.7 (0.26) (0.022) | 17 (206) | 12 (174) |

ANCOVA=analysis of covariance: LOCF=last observation carried forward, IR=incidence rate per 1000 person-years; NRS=numerical rating scale; Qxwk=every x weeks; SE=standard error.

[a] p−values and least squares means from ANCOVA model with treatment, baseline opioid use (use/no use), and baseline weight (<85 kg/≥85 kg) as factors and baseline average pain score as covariate.

[b] Nominal unadjusted p−values are presented.

Joint replacements available as of 08 July 2011 were analyzed based upon a diagnosis date. The diagnosis date was determined from the date of the first dose of study drug to the date of the diagnosis based on the date of the X-ray for the new joint symptom. If the date of the diagnostic X-ray was not available, the date of consultation or pathology report was used. As the information for the diagnosis date varied among subjects, the surgery date was considered to be a more reliable time point for the joint replacements analyses.

### 5.5.2. Non-Joint Replacement Events

#### 5.5.2.1. Fracture-Related Adverse Events

The sponsor conducted a search of the database for the 6 terminated Phase 2 fulranumab studies for adverse events with "fracture" as part of the preferred or verbatim term. Fracture-related events were categorized by etiology (unspecified/unknown, traumatic, osteoporotic, or pathologic) and by fracture type (lower extremity or upper extremity).

Fracture-related adverse events were reported for 4% (34/931) of subjects in the combined fulranumab group and 1% (4/285) of subjects in the placebo group; none were reported for the 50 subjects in the oxycodone CR group (Attachment 22). The incidence rates of traumatic fractures and fractures of unspecified or unknown etiology were similar for subjects in the combined fulranumab group (ie, any dose) and the placebo group. The incidence rates of osteoporotic and pathologic fractures were low (for each, <1% of subjects in the combined fulranumab group and none in the placebo group). The

incidence rates of lower and upper extremity fractures were similar for subjects in the combined fulranumab group and the placebo group.

#### 5.5.2.2. Other Non-Joint Replacement Cases

To identify subjects with possible joint-related adverse events who did not have joint replacement, adverse event listings from the 7 Phase 2 fulranumab clinical studies were reviewed for preferred terms that might have been associated with an adverse event of possible joint destruction. A complete description of the preferred terms is provided in Attachment 23.

Five subjects (involving 7 joints) identified as having an adverse event possibly related to joint destruction and who did not have joint replacement, had sufficient radiologic images for adjudication (see Section 5.6). All 5 subjects (involving 7 joints) were diagnosed as having normal OA progression and the adverse events were considered not related to study drug by the Adjudication Committee.

### 5.6. Adjudication of Joint Replacement Cases

The Adjudication Committee was convened to adjudicate all joint replacement cases in the fulranumab program. Adjudication provided a consistent evaluation of joint replacements by using an expert, independent, and blinded panel assessing cases from all clinical studies. In addition, cases with adverse events that indicated possible joint destruction, but without joint replacement, were also adjudicated (see Section 5.5.2.2).

#### 5.6.1. Objectives

The objectives for performing the adjudication of cases from studies conducted by the sponsor for the study of fulranumab in the treatment of pain were:

- Gain the adjudicators agreement on the definition of osteonecrosis and RPOA;
- Obtain their diagnosis of cases based on X-rays and clinical data; and
- Receive their opinion of the attribution of their diagnosis of cases based on blinded treatment.

#### 5.6.2. Methods

#### 5.6.2.1. Adjudicators

The adjudicators were selected for their expertise in the areas of ON, RPOA, rheumatology, orthopedic surgery or radiology. Their names and backgrounds are provided in Table 15. Full curriculum vitae are available upon request.

**Table 15:** Background of Adjudicators

| Adjudicator | Title/Institution | Specialty | Committee Participation |
|---|---|---|---|
| Roy Aaron, MD (Providence, RI, USA) | Professor, Orthopaedic Surgery and Molecular Pharmacology, Physiology and Biotechnology<br>Director, Orthopaedic Cell Biology Laboratory and Center for Restorative and Regenerative Medicine, The Warren Alpert Medical School of Brown University | Orthopaedic Surgery | By phone meeting 1 |
| Kenneth Brandt, MD (Fairway, KS, USA) | Clinical Professor of Medicine University of Kansas Medical Center | Rheumatology | Face to face meeting 1, 2, 3, 4<br>Web conference and teleconference meeting 5 |
| Philip Conaghan, MD (Leeds, UK) | NIHR UK Senior Investigator<br>Section of Musculoskeletal Disease<br>Chapel Allerton Hospital | Rheumatology | By phone meeting 1 |
| Thomas Einhorn, MD (Boston, MA, USA) | Chairman and Chief, Department of Orthopaedic Surgery, Boston Medical Center | Orthopaedic Surgery | Face to face meeting 1 |
| Bruce Kneeland, MD (Philadelphia, PA, USA) | Professor, Dept. of Radiology<br>Pennsylvania Hospital | Radiology | Face to face meeting 1, 2, 3, 4<br>Web conference and teleconference meeting 5 |
| Michel Lequesne, MD (Paris, France) | Professor and Chairman, Rheumatology Department, Hospital Leopold Bellan | Rheumatology | Face to face meeting 1,<br>By phone meeting 2, 3, 4<br>Web conference and teleconference meeting 5 |
| Michael Mont, MD (Baltimore, MD, USA) | Director, Rubin Institute for Advanced Orthopedics and Center for Joint Preservation & Replacement, The Sinai Hospital of Baltimore, Baltimore, MD | Orthopaedic Surgery | Face to face meeting 1, 2, 3, 4<br>Web conference and teleconference meeting 5 |
| Roland Moskovitz, MD (Cleveland, OH, USA) | Director, Rheumatology Clinical Research Unit, University Hospitals of Cleveland/Case Research Institute | Rheumatology | Face to face meeting 1, 2, 4<br>Web conference and teleconference meeting 5 |

#### 5.6.2.2. Process of Adjudication

The adjudication process required that the adjudication team agree (with a majority vote) on the definition used for the diagnosis assigned to each case: ON, RPOA, RPOA with features of ON, other, normal progression of OA, or insufficient information. These definitions are provided in Section 5.6.2.3. The first adjudicated cases of joint replacement were those that the investigator, sponsor and/or FDA evaluated as due to ON or RPOA based on the assessment of joint radiographs, joint MRIs, pathology information, and other clinical information collected during the study including medical history, medication history including corticosteroid therapy, and pain and activity levels during the study. All subsequent joint replacement cases and any case with adverse events that indicated possible joint destruction but without joint replacement (see

Section 5.5.2.2 for details on identification process) from the fulranumab clinical program were adjudicated as available supporting documents were collected.

In closed sessions, with blinded sponsor representatives, the adjudicators first assessed case diagnosis (using definitions provided in Section 5.6.2.3) based upon structural evidence in available joint radiographs. Then case attributions were assessed based upon both structural and clinical evidence (provided in Section 5.6.2.4). All clinical evidence was free of study therapy identification. Images were provided through an outside vendor (Perceptive) and had been deidentified.

#### 5.6.2.3. Case Definitions

The diagnoses were developed by the sponsor in consultation with a subgroup of adjudicators and subsequently confirmed by the entire group of adjudicators as appropriate to apply to the cases after discussion at the first adjudication meeting held on 07 April 2011 (Table 16).

The protocols for the OA studies involved did not consistently specify radiological assessment except at screening (PAI-2004 Add-on and PAI-2006 Monotherapy). Study PAI-2006 only mandated an X-ray at screening, while study PAI-2004 mandated X-rays at screening, and 1 year and 2 years after start of treatment. The protocols did not specifically mandate X-rays prior to joint replacements or a centralized standard imaging when X-rays were taken; thus, there was no standard timing of joint X-rays or standard visualization across joint replacement cases. No study required post surgical pathology. Therefore, subjects did not have uniform documentation.

The assessment was based on available radiologic evidence (X-ray or MRI findings), clinical information, and histopathology evidence (if available). The same methodology was used during each adjudication meeting.

**Table 16:** Adjudication Case Definitions

**Osteonecrosis:**

Radiologic Evidence:

- X-Ray: Diagnosis of ON (find: Cystic and sclerotic changes; collapse of the femoral head, femoral condyle or tibial plateau; change in the contour of the femoral head, femoral/tibial condyle or tibial plateau, crescent sign)
- MRI: Diagnosis of ON (find: well-defined margin surrounding a focus of fat-like or fluid-like or low signal +/- surrounding edema, change in femoral head contour/tibial condyle or tibial plateau)

Histopathology Evidence (if available):

- Histopathology: Evidence of ON based on surgery histopathology/gross specimen report. Histopathology must correspond to radiographic evidence.

**Rapidly Progressive Osteoarthritis:**

Radiologic Evidence:

- Required availability of baseline comparison film(s)
- Initial radiographs: OA Kellgren Lawrence grade of 0-3 in the replaced joint
- Follow-up radiograph:
  - Focal JS narrowing of ≥50% or 2 mm per year (may need to adjust if visualization is not standard)
  - Flattening of the femoral head
  - Flattening of the femoral/tibial condyle or tibial plateau (knee)

Histopathology Evidence (if available):

- Histopathology consistent with totality of clinical and radiographic findings
- If ON present, evidence of focal ON only

**Rapidly Progressive Osteoarthritis With Features of ON:**

The same radiologic evidence as stated above for RPOA was used for RPOA but there were also features of ON.

**Normal Progression of OA:**

The diagnosis was based on evidence that was associated with a normal progression of OA.

**Other:**

The diagnosis of Other was based on the lack of evidence supporting a diagnosis of ON, RPOA, or normally progressing OA and was defined on a case-by-case basis.

**Insufficient Information:**

Cases with no obtainable radiologic images or cases with only pre-dose radiologic images available were considered insufficient by the adjudicators. These cases were considered not diagnosable based on the limited radiologic and/or clinical information that was available at the time of adjudication.

**Not Applicable:**

Cases of joint replacement revisions and/or device failures were considered not applicable for adjudication.

#### 5.6.2.4. Case Attribution

The adjudicators were also asked to attribute the diagnosis to treatment (active drug or placebo) and applied the following attributes: definitely related, probably related, possibly related, not related, and insufficient information for attribution assessment.

For those cases considered to have insufficient information for attribution assessment, the adjudicators were requested to identify what information was lacking. The sponsor would then attempt to obtain any missing information. If the missing information was obtained, this case would be reassessed by the adjudicators at a later date. If no further information was available, then this case was excluded from attribution assessment.

The following clinical information (if available) was used by the adjudicators to determine attribution to study drug: age, sex, body mass index, relevant prior/concurrent medical history, relevant concomitant/prior medications, number of doses of study drug, dates of first and last dose, latency (time from the date of the first dose of study drug to the date of diagnosis was based on the date of X-ray for new joint symptoms; for those few cases where this was not available, the date of consultation or pathology report was used), target joint and Kellgren-Lawrence score, pre-dose radiographs of replaced joint (dates, timing before first dose), post-dose radiographs (X-ray/MRI) and dates, relevant clinical course during study, joint replaced (date), Graphic displays of subject clinical study data including pain scores and physical activity (ie., subject profiles), date of diagnosis was a medical judgment based upon clinical review of investigator and/or orthopedic consult reports, radiologic reports (X-ray/MRI), surgery and pathology reports where available. The adjudicators assessed the relationship of joint replacements to blinded study drug after all available clinical information was provided to the adjudicators.

### 5.6.3. Results

As of 08 July 2011, 88 subjects with joint replacement (involving 101 joints) were identified in the fulranumab clinical program; the adjudicated findings for these cases are provided in Section 5.6.3.1. Based on post-study information collected through 15 November 2011, 7 joint replacements in 6 subjects were adjudicated at the fifth adjudication meeting held on 08 December 2011; the adjudicated findings for these joint replacements are provided in Attachment 16.

In addition, one subject (Subject 131607) in PAI 2003 had a lumbar device failure that was adjudicated. As this case was a lumbar device failure and not a joint replacement, the case is not included in the discussion of adjudicated joint replacements in this section.

#### 5.6.3.1. Adjudication of Joint Replacements as of 08 July 2011

As of 08 July 2011, 101 joint replacements (97 initial replacements and 4 revisions of replacements) in 88 subjects and 1 device failure in 1 subject have been assessed over the course of 4 adjudication meetings. Attachment 24 shows the diagnosis and attribution to study drug assigned by the adjudication team.

**Adjudicated Diagnoses**

Overall, the majority of the joint replacements were classified as normal progression of OA (65 of 101), representing 64% of the cases adjudicated as of 08 July 2011 (Table 17). Eighteen joint replacements were classified as RPOA, 18% of cases adjudicated as of 08 July 2011. No cases were assessed as either ON or RPOA with features of ON.

Fourteen cases had insufficient information to assess and 4 cases were considered as NA as they were revisions of joint replacements. The lumbar device failure was considered as NA. The number of subjects classified as having insufficient information of NA was evenly distributed across the fulranumab dose groups.

A dose effect cannot be excluded among patients with an adjudicated diagnosis of normal progression of OA.

All 17 joint replacement cases initially reported as ON were adjudicated as being consistent with RPOA (9 joints), normal progression of OA (7 joints), or insufficient information for a diagnosis (1 joint). One additional case initially reported as ON was adjudicated as normal progression of OA; joint replacement information was received after the case was adjudicated.

Joint Replacements Adjudicated as RPOA

Eighteen joints in 17 subjects were adjudicated as RPOA (Table 17). All 18 joints adjudicated as RPOA were in one of the fulranumab-treated groups. In each of 2 non-OA pain studies, NPP-2001 (PHN/PTN) and PAI-2003 (LBP), 1 subject in the fulranumab group and no subjects in the placebo group had RPOA. In PAI-2004 (Add-on OA), 15 (involving 16 joints) of 388 subjects treated with fulranumab had RPOA (3.9%; 95% CI, 2.2%-6.3%) compared with none of the 78 subjects in the placebo group (95% CI, 0-3.7%). A Kaplan-Meier plot of the time to joint replacement surgery for subjects with RPOA is provided in Attachment 25. There is no safety signal for ON, but a safety signal for RPOA was detected. Due to the small number of RPOA cases per treatment group, a dose effect for RPOA cannot be evaluated.

All joints diagnosed with RPOA in the fulranumab clinical studies occurred in subjects for whom a history of OA could be documented. All joints diagnosed with RPOA occurred in subjects who were taking NSAIDs.

**Table 17:** Joint Replacements in Fulranumab Clinical Studies by Study Drug and Fulranumab Dose - Adjudicated as of 08 July 2011

| Treatment | Number of Adjudicated Joint Replacements[a] | Adjudicated Case Definitions | | | | | |
|---|---|---|---|---|---|---|---|
| | | ON | RPOA | RPOA With Features of ON | Normal Progression of OA | NA[b] | Insufficient Information |
| Placebo | 12 | 0 | 0 | 0 | 10 | 1 | 1 |
| Fulranumab | 88 | 0 | 18 | 0 | 55 | 3 | 12 |
| Oxycodone CR | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| **Total** | **101** | **0** | **18** | **0** | **65** | **4** | **14** |
| By fulranumab dose[c]: | | | | | | | |
| 1mgQ4wk | 11 | 0 | 2 | 0 | 6 | 1 | 2 |
| 3mgQ8wk | 9 | 0 | 2 | 0 | 5 | 0 | 2 |
| 3mgQ4wk | 20 | 0 | 6 | 0 | 13 | 1 | 0 |
| 6mgLD+3mgQ4wk | 3 | 0 | 0 | 0 | 2 | 0 | 1 |
| 6mgQ8wk | 15 | 0 | 2 | 0 | 11 | 1 | 1 |
| 9mgQ4wk | 3 | 0 | 0 | 0 | 2 | 0 | 1 |
| 10mgQ8wk | 19 | 0 | 5 | 0 | 11 | 0 | 3 |
| 10mgQ4wk | 6 | 0 | 1 | 0 | 5 | 0 | 0 |
| 20mgQ4wk | 2 | 0 | 0 | 0 | 0 | 0 | 2 |

LD=loading dose; NA=not applicable; OA=osteoarthritis; ON=osteonecrosis: Qxwk=every x weeks; RPOA=rapidly progressive osteoarthritis.

[a] Percentages are not be calculated in this table as this table summarizes the number of joints replaced; the percentages of subjects with joint replacements are provided in Table 5.

[b] Cases of joint replacements revisions were considered not applicable for adjudication.

[c] Arranged in increasing order based upon initial dose.

### Attribution to Study Drug

The majority (65/101) of the joint replacements were assessed as not related to blinded study drug; 17 were assessed as possibly related, and 14 were considered to have insufficient data for assessment of relationship (Table 18). Of the 18 cases that were classified as RPOA, 17 were considered to be possibly related to study drug, and 1 case was considered not related.

**Table 18:** Adjudicated Joint Replacements by Diagnosis and Attribution - Adjudicated as of 08 July 2011

| | Joints | Diagnosis | Possibly Related | Not Related | Insufficient Information |
|---|---|---|---|---|---|
| **Joint replacements (subjects)** | **101 (88)[a]** | | | | |
| *Joint replacement (initial)[b]* | 97 | | | | |
| | 0 | ON | - | - | - |
| | 0 | RPOA + ON | - | - | - |
| | 18 | RPOA | 17[c] | 1 | 0 |
| | 65 | NP OA | 0 | 65 | 0 |
| | 14 | Insufficient Information | 0 | 0 | 14 |
| *Joint replacement (revision)[b]* | 4 | NA | - | - | - |

OA=osteoarthritis; ON=osteonecrosis; RPOA + ON=rapidly progressive OA with features of osteonecrosis; NP OA=normal progression of OA; Insufficient=information was insufficient for adjudication; NA=case not applicable for adjudication (ie. revision of a previous joint replacement)

Note: Each case (joint replacement) with a diagnosis had an attribution.

[a] The adjudicated finding for a lumbar device failure (Subject 131607 in PAI 2003) and 7 joints in 5 subjects identified as having an adverse event possibly related to joint destruction but who did not have a joint replacement (see Section 5.5.2.2) are not included in this table.

[b] Joint replacements were either the first occurrence for a subject (initial) or a revision of a previous joint replacement.

[c] One case received a tie between an attribution of possibly related and insufficient information. For the purposes of this summary, the attribution was counted under possibly related.

#### 5.6.3.1.1. Comparison of Subjects With and Without Joint Replacement and RPOA in PAI-2004 (OA Add-on)

In the fulranumab clinical studies, all cases adjudicated as RPOA went to joint replacement. The majority of joint replacement and RPOA cases occurred in the OA population.

Among the 15 subjects with RPOA in PAI-2004 (OA Add-on), the mean age was 65 years, most (73%) were women, and 47% had a BMI ≥30 kg/m$^2$. There appeared to be slightly more women and subjects ≥65 years old among subjects who developed RPOA, compared to joint replacement non-RPOA or non-joint replacement populations. In PAI-2004, subjects who developed RPOA appeared to have somewhat higher NRS pain scores and WOMAC function scores at baseline, compared to joint replacement non-RPOA or non-joint replacement populations. All subjects with RPOA were receiving a combination of NSAIDs and fulranumab. Demographic and baseline characteristics for subjects with RPOA are summarized in Attachment 26. Subjects with RPOA received a median of 11 injections (range: 5 to 15 injections) before joint replacement surgery (Attachment 27).

In PAI-2004 (OA Add-on), 13% (2/15) of subjects with RPOA had a TEAE that was included in the broad scope of the peripheral neuropathy SMQ (Table 19;

Attachment 28). The percentages of fulranumab-treated subjects with TEAEs that were included in the broad scope of the peripheral neuropathy SMQ were similar for the joint replacement non-RPOA and the non-joint replacement populations.

A systematic search of the fulranumab clinical database for neuropathic arthropathy, the preferred term that includes Charcot joint, did not reveal any cases of Charcot joint. A case of Charcot of the foot was reported for one subject with advanced DPN in NPP-2002 (DPN) after database lock (Attachment 15). Charcot neuroosteoarthropathy is a major complication of diabetes and is not an unexpected finding in patients with advanced DPN.[55]

**Table 19:** Peripheral Neuropathy SMQ (Broad Scope) for All Combined Phases in PAI-2004 (OA Add-on) as of 08 July 2011

| | RPOA | | Joint Replacement with No RPOA | | Non-Joint Replacement | |
|---|---|---|---|---|---|---|
| | Placebo (n=0) | Fulranumab (n=15) | Placebo (N=8) | Fulranumab (N=48) | Placebo (N=70) | Fulranumab (N=325) |
| Subjects with TEAEs included in the Broad Scope Peripheral Neuropathy SMQ, n (%) | 0 | 2 (13) | 0 | 9 (19) | 11 (16) | 69 (21) |

RPOA=rapidly progressive osteoarthritis; SMQ=Standardized MedDRA Queries; TEAE=treatment-emergent adverse event.

### 5.6.4. Conclusions

- All joint replacements identified in the fulranumab program as of 08 July 2011 have been adjudicated.
- As of 8 July 2011:
  - 101 joint replacements in 88 subjects have been adjudicated by an independent committee comprised of external clinical experts (orthopedic surgeons, rheumatologists, and a radiologist) who have clinical experience with patients with ON or RPOA and were blinded to randomized treatment assignment. The case definitions were developed and agreed upon by the adjudicators.
  - No cases were adjudicated as ON or RPOA with features of ON.
  - A safety signal for RPOA was detected in that 18 cases were adjudicated as RPOA in the fulranumab group compared with none in the placebo group. Due to the small number of RPOA cases per treatment group, a dose effect for RPOA cannot be evaluated.

# 6. RISK MANAGEMENT FOR FUTURE FULRANUMAB STUDIES

# 6. RISK MANAGEMENT FOR FUTURE FULRANUMAB STUDIES

## 6.1. Fulranumab Clinical Studies in OA Pain

The sponsor proposes to institute 2 new modifications in future fulranumab clinical studies in OA pain to lower the incidence of RPOA. Based upon findings from tanezumab trials and corroborated in the fulranumab data, it is expected that prohibiting concomitant chronic NSAID use and excluding higher fulranumab doses (6 mg and 10 mg) in future OA trials will substantially reduce the incidence of RPOA. In order to assess the effectiveness of these measures and to detect a safety signal early in the study, the sponsor proposes to monitor joint safety by establishing measures to identify cases of RPOA (monitoring joint-related AEs and associated investigations, utilizing surveillance with standardized x-rays at predefined intervals; establishing an independent adjudication committee to evaluate and render a diagnosis for all joint replacements and other joint-related AEs in a blinded fashion, and establishing an independent DMC to assess joint safety in an unblinded fashion). Depending upon findings, individual cases may be identified for additional follow-up; potentially resulting in earlier recognition of RPOA and allowing earlier and potentially less complex joint replacement surgery. An independent, unblinded DMC will monitor the cumulative benefit/risk profile of fulranumab and advise the sponsor of safety issues that may necessitate the termination of specific treatment arms in trials or termination of trials altogether.

At present, there is insufficient evidence in the clinical studies with fulranumab to conclude that RPOA is a dose-related phenomenon; however, available data from studies of another anti-NGF antibody (tanezumab) suggest that the risk of RPOA appears to be dose related. In the 2 Phase 2 fulranumab OA studies there appears to be no increased efficacy in doses greater than 3 mg, thus, the sponsor would consider excluding doses greater than 3 mg from future fulranumab OA studies.

Based upon the available data from studies of another anti-NGF antibody (tanezumab), the sponsor proposes to limit concomitant chronic NSAID use.

Subject selection criteria will be used to increase the benefit to the individual subject by selection of subjects who require alternative analgesic therapies (eg, subjects inadequately treated with or intolerant to current therapies, ie, opioids and/or NSAIDs, at adequate doses) or who are waiting for joint replacement surgery.

Subjects who are poor surgical candidates (eg, subjects with cardiovascular risks) will be excluded from fulranumab clinical studies to reduce the risk of surgery, which may be needed to manage RPOA.

At baseline, the sponsor plans to collect the following information on potential risk factors:

- Record use of NSAIDs prior to the study
- X-rays of both joints for shoulders, hips and knees using standardized X-ray methods will be obtained and read centrally.
- A comprehensive OA history, including signs and symptoms of OA and medical history will be obtained.
- Serum and urine samples will be collected to study the potential association of biomarkers in the progression of OA (eg, those related to cartilage synthesis and degradation, bone synthesis and desorption, and markers of inflammation).
- The presence of other possible risk factors for OA progression (eg, congenital hip dysplasia, Legg-Calvé-Perthe's disease, gout, pseudo gout, varus deformities, etc) will be documented.

The following ongoing assessments of subjects will be performed to monitor the potential risk of RPOA:

- Monitor joint signs and symptoms
- Obtain radiographic studies of each knee, shoulder, and hip at pre-defined scheduled times (eg, annually)
- Obtain radiographic studies as part of the diagnostic work-up for subjects who develop a sustained unexplained increase in OA symptoms
- Continue to monitor posttreatment safety for 6 months after the last dose of study drug
- Monitor OMERACT-OARSI Responder Index

The sponsor plans to collect the following subject-specific safety data to characterize all joint replacements and joint-related adverse events:

- Additional joint imaging may be requested by the sponsor as part of the diagnostic work-up for joint-related adverse events
- External sources of information that inform the assessment of joint-related adverse events may be required. These external sources of information may include consultation reports; operative reports; imaging (X-rays, MRIs, ultrasounds etc); and histology and/or tissue specimens
- Extended follow-up post-study to detect safety signals
- Extended follow-up after joint replacement surgery to assess impact of study treatment
- Explore subject activity levels

Risk Reduction for the Individual Subject

- Dosing of individuals can be stopped at any time by the investigator based on clinical assessment of joint-related adverse events.
- Dosing of any individual subject will be held if a persistent and unexplained clinically significant joint-related event occurs. The subject will be assessed, and findings will be submitted to the independent Adjudication Committee for case review and recommendation if dosing needs to be either stopped or resumed.
- Radiologic changes consistent with RPOA may be identified early based on increased frequency of surveillance radiographs and focused monitoring of change in joint symptoms

Risk Reduction for the Study Population as a Whole:

- Limit concomitant chronic NSAID use.
- Joint replacements and other joint-related AEs (JRAEs) will be considered as events of interest
- All JRAEs to be prospectively assessed by an independent Adjudication Committee (with expertise in rheumatology, orthopedics & radiology) as to diagnosis and relationship to study drug
- The Adjudication Committee will provide advice/consultation to the Independent DMC who will provide a recommendation to the sponsor
- Possibly institute a central Adjudication Committee for all sponsors a sponsor/drug-specific Independent DMC
- Based on the benefit/risk profile, the Independent DMC will determine whether an individual dosing group or the study needs to be changed or stopped

## 6.2. Fulranumab Clinical Studies in Non-OA Pain Conditions

The incidences of joint replacements in fulranumab clinical studies in non-OA pain conditions were low (Table 9). If doses greater than 3 mg are required based on the benefit-risk profile of fulranumab in a specific patient population, then subjects with significant concomitant OA will be excluded. The concomitant use of NSAIDs will be restricted.

All subjects will be screened for the presence of OA at baseline. The sponsor will monitor all subjects using measures similar to those in the OA pain studies (eg, pre-defined scheduled X-ray of bilateral hip, knee and shoulder, OA history, and joint-related adverse events.

# 7. BENEFIT/RISK ASSESSMENT/DISCUSSION OF FULRANUMAB

# 7. BENEFIT/RISK ASSESSMENT OF FULRANUMAB AND THE BASIS FOR RESUMPTION OF STUDIES

The available data from the clinical studies suggest that fulranumab may provide clinically meaningful efficacy for improvement in pain and functional impairment and was well tolerated in subjects with moderate to severe pain due to OA whose pain is not sufficiently treated with standard of care (PAI-2004; OA Add-on). The maximum effect of fulranumab has been observed with an intermediate dose (3mgQ4wk) in the range tested; further dose increase did not appear to provide additional benefit in the OA patient population.

As of 08 July, 88 of 1,353 subjects treated in the 9 Phase 1/1b and Phase 2 studies of fulranumab had at least 1 joint replacement. Most (75/88) of the subjects with joint replacement(s) were treated in studies in subjects with moderate to severe OA pain (2004145; PAI-2004, and PAI-2006). This finding is expected as OA is a known risk factor for joint replacement surgery. In PAI-2004 (OA Add-on), the study contributing most of the joint replacements, the incidence rate was 143 per 1000 person-years in the fulranumab group (any dose) and 100 per 1000 person-years in the placebo group. The incidence rate in the placebo group is similar to that reported for patients with severe OA with pain scores ≥5 in the OAI study, suggesting that the population in PAI-2004 is consistent with a population with severe, symptomatic OA.

In the fulranumab program, joint replacements occurred both on treatment and after study drug discontinuation. The overall hazard ratio for joint replacement for subjects treated with fulranumab versus placebo was greater after study drug discontinuation (1.41; 90% CI, 0.76%-2.61%) compared with "on treatment" (0.90; 90% CI, 0.46%-1.78%). In the 2 lowest fulranumab dose groups (1mgQ4wk and 3mgQ8wk), the hazard ratios increased after study drug discontinuation but remained below that of placebo. In the placebo group, the incidence of joint replacements remained essentially unchanged after study drug discontinuation (ie, from 20 January 2011 to 08 July 2011), whereas the incidence increased in the fulranumab groups. At both time points (20 January 2011 and 08 July 2011), the hazard ratio for joint replacement was highest in the fulranumab 10mgQ8wk versus placebo group.

Further investigation is required to understand joint replacement in relation to fulranumab treatment. The abrupt cessation of therapy makes interpretation of the current data difficult. Possible explanations for the occurrence of joint replacements after the discontinuation of therapy include: 1) subjects deferred joint replacement surgery while on therapy due to adequate pain relief; 2) subjects had resumption of pain following discontinuation of fulranumab therapy and sought joint replacement; and 3) subjects had

joint deterioration during study therapy, which resulted in joint replacement after the cessation of study therapy. Monitoring of joint replacement in a setting of ongoing treatment in future fulranumab studies will be conducted to provide more definitive information.

All joint replacements identified in the fulranumab program as of 08 July 2011 have been adjudicated by independent experts. No cases were adjudicated as ON. All joint replacement cases originally reported as being ON or AVN were adjudicated as normal progression of OA or RPOA. A safety signal for RPOA was detected in that 18 cases were adjudicated as RPOA in the fulranumab group compared with none in the placebo group. All joints diagnosed with RPOA in the fulranumab program occurred in subjects who were receiving a combination of NSAIDs and fulranumab. Based upon the available data from studies of another anti-NGF antibody (tanezumab), the sponsor proposes to limit concomitant chronic NSAID use in future fulranumab studies.

Due to the small number of RPOA cases per treatment group, a dose effect for RPOA cannot be excluded. In the fulranumab clinical studies, all cases adjudicated as RPOA went to joint replacement. All joint replacements and all joints diagnosed with RPOA occurred in subjects for whom a history of OA could be documented by radiologic images and/or symptomatology. RPOA is part of the spectrum of OA, and OA is known to be a risk factor for joint replacement. Additionally, long-term outcomes for subjects who undergo joint replacement for RPOA do not appear to differ from those who undergo joint replacement for end-stage OA.[101]

At present, there is insufficient evidence from the fulranumab clinical studies to determine whether RPOA is a dose-related phenomenon; however, available data from studies of another anti-NGF antibody (tanezumab) suggest that the risk of RPOA appears to be dose related. In future fulranumab studies, doses will be selected based on the efficacy and tolerability profile for each specific patient population.

In addition, the sponsor proposes to institute new procedures in future fulranumab clinical studies of OA pain to manage the risk of developing RPOA through clinical and radiological monitoring of joint safety; and ensuring prompt reporting of joint replacement; maintaining safety surveillance, including adjudication to determine the incidence of RPOA by an independent adjudication committee that would report to an independent DMC; and to intervene if a significant hazard is detected. Additionally, potential for favorable benefit-risk will be increased by ensuring that enrolled OA patients have significant levels of pain and functional impairment. In future fulranumab studies in chronic pain conditions other than OA pain, measures will be taken to ensure

that OA patients are appropriately enrolled and monitored to ensure prompt reporting of RPOA and joint replacements.

**Benefit/Risk Conclusion:**

Based on the current clinical data, literature review, and results of the adjudication of joint replacement cases, the sponsor proposes that the risk reduction strategy will be adequate to address the FDA's safety concerns and appropriately manage risk in further studies. As such, the potential benefits for treating pain in patients who may not have an alternative analgesic treatment or for whom alternative treatments carry substantial risks, warrant the continued development to further characterize the benefit-risk ratio of fulranumab in the treatment of OA pain and other chronic pain conditions. Additionally, fulranumab may provide potential benefits for improving functional impairment in patients with OA pain and may potentially delay or prevent joint replacement in some patients.

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## REFERENCES

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# SUPPORTING DATA

## Attachment 1: Phase 1/1b and Phase 2 Fulranumab Clinical Studies

**Summary of Phase 1/1b and Phase 2 Fulranumab Clinical Studies as of 01 June 2011**

| Study Number<br>Start / End Dates | Objective/Design | Population<br>Number of Treated Subjects[a] | Treatment Duration |
|---|---|---|---|
| **Phase 1 Completed Study** | | | |
| 20040195<br>(Amgen)<br>18 Jan 2005/<br>12 Jan 2006 | Single-center, randomized, double-blind, placebo-controlled, sequential, rising, single-dose, Phase 1 study to examine safety, tolerability, pharmacokinetics, and pharmacodynamics of IV and SC administration of fulranumab | 46 Healthy subjects<br><br>Fulranumab, n=34<br>Placebo, n=12 | Single fixed-dose of Fulranumab<br><br>- Fulranumab IV 1, 3, 10, 30, 100 or 300 mg or placebo<br><br>- Fulranumab SC 10, 30, 100 or 300 mg or placebo |
| **Phase 1b Completed Study** | | | |
| 20060145<br>(Amgen)<br>13 Dec 2006/<br>17 Jan 2008 | Multi-center, randomized, double-blind, placebo-controlled, sequential, multiple-dose, dose-escalation, Phase 1 study to examine the safety, tolerability, and pharmacokinetics of SC administration of fulranumab | 24 Subjects with OA of the knee<br><br>Fulranumab, n=18<br>Placebo, n=6 | Fixed dose of fulranumab; 12 week study, 4 injections once every 4 weeks<br><br>- Fulranumab SC 3, 10, 20 mg or placebo |
| **Phase 2 Ongoing Study** | | | |
| PAI-2001<br>24 Sep 2009/<br>ongoing | Multi-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety , and tolerability of fulranumab as adjunctive therapy in subjects with moderate to severe cancer-related pain with an open-label extension phase to evaluate long-term safety | 17 subjects with cancer-related pain<br><br>DB:<br>Fulranumab, 9mgQ4wk, n=unknown (planned:6 0)<br>Placebo, n=unknown (planned: 30)<br>Randomization 2:1 (fulranumab:placebo) | 52 weeks, injections every 4 weeks<br><br>4-week double-blind efficacy phase, 48-week open-label extension phase, and a 12-week follow-up phase |
| **Phase 2 Terminated Studies** | | | |
| PAI-2003<br>10 Sep 2009/<br>November 2010<br>(Study stopped early by the sponsor) | Multi-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of fulranumab in subjects with moderate to severe chronic low back pain not adequately controlled by standard pain therapy followed by a double-blind extension phase | 385 subjects with chronic lower back pain<br><br>12-Week DB Phase:<br>Fulranumab:<br>1mgQ4wk, n=77<br>3mgQ4wk, n=77<br>6mgLD+3mgQ4wk, n=78<br>10mgQ4wk, n=77<br>Placebo, n=76 | 104 weeks; injection every 4 weeks<br><br>12- week double-blind efficacy phase, a 92-week double-blind extension phase, and a 26-week post-treatment phase |

**Attachment 1: Phase 1/1b and Phase 2 Fulranumab Clinical Studies (Continued)**

**Summary of Phase 1/1b and Phase 2 Fulranumab Clinical Studies as of 01 June 2011**

| Study Number<br>Start / End Dates | Objective/Design | Population<br>Number of Treated Subjects[a] | Treatment Duration |
|---|---|---|---|
| PAI-2004<br>08 Sep 2009/<br>30 June 2011<br>(Study stopped early by the sponsor) | Multi-center, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of fulranumab in subjects with moderate to severe chronic OA knee or hip pain not adequately controlled by standard pain therapy followed by a double-blind extension phase | 466 subjects with chronic knee or hip pain due to OA<br><br>12-Week Double-blind Efficacy Phase:<br>Fulranumab<br>1mgQ4wk, n=77<br>3mgQ8wk, n=76<br>3mgQ4wk, n=79<br>6mgQ8wk, n=78<br>10mgQ8wk, n=78<br>Placebo, n=78 | 104 weeks; injection every 4 or 8 weeks<br><br>a 12- week double-blind efficacy phase, a 92-week double-blind extension phase, and a 26-week post-treatment phase |
| PAI-2005<br>22 Mar 2010/<br>24 Jun 2011<br>(Study stopped early by the sponsor) | Multi-center, randomized, double-blind, placebo-controlled study to explore the efficacy, safety, and tolerability of fulranumab in subjects with interstitial cystitis/painful bladder syndrome | 31 subjects with interstitial cystitis/ painful bladder syndrome<br><br>Fulranumab, 9mgQ4wk, n=14<br>Placebo, n=17<br>1:1 randomization | 12 weeks; injection every 4 weeks |
| PAI-2006<br>06 Apr 2010/<br>01 July 2011<br>(Study stopped early by the sponsor) | Multi-center, randomized, double-blind, placebo- and active-controlled study to evaluate the efficacy, safety, and tolerability of fulranumab monotherapy in subjects with moderate to severe chronic knee pain from OA not adequately controlled by standard pain therapy followed by a double-blind extension phase | 196 subjects with chronic knee pain due to OA<br><br>16-week Double-Blind Phase:<br>Fulranumab:<br>3mgQ4wk, n=48<br>9mgQ4wk, n=50<br><br>Oxycodone CR:<br>20 to 50 mg BID, n=50<br><br>Placebo, n=48 | Monotherapy<br>16 weeks; injection every 4 weeks<br><br>A 16-week double-blind phase (consisting of a 4-week titration period and a 12-week maintenance period), and a 26-week post-treatment phase |

**Attachment 1: Phase 1/1b and Phase 2 Fulranumab Clinical Studies (Continued)**

**Summary of Phase 1/1b and Phase 2 Fulranumab Clinical Studies as of 01 June 2011**

| Study Number<br>Start / End Dates | Objective/Design | Population<br>Number of Treated Subjects[a] | Treatment Duration |
|---|---|---|---|
| NPP-2001/<br>27 Aug 2009/<br>11 Oct 2011<br>(Study stopped early by the sponsor) | Multicenter, randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy, safety, and tolerability of fulranumab in subjects with postherpetic neuralgia and post-traumatic neuralgia.<br>Double-blind phase followed by a double-blind safety extension and an open-label safety extension | 111 subjects with postherpetic neuralgia or post-traumatic neuralgia<br><br>12-week Double-Blind Phase<br>Fulranumab<br>1mgQ4wks, n=13 (planned:30)<br>3mgQ4wk, n=14 (planned:30)<br>10mgQ4wk, n=42 (planned:70)<br>Placebo, n=42 (planned:70)<br>Randomization: 1:1:1:1 (fulranumab 1, 3, or 10 mg or placebo) | 104 weeks; injection every 4 weeks<br><br>A 12-week double-blind efficacy phase, a 40-week double-blind safety extension phase, a 52-week open-label safety extension phase, and a 26-week post-treatment/follow-up The study will consist of 5 sequential phases: screening, 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 |
| NPP-2002/<br>9 Sep 2009/<br>23 June 2011<br>(Study stopped early by the sponsor) | Multicenter, randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy, safety, and tolerability of fulranumab in subjects with diabetic painful neuropathy.<br>Double-blind phase followed by a double-blind safety extension and an open-label safety extension | 77 subjects with diabetic painful neuropathy<br><br>12-week double-blind efficacy phase:<br>Fulranumab<br>1mgQ4wks, n=16 (planned:40)<br>3mgQ4wk, n=14 (planned:40)<br>10mgQ4wk, n=23 (planned:60)<br>Placebo, n=24 (planned:60)<br>Randomization: 3:2:2:3 (fulranumab 1, 3, or 10 mg or placebo) | 104 weeks; injection every 4 weeks<br><br>The study consists of 5 sequential phases: screening, 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. |

[a] Number of subject in the intent-to-treat population (ie, randomized subjects who received at least 1 dose of study drug).

BID=twice daily; IV=intravenous; LD=loading dose; OA=osteoarthritis; Q4wk=every 4 weeks; Q8wk=every 8 weeks; SC=subcutaneous

## Attachment 2: Demographic and Baseline Characteristics (PAI-2004 OA Add-on)

Demographic and Baseline Characteristics
(Study 42160443-PAI2004 – Double Blind Efficacy Phase: Intent-To-Treat Analysis Set)

| | Placebo (N=78) | Fulranumab 1mgQ4wk (N=77) | Fulranumab 3mgQ8wk (N=76) | Fulranumab 3mgQ4wk (N=79) | Fulranumab 6mgQ8wk (N=78) | Fulranumab 10mgQ8wk (N=78) | Total (N=466) |
|---|---|---|---|---|---|---|---|
| **Sex, n (%)** | | | | | | | |
| N | 78 | 77 | 76 | 79 | 78 | 78 | 466 |
| Female | 43 (55.1) | 45 (58.4) | 45 (59.2) | 46 (58.2) | 47 (60.3) | 42 (53.8) | 268 (57.5) |
| Male | 35 (44.9) | 32 (41.6) | 31 (40.8) | 33 (41.8) | 31 (39.7) | 36 (46.2) | 198 (42.5) |
| **Race, n (%)** | | | | | | | |
| N | 78 | 77 | 76 | 79 | 78 | 78 | 466 |
| White | 67 (85.9) | 65 (84.4) | 68 (89.5) | 67 (84.8) | 65 (83.3) | 66 (84.6) | 398 (85.4) |
| Black or African American | 7 ( 9.0) | 7 ( 9.1) | 6 ( 7.9) | 11 (13.9) | 9 (11.5) | 7 ( 9.0) | 47 (10.1) |
| Asian | 3 ( 3.8) | 3 ( 3.9) | 2 ( 2.6) | 1 ( 1.3) | 2 ( 2.6) | 4 ( 5.1) | 15 ( 3.2) |
| American Indian or Alaska native | 1 (1.3) | 1 (1.3) | 0 | 0 | 0 | 0 | 2 ( 0.4) |
| Multiple | 0 | 1 (1.3) | 0 | 0 | 1 (1.3) | 0 | 2 ( 0.4) |
| Other | 0 | 0 | 0 | 0 | 1 (1.3) | 1 (1.3) | 2 ( 0.4) |
| **Age** | | | | | | | |
| N | 78 | 77 | 76 | 79 | 78 | 78 | 466 |
| Category, n (%) | | | | | | | |
| < 65 | 50 (64.1) | 49 (63.6) | 49 (64.5) | 49 (62.0) | 53 (67.9) | 48 (61.5) | 298 (63.9) |
| ≥ 65 | 28 (35.9) | 28 (36.4) | 27 (35.5) | 30 (38.0) | 25 (32.1) | 30 (38.5) | 168 (36.1) |
| Mean (SD) | 61.3 (8.26) | 61.2 (9.23) | 60.5 (8.81) | 60.8 (9.42) | 60.7 (8.96) | 61.4 (9.50) | 61.0 (9.00) |
| Median | 61.0 | 62.0 | 60.5 | 62.0 | 59.5 | 62.5 | 61.0 |
| Range | (42;80) | (42;78) | (42;78) | (40;80) | (41;80) | (40;79) | (40;80) |
| **Baseline weight (kg)** | | | | | | | |
| N | 78 | 77 | 76 | 79 | 78 | 78 | 466 |
| Mean (SD) | 92.2 (22.50) | 86.8 (17.17) | 90.1 (18.54) | 90.7 (16.80) | 91.8 (19.83) | 90.4 (20.93) | 90.3 (19.37) |
| Median | 90.0 | 87.6 | 88.8 | 90.0 | 93.3 | 89.6 | 89.5 |
| Range | (59;198) | (49;127) | (51;134) | (50;128) | (55;138) | (57;143) | (49;198) |
| **Baseline height (cm)** | | | | | | | |
| N | 78 | 77 | 76 | 79 | 78 | 78 | 466 |
| Mean (SD) | 167.6 (15.04) | 168.3 (11.17) | 168.6 (10.32) | 169.4 (9.13) | 167.5 (10.83) | 169.1 (12.19) | 168.4 (11.56) |
| Median | 168.2 | 166.0 | 167.8 | 169.0 | 168.0 | 168.4 | 168.0 |
| Range | (69;194) | (147;194) | (145;191) | (152;189) | (137;191) | (143;206) | (69;206) |
| **Baseline BMI (kg/m2)** | | | | | | | |
| N | 78 | 77 | 76 | 79 | 78 | 78 | 466 |
| Mean (SD) | 34.4 (20.30) | 30.6 (5.28) | 31.6 (5.36) | 31.5 (5.19) | 32.7 (6.05) | 31.5 (5.86) | 32.0 (9.75) |
| Median | 31.0 | 29.8 | 32.1 | 30.5 | 31.8 | 31.1 | 31.2 |
| Range | (21;201) | (19;47) | (19;45) | (20;47) | (22;46) | (21;47) | (19;201) |
| **Stratum 1 - baseline opioid use, n (%)** | | | | | | | |
| N | 78 | 77 | 76 | 79 | 78 | 78 | 466 |
| No opioids | 53 (67.9) | 52 (67.5) | 53 (69.7) | 53 (67.1) | 53 (67.9) | 53 (67.9) | 317 (68.0) |
| Use opioids | 25 (32.1) | 25 (32.5) | 23 (30.3) | 26 (32.9) | 25 (32.1) | 25 (32.1) | 149 (32.0) |
| **Stratum 2 - baseline body weight group, n (%)** | | | | | | | |
| N | 78 | 77 | 76 | 79 | 78 | 78 | 466 |
| <85kg | 31 (39.7) | 31 (40.3) | 30 (39.5) | 31 (39.2) | 31 (39.7) | 31 (39.7) | 185 (39.7) |
| ≥ 85kg | 47 (60.3) | 46 (59.7) | 46 (60.5) | 48 (60.8) | 47 (60.3) | 47 (60.3) | 281 (60.3) |
| **Type of study joint, n (%)** | | | | | | | |
| N | 78 | 77 | 76 | 79 | 78 | 78 | 466 |
| Hip | 13 (16.7) | 17 (22.1) | 21 (27.6) | 18 (22.8) | 22 (28.2) | 16 (20.5) | 107 (23.0) |
| Knee | 65 (83.3) | 60 (77.9) | 55 (72.4) | 61 (77.2) | 56 (71.8) | 62 (79.5) | 359 (77.0) |

## Attachment 3: Demographic and Baseline Characteristics for Subjects by Joint Replacement Status (PAI-2004 OA Add-on)

**Output TSUB02_JRJUL8:** Demographic and Baseline Characteristics by Joint Replacement Status
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-To-Treat Analysis Set)

| | ----- RPOA ---- (N=15) | JR minus RPOA (N=56) | ---- Non-JR --- (N=395) | ---- Total ---- (N=466) |
|---|---|---|---|---|
| **Age** | | | | |
| N | 15 | 56 | 395 | 466 |
| Category, n (%) | | | | |
| < 65 | 6 (40.0) | 33 (58.9) | 259 (65.6) | 298 (63.9) |
| ≥ 65 | 9 (60.0) | 23 (41.1) | 136 (34.4) | 168 (36.1) |
| Mean (SD) | 65.1 (9.12) | 63.2 (8.44) | 60.5 (9.01) | 61.0 (9.01) |
| Median | 66.0 | 63.0 | 61.0 | 61.0 |
| Range | (49;80) | (45;80) | (40;80) | (40;80) |
| **Sex, n (%)** | | | | |
| N | 15 | 56 | 395 | 466 |
| Female | 11 (73.3) | 37 (66.1) | 220 (55.7) | 268 (57.5) |
| Male | 4 (26.7) | 19 (33.9) | 175 (44.3) | 198 (42.5) |
| **Race, n (%)** | | | | |
| N | 15 | 56 | 395 | 466 |
| White | 14 (93.3) | 52 (92.9) | 332 (84.1) | 398 (85.4) |
| Black | 0 | 4 ( 7.1) | 43 (10.9) | 47 (10.1) |
| Asian | 1 ( 6.7) | 0 | 14 ( 3.5) | 15 ( 3.2) |
| Other | 0 | 0 | 6 ( 1.5) | 6 ( 1.3) |
| **Baseline BMI (kg/m2), n (%)** | | | | |
| N | 15 | 56 | 395 | 466 |
| < 30 | 8 (53.3) | 22 (39.3) | 170 (43.0) | 200 (42.9) |
| 30 to < 40 | 6 (40.0) | 30 (53.6) | 205 (51.9) | 241 (51.7) |
| ≥ 40 | 1 ( 6.7) | 4 ( 7.1) | 20 ( 5.1) | 25 ( 5.4) |
| **Strata 1 - baseline opioid use, n (%)** | | | | |
| N | 15 | 56 | 395 | 466 |
| No opioids | 10 (66.7) | 40 (71.4) | 267 (67.6) | 317 (68.0) |
| Use opioids | 5 (33.3) | 16 (28.6) | 128 (32.4) | 149 (32.0) |
| **Strata 2 - baseline body weight group, n (%)** | | | | |
| N | 15 | 56 | 395 | 466 |
| <85kg | 7 (46.7) | 24 (42.9) | 154 (39.0) | 185 (39.7) |
| ≥ 85kg | 8 (53.3) | 32 (57.1) | 241 (61.0) | 281 (60.3) |
| **Type of study joint, n (%)** | | | | |
| N | 15 | 56 | 395 | 466 |
| Hip | 6 (40.0) | 20 (35.7) | 82 (20.8) | 108 (23.2) |
| Knee | 9 (60.0) | 36 (64.3) | 313 (79.2) | 358 (76.8) |

## Attachment 3: Demographic and Baseline Characteristics for Subjects by Joint Replacement Status (PAI-2004 OA Add-on) (Continued)

**Output TSUB02_JRJUL8: Demographic and Baseline Characteristics by Joint Replacement Status (Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-To-Treat Analysis Set)**

| | ----- RPOA ---- (N=15) | JR minus RPOA (N=56) | ---- Non-JR --- (N=395) | ---- Total ---- (N=466) |
|---|---|---|---|---|
| **Womac baseline pain category, n (%)** | | | | |
| N | 15 | 56 | 394 | 465 |
| None to mild | 0 | 2 ( 3.6) | 31 ( 7.9) | 33 ( 7.1) |
| Moderate | 10 (66.7) | 32 (57.1) | 236 (59.9) | 278 (59.8) |
| Severe | 5 (33.3) | 22 (39.3) | 127 (32.2) | 154 (33.1) |
| **KL grade at baseline, n (%)** | | | | |
| N | 15 | 56 | 394 | 465 |
| 2 | 8 (53.3) | 9 (16.1) | 183 (46.4) | 200 (43.0) |
| 3 | 4 (26.7) | 29 (51.8) | 154 (39.1) | 187 (40.2) |
| 4 | 3 (20.0) | 18 (32.1) | 57 (14.5) | 78 (16.8) |
| **Baseline average NRS pain score** | | | | |
| N | 15 | 56 | 395 | 466 |
| Category, n (%) | | | | |
| < 6 | 3 (20.0) | 12 (21.4) | 101 (25.6) | 116 (24.9) |
| ≥ 6 | 12 (80.0) | 44 (78.6) | 294 (74.4) | 350 (75.1) |
| Mean (SD) | 7.1 (1.30) | 7.0 (1.25) | 6.8 (1.17) | 6.8 (1.19) |
| Median | 7.0 | 7.0 | 6.8 | 6.8 |
| Range | (5;10) | (5;10) | (5;10) | (5;10) |
| **Womac baseline pain score** | | | | |
| N | 15 | 56 | 394 | 465 |
| Mean (SD) | 6.6 (1.56) | 6.7 (1.54) | 6.3 (1.54) | 6.3 (1.54) |
| Median | 6.2 | 6.7 | 6.2 | 6.2 |
| Range | (5;9) | (3;10) | (1;10) | (1;10) |
| **Womac baseline physical function** | | | | |
| N | 15 | 56 | 394 | 465 |
| Mean (SD) | 6.8 (1.44) | 6.6 (1.54) | 6.3 (1.65) | 6.3 (1.64) |
| Median | 6.5 | 6.7 | 6.4 | 6.4 |
| Range | (5;10) | (2;10) | (0;10) | (0;10) |
| **Womac baseline stiffness score** | | | | |
| N | 15 | 56 | 394 | 465 |
| Mean (SD) | 6.8 (1.94) | 7.0 (1.65) | 6.8 (1.64) | 6.8 (1.65) |
| Median | 7.0 | 7.0 | 7.0 | 7.0 |
| Range | (3;10) | (2;10) | (1;10) | (1;10) |

tsub02_jrjul8.rtf generated by rdm_jrjul8.sas, 23JAN2012 11:25

## Attachment 4: Average Pain Scores (11-Point NRS) at the End of Double-Blind Efficacy Phase and at Week 16 of Double-Blind Treatment (PAI-2004 OA Add-on)

**Table TEFF01A:** Change From Baseline to the End of the DB Efficacy Phase in the Average Pain Intensity Score (LOCF) (Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-to-Treat Analysis Set)

| | Placebo (N=78) | Fulranumab 1mgQ4wk (N=77) | Fulranumab 3mgQ8wk (N=76) | Fulranumab 3mgQ4wk (N=79) | Fulranumab 6mgQ8wk (N=78) | Fulranumab 10mgQ8wk (N=78) |
|---|---|---|---|---|---|---|
| **Average Pain Scores** | | | | | | |
| WEEK 12 (LOCF) | | | | | | |
| Value at Baseline | | | | | | |
| N | 78 | 77 | 76 | 79 | 78 | 78 |
| Mean (SD) | 7.0 (1.10) | 6.9 (1.49) | 6.7 (1.19) | 6.6 (1.07) | 6.8 (1.08) | 6.9 (1.14) |
| Median (Range) | 7.0 (5;10) | 6.7 (5;10) | 6.5 (5;10) | 6.6 (5;10) | 7.0 (5;10) | 6.9 (5;9) |
| Value | | | | | | |
| N | 78 | 77 | 76 | 79 | 78 | 78 |
| Mean (SD) | 5.1 (2.27) | 4.5 (2.53) | 4.3 (2.40) | 3.6 (2.31) | 4.2 (2.61) | 4.2 (2.39) |
| Median (Range) | 5.1 (0;9) | 4.0 (0;10) | 4.2 (0;10) | 3.2 (0;8) | 4.4 (0;10) | 4.6 (0;9) |
| Change from Baseline | | | | | | |
| N | 78 | 77 | 76 | 79 | 78 | 78 |
| Mean (SD) | -1.9 (2.12) | -2.4 (2.27) | -2.4 (2.26) | -3.1 (2.38) | -2.6 (2.40) | -2.6 (2.14) |
| Median (Range) | -1.4 (-8;2) | -2.2 (-8;4) | -2.3 (-10;2) | -3.3 (-8;2) | -2.1 (-8;2) | -2.3 (-8;1) |
| LS Mean Change | -1.8 | -2.4 | -2.4 | -3.1 | -2.6 | -2.6 |
| P-value(minus Placebo)(a,b) | | 0.133 | 0.108 | <0.001 | 0.030 | 0.030 |
| Diff. of LS Means (SE) | | -0.5 (0.36) | -0.6 (0.36) | -1.3 (0.36) | -0.8 (0.36) | -0.8 (0.36) |
| 95% CI | | (-1.25;0.17) | (-1.30;0.13) | (-1.97;-0.56) | (-1.49;-0.08) | (-1.49;-0.08) |

(a) P-values and least squares means from ANCOVA model with treatment, baseline opioid use (use/no use), and baseline weight (<85 kg/ ≥ 85 kg) as factors and baseline average pain score as covariate.
(b) Nominal unadjusted p-values are presented.
LOCF=last observation carried forward.
teff01a.rtf generated by reffnrs.sas, 07NOV2011 10:26

Change from Baseline to the End of the First 16 weeks of Double-Blind Treatment in the Average Pain Intensity Score (LOCF)
(Study 42160443-PAI2004: Intent-to-Treat Analysis Set)

| Parameter | Treatment | N | L.S. Mean(SE) | Difference in LS Means(95% CI) (vs. Placebo) | P-value(a) |
|---|---|---|---|---|---|
| **Time Interval: WEEK 16 (LOCF)** | | | | | |
| Average Pain Scores | Placebo | 78 | -1.845(0.26) | | |
| | Fulranumab 1mgQ4wk | 77 | -2.664(0.26) | -0.82(-1.54,-0.10) | 0.026 |
| | Fulranumab 3mgQ8wk | 76 | -2.389(0.27) | -0.54(-1.27,0.18) | 0.141 |
| | Fulranumab 3mgQ4wk | 79 | -3.121(0.26) | -1.28(-1.99,-0.56) | <0.001 |
| | Fulranumab 6mgQ8wk | 78 | -2.445(0.26) | -0.60(-1.32,0.12) | 0.102 |
| | Fulranumab 10mgQ8wk | 78 | -2.681(0.26) | -0.84(-1.55,-0.12) | 0.023 |

(a) Test for no difference between treatments from ANCOVA model with factor(s) treatment,base,stratum1,stratum2 (type III SS).
Pairwise Comparison: unadjusted P-values and CIs
LOCF=last observation carried forward.
stratum1=baseline opioid use
stratum2=baseline body weight group (<85 kg/ ≥ 85 kg)

## Attachment 5: WOMAC Subscale of Pain at Week 12 (PAI-2004 OA Add-on)

**Table TEFF12A:** Change From Baseline to the End of the DB Efficacy Phase in the WOMAC Subscales and Global Scale Scores (LOCF)
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-to-Treat Analysis Set)

| | Placebo (N=78) | JNJ-42160443 1mgQ4wk (N=77) | JNJ-42160443 3mgQ8wk (N=76) | JNJ-42160443 3mgQ4wk (N=79) | JNJ-42160443 6mgQ8wk (N=78) | JNJ-42160443 10mgQ8wk (N=78) |
|---|---|---|---|---|---|---|
| **Subscale of Pain** | | | | | | |
| DOUBLE BLIND EFFICACY | | | | | | |
| END POINT (DB EF) | | | | | | |
| Value at Baseline | | | | | | |
| N | 77 | 76 | 76 | 78 | 76 | 77 |
| Mean (SD) | 6.6 (1.46) | 6.3 (1.84) | 6.4 (1.46) | 6.1 (1.48) | 6.3 (1.58) | 6.4 (1.42) |
| Median (Range) | 6.4 (3;10) | 6.3 (1;10) | 6.5 (3;10) | 6.1 (2;9) | 6.2 (1;10) | 6.2 (3;10) |
| Value | | | | | | |
| N | 77 | 76 | 76 | 79 | 76 | 77 |
| Mean (SD) | 4.8 (2.53) | 4.1 (2.54) | 3.8 (2.20) | 3.3 (2.29) | 3.8 (2.59) | 3.8 (2.42) |
| Median (Range) | 4.8 (0;10) | 3.6 (0;9) | 3.5 (0;9) | 3.0 (0;8) | 3.7 (0;9) | 3.6 (0;8) |
| Change from Baseline | | | | | | |
| N | 77 | 76 | 76 | 78 | 76 | 77 |
| Mean (SD) | -1.8 (2.02) | -2.2 (2.48) | -2.6 (2.34) | -2.8 (2.27) | -2.5 (2.48) | -2.6 (2.14) |
| Median (Range) | -1.6 (-6;3) | -2.1 (-8;3) | -2.4 (-10;3) | -2.7 (-8;2) | -2.2 (-8;4) | -2.4 (-7;1) |
| LS Mean Change | -1.7 | -2.2 | -2.5 | -2.9 | -2.4 | -2.6 |
| P-value(minus Placebo)(a,b) | | 0.175 | 0.020 | <0.001 | 0.034 | 0.013 |
| Diff. of LS Means (SE) | | -0.5 (0.36) | -0.8 (0.36) | -1.2 (0.36) | -0.8 (0.36) | -0.9 (0.36) |
| 95% CI | | (-1.19;0.22) | (-1.54;-0.13) | (-1.89;-0.48) | (-1.47;-0.06) | (-1.59;-0.19) |

(a) P-values and least squares means from ANCOVA model with treatment, baseline opioid use (use/no use), and baseline weight (<85 kg/ ≥ 85 kg) as factors and baseline total score as covariate.
(b) Nominal unadjusted p-values are presented.

## Attachment 6: NSAID Use by Joint Replacement Status (PAI-2004 OA Add-on)

**Output TCM_NSAID2_JRJUL8:** NSAID Use in DB EFF or DB EXT Phases by RPOA and Joint Replacement Status and Treatment Group
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-To-Treat Analysis Set)

| | RPOA | | | JR minus RPOA | | | Non-JR | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total | Treatment, n (%) | | Total | Treatment, n (%) | | Total | Treatment, n (%) | |
| Standardized Medication Name | (N=15) n (%) | Placebo (N=0) | Fulranumab (N=15) | (N=56) n (%) | Placebo (N=8) | Fulranumab (N=48) | (N=395) n (%) | Placebo (N=70) | Fulranumab (N=325) |
| **Total no. subjects With NSAID use** | 15 (100) | | 15 (100) | 49 ( 88) | 6 ( 75) | 43 ( 90) | 332 ( 84) | 57 ( 81) | 275 ( 85) |
| Ibuprofen | 3 ( 20) | 0 | 3 ( 20) | 17 ( 30) | 3 ( 38) | 14 ( 29) | 121 ( 31) | 21 ( 30) | 100 ( 31) |
| Celecoxib | 4 ( 27) | 0 | 4 ( 27) | 11 ( 20) | 0 | 11 ( 23) | 59 ( 15) | 10 ( 14) | 49 ( 15) |
| Naproxen sodium | 1 ( 7) | 0 | 1 ( 7) | 10 ( 18) | 1 ( 13) | 9 ( 19) | 52 ( 13) | 8 ( 11) | 44 ( 14) |
| Naproxen | 0 | 0 | 0 | 5 ( 9) | 1 ( 13) | 4 ( 8) | 46 ( 12) | 8 ( 11) | 38 ( 12) |
| Meloxicam | 4 ( 27) | 0 | 4 ( 27) | 8 ( 14) | 0 | 8 ( 17) | 38 ( 10) | 8 ( 11) | 30 ( 9) |
| Diclofenac | 2 ( 13) | 0 | 2 ( 13) | 3 ( 5) | 1 ( 13) | 2 ( 4) | 25 ( 6) | 5 ( 7) | 20 ( 6) |
| Diclofenac sodium | 0 | 0 | 0 | 1 ( 2) | 1 ( 13) | 0 | 13 ( 3) | 4 ( 6) | 9 ( 3) |
| Etodolac | 1 ( 7) | 0 | 1 ( 7) | 2 ( 4) | 0 | 2 ( 4) | 9 ( 2) | 1 ( 1) | 8 ( 2) |
| Acetylsalicylic acid | 1 ( 7) | 0 | 1 ( 7) | 2 ( 4) | 1 ( 13) | 1 ( 2) | 6 ( 2) | 0 | 6 ( 2) |
| Indometacin | 0 | 0 | 0 | 1 ( 2) | 0 | 1 ( 2) | 8 ( 2) | 2 ( 3) | 6 ( 2) |
| Nabumetone | 1 ( 7) | 0 | 1 ( 7) | 1 ( 2) | 0 | 1 ( 2) | 6 ( 2) | 1 ( 1) | 5 ( 2) |
| Sulindac | 1 ( 7) | 0 | 1 ( 7) | 1 ( 2) | 0 | 1 ( 2) | 5 ( 1) | 0 | 5 ( 2) |
| Arthrotec | 2 ( 13) | 0 | 2 ( 13) | 0 | 0 | 0 | 4 ( 1) | 0 | 4 ( 1) |
| Ketorolac tromethamine | 0 | 0 | 0 | 3 ( 5) | 0 | 3 ( 6) | 2 ( 1) | 1 ( 1) | 1 ( <1) |
| Piroxicam | 0 | 0 | 0 | 0 | 0 | 0 | 5 ( 1) | 1 ( 1) | 4 ( 1) |
| Thomapyrin n | 0 | 0 | 0 | 0 | 0 | 0 | 5 ( 1) | 0 | 5 ( 2) |
| Oxaprozin | 0 | 0 | 0 | 0 | 0 | 0 | 4 ( 1) | 2 ( 3) | 2 ( 1) |
| Ketorolac | 0 | 0 | 0 | 0 | 0 | 0 | 3 ( 1) | 1 ( 1) | 2 ( 1) |
| Alka-seltzer | 0 | 0 | 0 | 0 | 0 | 0 | 2 ( 1) | 1 ( 1) | 1 ( <1) |
| Diclofenac diethylamine | 0 | 0 | 0 | 1 ( 2) | 0 | 1 ( 2) | 1 ( <1) | 0 | 1 ( <1) |
| Diclofenac w/misoprostol | 0 | 0 | 0 | 0 | 0 | 0 | 2 ( 1) | 1 ( 1) | 1 ( <1) |
| Ketoprofen | 1 ( 7) | 0 | 1 ( 7) | 0 | 0 | 0 | 1 ( <1) | 0 | 1 ( <1) |
| Vicks formula 44m | 0 | 0 | 0 | 1 ( 2) | 0 | 1 ( 2) | 1 ( <1) | 1 ( 1) | 0 |
| Aceclofenac | 0 | 0 | 0 | 0 | 0 | 0 | 1 ( <1) | 0 | 1 ( <1) |
| Anacin | 0 | 0 | 0 | 0 | 0 | 0 | 1 ( <1) | 0 | 1 ( <1) |
| Asasantin | 0 | 0 | 0 | 0 | 0 | 0 | 1 ( <1) | 1 ( 1) | 0 |

Note: Percentages in 'Total' column for each group calculated with the number of subjects in each group as denominator.
Percentages of treatment sub-groups calculated with number of subjects per sub-group as denominator.

## Attachment 6: NSAID Use by Joint Replacement Status (PAI-2004 OA Add-on) (Continued)

**Output TCM_NSAID2_JRJUL8:** NSAID Use in DB EFF or DB EXT Phases by RPOA and Joint Replacement Status and Treatment Group
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-To-Treat Analysis Set)

| | ---------- Total ---------- | | |
|---|---|---|---|
| | Total | --- Treatment, n (%) --- | |
| | (N=466) | Placebo | Fulranumab |
| Standardized Medication Name | n (%) | (N=78) | (N=388) |
| **Total no. subjects With NSAID use** | 396 ( 85) | 63 ( 81) | 333 ( 86) |
| Ibuprofen | 141 ( 30) | 24 ( 31) | 117 ( 30) |
| Celecoxib | 74 ( 16) | 10 ( 13) | 64 ( 16) |
| Naproxen sodium | 63 ( 14) | 9 ( 12) | 54 ( 14) |
| Naproxen | 51 ( 11) | 9 ( 12) | 42 ( 11) |
| Meloxicam | 50 ( 11) | 8 ( 10) | 42 ( 11) |
| Diclofenac | 30 ( 6) | 6 ( 8) | 24 ( 6) |
| Diclofenac sodium | 14 ( 3) | 5 ( 6) | 9 ( 2) |
| Etodolac | 12 ( 3) | 1 ( 1) | 11 ( 3) |
| Acetylsalicylic acid | 9 ( 2) | 1 ( 1) | 8 ( 2) |
| Indometacin | 9 ( 2) | 2 ( 3) | 7 ( 2) |
| Nabumetone | 8 ( 2) | 1 ( 1) | 7 ( 2) |
| Sulindac | 7 ( 2) | 0 | 7 ( 2) |
| Arthrotec | 6 ( 1) | 0 | 6 ( 2) |
| Ketorolac tromethamine | 5 ( 1) | 1 ( 1) | 4 ( 1) |
| Piroxicam | 5 ( 1) | 1 ( 1) | 4 ( 1) |
| Thomapyrin n | 5 ( 1) | 0 | 5 ( 1) |
| Oxaprozin | 4 ( 1) | 2 ( 3) | 2 ( 1) |
| Ketorolac | 3 ( 1) | 1 ( 1) | 2 ( 1) |
| Alka-seltzer | 2 ( <1) | 1 ( 1) | 1 ( <1) |
| Diclofenac diethylamine | 2 ( <1) | 0 | 2 ( 1) |
| Diclofenac w/misoprostol | 2 ( <1) | 1 ( 1) | 1 ( <1) |
| Ketoprofen | 2 ( <1) | 0 | 2 ( 1) |
| Vicks formula 44m | 2 ( <1) | 1 ( 1) | 1 ( <1) |
| Aceclofenac | 1 ( <1) | 0 | 1 ( <1) |
| Anacin | 1 ( <1) | 0 | 1 ( <1) |
| Asasantin | 1 ( <1) | 1 ( 1) | 0 |

See footnotes on the first page of the table.

## Attachment 6: NSAID Use by Joint Replacement Status (PAI-2004 OA Add-on) (Continued)

**Output TCM_NSAID2_JRJUL8:** NSAID Use in DB EFF or DB EXT Phases by RPOA and Joint Replacement Status and Treatment Group
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-To-Treat Analysis Set)

| | RPOA | | | JR minus RPOA | | | Non-JR | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total | Treatment, n (%) | | Total | Treatment, n (%) | | Total | Treatment, n (%) | |
| Standardized Medication Name | (N=15) n (%) | Placebo (N=0) | Fulranumab (N=15) | (N=56) n (%) | Placebo (N=8) | Fulranumab (N=48) | (N=395) n (%) | Placebo (N=70) | Fulranumab (N=325) |
| Benzydamine hydrochloride | 0 | 0 | 0 | 0 | 0 | 0 | 1 ( <1) | 0 | 1 ( <1) |
| Cerebrex | 1 ( 7) | 0 | 1 ( 7) | 0 | 0 | 0 | 0 | 0 | 0 |
| Dexketoprofen trometamol | 0 | 0 | 0 | 0 | 0 | 0 | 1 ( <1) | 0 | 1 ( <1) |
| Diclofenac epolaminum | 0 | 0 | 0 | 1 ( 2) | 0 | 1 ( 2) | 0 | 0 | 0 |
| Excedrin | 0 | 0 | 0 | 0 | 0 | 0 | 1 ( <1) | 0 | 1 ( <1) |
| Fenoprofen | 0 | 0 | 0 | 0 | 0 | 0 | 1 ( <1) | 0 | 1 ( <1) |
| Morniflumate | 0 | 0 | 0 | 0 | 0 | 0 | 1 ( <1) | 0 | 1 ( <1) |
| Naproxen sodium w/pseudoephedrine hcl | 0 | 0 | 0 | 0 | 0 | 0 | 1 ( <1) | 0 | 1 ( <1) |
| Naproxen sodium/sumatriptan succinate | 0 | 0 | 0 | 0 | 0 | 0 | 1 ( <1) | 1 ( 1) | 0 |
| Nimesulide | 0 | 0 | 0 | 0 | 0 | 0 | 1 ( <1) | 0 | 1 ( <1) |
| No-flu F | 0 | 0 | 0 | 0 | 0 | 0 | 1 ( <1) | 0 | 1 ( <1) |
| Trolamine salicylate | 0 | 0 | 0 | 0 | 0 | 0 | 1 ( <1) | 0 | 1 ( <1) |
| Vincents | 0 | 0 | 0 | 0 | 0 | 0 | 1 ( <1) | 0 | 1 ( <1) |

See footnotes on the first page of the table.

## Attachment 6: NSAID Use by Joint Replacement Status (PAI-2004 OA Add-on) (Continued)

**Output TCM_NSAID2_JRJUL8:** NSAID Use in DB EFF or DB EXT Phases by RPOA and Joint Replacement Status and Treatment Group
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-To-Treat Analysis Set)

| | ---------- Total ---------- | | |
|---|---|---|---|
| | Total | --- Treatment, n (%) --- | |
| | (N=466) | Placebo | Fulranumab |
| Standardized Medication Name | n (%) | (N=78) | (N=388) |
| Benzydamine hydrochloride | 1 ( <1) | 0 | 1 ( <1) |
| Cerebrex | 1 ( <1) | 0 | 1 ( <1) |
| Dexketoprofen trometamol | 1 ( <1) | 0 | 1 ( <1) |
| Diclofenac epolaminum | 1 ( <1) | 0 | 1 ( <1) |
| Excedrin | 1 ( <1) | 0 | 1 ( <1) |
| Fenoprofen | 1 ( <1) | 0 | 1 ( <1) |
| Morniflumate | 1 ( <1) | 0 | 1 ( <1) |
| Naproxen sodium w/pseudoephedrine hcl | 1 ( <1) | 0 | 1 ( <1) |
| Naproxen sodium/sumatriptan succinate | 1 ( <1) | 1 ( 1) | 0 |
| Nimesulide | 1 ( <1) | 0 | 1 ( <1) |
| No-flu F | 1 ( <1) | 0 | 1 ( <1) |
| Trolamine salicylate | 1 ( <1) | 0 | 1 ( <1) |
| Vincents | 1 ( <1) | 0 | 1 ( <1) |

See footnotes on the first page of the table.
tcm_nsaid2_jrjul8.rtf generated by rcm_nsaid1.sas, 25OCT2011 09:34

## Attachment 7: Study Completion/Withdrawal Information and Exposure Data (PAI-2004 OA Add-on)

**Table TSUB03A:** Study Completion/Withdrawal Information for the DB Efficacy Phase
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: All Randomized Subjects Analysis Set)

| Subject Completed Treatment/Trial<br>Reason For Withdrawal/Termination | Placebo<br>(N=78)<br>n (%) | Fulranumab 1mgQ4wk<br>(N=78)<br>n (%) | Fulranumab 3mgQ8wk<br>(N=77)<br>n (%) | Fulranumab 3mgQ4wk<br>(N=79)<br>n (%) | Fulranumab 6mgQ8wk<br>(N=78)<br>n (%) | Fulranumab 10mgQ8wk<br>(N=78)<br>n (%) | Total<br>(N=468)<br>n (%) |
|---|---|---|---|---|---|---|---|
| **Total no. subjects with Disposition** | 78 (100) | 78 (100) | 77 (100) | 79 (100) | 78 (100) | 78 (100) | 468 (100) |
| **Completed** | 67 ( 86) | 73 ( 94) | 72 ( 94) | 72 ( 91) | 70 ( 90) | 69 ( 88) | 423 ( 90) |
| **Withdrawn** | 11 ( 14) | 5 ( 6) | 5 ( 6) | 7 ( 9) | 8 ( 10) | 9 ( 12) | 45 ( 10) |
| Adverse event | 0 | 0 | 2 ( 3) | 0 | 3 ( 4) | 1 ( 1) | 6 ( 1) |
| Investigator decision | 0 | 0 | 1 ( 1) | 1 ( 1) | 0 | 1 ( 1) | 3 ( 1) |
| Lack of efficacy | 4 ( 5) | 0 | 0 | 1 ( 1) | 2 ( 3) | 2 ( 3) | 9 ( 2) |
| Lost to follow up | 0 | 0 | 0 | 0 | 2 ( 3) | 0 | 2 ( <1) |
| Subject choice (subject withdrew consent) | 5 ( 6) | 3 ( 4) | 1 ( 1) | 2 ( 3) | 0 | 1 ( 1) | 12 ( 3) |
| Other | 2 ( 3) | 2 ( 3) | 1 ( 1) | 3 ( 4) | 1 ( 1) | 4 ( 5) | 13 ( 3) |

Note: Percentages calculated with the number of subjects in each group as denominator.
tsub03a.rtf generated by rds.sas, 18OCT2011 11:22

Distribution of Number of Dose Administrations
(Study 42160443-PAI2004 - Intent-To-Treat Analysis Set)

| | Placebo | | Fulranumab 1mgQ4wk | | Fulranumab 3mgQ8wk | | Fulranumab 3mgQ4wk | | Fulranumab 6mgQ8wk | | Fulranumab 10mgQ8wk | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | n | % | n | % | n | % |
| **Number of injections** | | | | | | | | | | | | | | |
| First 16 weeks | | | | | | | | | | | | | | |
| 1 | 4 | 5.1 | 1 | 1.3 | 2 | 2.6 | 2 | 2.5 | 3 | 3.8 | 5 | 6.4 | 17 | 3.6 |
| 2 | 5 | 6.4 | 2 | 2.6 | 1 | 1.3 | 3 | 3.8 | 2 | 2.6 | 4 | 5.1 | 17 | 3.6 |
| 3 | 10 | 12.8 | 5 | 6.5 | 8 | 10.5 | 9 | 11.4 | 6 | 7.7 | 5 | 6.4 | 43 | 9.2 |
| 4 | 59 | 75.6 | 69 | 89.6 | 65 | 85.5 | 65 | 82.3 | 67 | 85.9 | 64 | 82.1 | 389 | 83.5 |
| ------- | ----- | | ----- | | ----- | | ----- | | ----- | | ----- | | ----- | |
| Total | 78 | | 77 | | 76 | | 79 | | 78 | | 78 | | 466 | |

## Attachment 8: WOMAC Subscale of Physical Function at Week 12 (PAI-2004 OA Add-on)

**Table TEFF12A:** Change From Baseline to the End of the DB Efficacy Phase in the WOMAC Subscales and Global Scale Scores (LOCF)
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-to-Treat Analysis Set)

| | Placebo (N=78) | JNJ-42160443 1mgQ4wk (N=77) | JNJ-42160443 3mgQ8wk (N=76) | JNJ-42160443 3mgQ4wk (N=79) | JNJ-42160443 6mgQ8wk (N=78) | JNJ-42160443 10mgQ8wk (N=78) |
|---|---|---|---|---|---|---|
| **Subscale of Physical Function** | | | | | | |
| DOUBLE BLIND EFFICACY | | | | | | |
| END POINT (DB EF) | | | | | | |
| Value at Baseline | | | | | | |
| N | 77 | 76 | 76 | 78 | 76 | 77 |
| Mean (SD) | 6.6 (1.53) | 6.2 (2.02) | 6.5 (1.35) | 6.2 (1.58) | 6.2 (1.77) | 6.4 (1.51) |
| Median (Range) | 6.5 (3;10) | 6.0 (0;10) | 6.5 (2;9) | 6.1 (1;9) | 6.2 (1;10) | 6.5 (1;9) |
| Value | | | | | | |
| N | 77 | 76 | 76 | 79 | 76 | 77 |
| Mean (SD) | 4.9 (2.46) | 4.0 (2.53) | 3.9 (2.27) | 3.3 (2.21) | 3.8 (2.68) | 3.4 (2.58) |
| Median (Range) | 5.2 (0;10) | 3.4 (0;9) | 3.8 (0;9) | 3.3 (0;8) | 3.4 (0;10) | 3.4 (0;8) |
| Change from Baseline | | | | | | |
| N | 77 | 76 | 76 | 78 | 76 | 77 |
| Mean (SD) | -1.7 (2.05) | -2.3 (2.53) | -2.6 (2.13) | -2.8 (2.15) | -2.4 (2.65) | -2.9 (2.35) |
| Median (Range) | -1.9 (-7;3) | -2.1 (-8;3) | -2.4 (-8;2) | -2.9 (-8;2) | -2.1 (-8;6) | -3.4 (-7;1) |
| LS Mean Change | -1.6 | -2.3 | -2.5 | -2.9 | -2.4 | -2.9 |
| P-value(minus Placebo)(a,b) | | 0.048 | 0.009 | <0.001 | 0.019 | <0.001 |
| Diff. of LS Means (SE) | | -0.7 (0.36) | -0.9 (0.36) | -1.3 (0.36) | -0.9 (0.36) | -1.3 (0.36) |
| 95% CI | | (-1.43;-0.01) | (-1.65;-0.24) | (-2.00;-0.58) | (-1.56;-0.14) | (-2.03;-0.62) |

(a) P-values and least squares means from ANCOVA model with treatment, baseline opioid use (use/no use), and baseline weight (<85 kg/ ≥ 85 kg) as factors and baseline total score as covariate.
(b) Nominal unadjusted p-values are presented.

## Attachment 9: Patient Global Assessment at Endpoint (DB Efficacy) (PAI-2004 OA Add-on)

**Table TEFF18A:** Change From Baseline to the End of the DB Efficacy Phase in the PGA Score (LOCF)
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-to-Treat Analysis Set)

| | Placebo (N=78) | JNJ-42160443 1mgQ4wk (N=77) | JNJ-42160443 3mgQ8wk (N=76) | JNJ-42160443 3mgQ4wk (N=79) | JNJ-42160443 6mgQ8wk (N=78) | JNJ-42160443 10mgQ8wk (N=78) |
|---|---|---|---|---|---|---|
| **PATIENT GLOBAL ASSESSMENT (PGA)** | | | | | | |
| END POINT (DB EF) | | | | | | |
| Value at Baseline | | | | | | |
| N | 77 | 76 | 76 | 78 | 76 | 77 |
| Mean (SD) | 7.2 (1.54) | 6.9 (1.82) | 6.9 (1.41) | 6.8 (1.29) | 7.0 (1.33) | 7.1 (1.42) |
| Median (Range) | 7.0 (3;10) | 7.0 (2;10) | 7.0 (3;10) | 7.0 (4;10) | 7.0 (4;10) | 7.0 (1;10) |
| Value | | | | | | |
| N | 77 | 76 | 76 | 79 | 76 | 77 |
| Mean (SD) | 5.2 (2.53) | 4.7 (2.66) | 4.4 (2.41) | 3.7 (2.55) | 4.2 (2.70) | 4.3 (2.60) |
| Median (Range) | 5.0 (0;10) | 4.0 (0;10) | 4.0 (0;10) | 4.0 (0;9) | 4.0 (0;10) | 5.0 (0;9) |
| Change from Baseline | | | | | | |
| N | 77 | 76 | 76 | 78 | 76 | 77 |
| Mean (SD) | -2.1 (2.25) | -2.2 (2.74) | -2.6 (2.53) | -3.0 (2.62) | -2.8 (2.72) | -2.8 (2.35) |
| Median (Range) | -2.0 (-8;1) | -2.0 (-8;4) | -3.0 (-10;3) | -3.0 (-9;1) | -2.5 (-9;3) | -3.0 (-8;2) |
| LS Mean Change | -1.9 | -2.2 | -2.5 | -3.1 | -2.7 | -2.7 |
| P-value(minus Placebo)(a,b) | | 0.409 | 0.105 | 0.002 | 0.032 | 0.041 |
| Diff. of LS Means (SE) | | -0.3 (0.39) | -0.6 (0.39) | -1.2 (0.39) | -0.8 (0.39) | -0.8 (0.39) |
| 95% CI | | (-1.10;0.45) | (-1.41;0.14) | (-1.98;-0.44) | (-1.62;-0.07) | (-1.57;-0.03) |

(a) P-values and least squares means from ANCOVA model with treatment, baseline opioid use (use/no use), and baseline weight (<85 kg/ ≥ 85 kg) as factors and baseline value as covariate.
(b) Nominal unadjusted p-values are presented.
teff18a.rtf generated by reffpga.sas, 14OCT2011 13:47

## Attachment 10: Exposure Data (PAI-2006 OA Monotherapy)

Extent of Exposure
(Study 42160443-PAI2006 Interim Analysis: Intent-To-Treat Analysis Set)

| | ------ Placebo ----- (N=48) | Fulranumab 3mgQ4wk (N=48) | Fulranumab 9mgQ4wk (N=50) | - Oxycodone CR BID - (N=50) | ------- Total ------ (N=196) |
|---|---|---|---|---|---|
| **Double-blind** | | | | | |
| DB phase duration | | | | | |
| N | 48 | 48 | 50 | 50 | 196 |
| Category, n (%) | | | | | |
| 1 – 28 | 11 (22.9) | 12 (25.0) | 13 (26.0) | 23 (46.0) | 59 (30.1) |
| 29 – 56 | 11 (22.9) | 13 (27.1) | 10 (20.0) | 12 (24.0) | 46 (23.5) |
| 57 – 84 | 5 (10.4) | 6 (12.5) | 8 (16.0) | 5 (10.0) | 24 (12.2) |
| 85 – 112 | 11 (22.9) | 5 (10.4) | 12 (24.0) | 5 (10.0) | 33 (16.8) |
| > 112 | 10 (20.8) | 12 (25.0) | 7 (14.0) | 5 (10.0) | 34 (17.3) |
| Mean | 68.2 | 64.9 | 64.6 | 44.9 | 60.5 |
| SD | 40.77 | 39.49 | 38.96 | 36.55 | 39.75 |
| Median | 62.0 | 55.5 | 63.0 | 29.5 | 55.0 |
| Minimum | 2 | 8 | 7 | 4 | 2 |
| Maximum | 133 | 120 | 121 | 119 | 133 |
| First 12 weeks duration | | | | | |
| N | 48 | 48 | 50 | 50 | 196 |
| Category, n (%) | | | | | |
| 1 – 28 | 11 (22.9) | 12 (25.0) | 13 (26.0) | 23 (46.0) | 59 (30.1) |
| 29 – 56 | 11 (22.9) | 13 (27.1) | 10 (20.0) | 12 (24.0) | 46 (23.5) |
| 57 – 84 | 11 (22.9) | 7 (14.6) | 11 (22.0) | 8 (16.0) | 37 (18.9) |
| 85 – 112 | 15 (31.3) | 16 (33.3) | 16 (32.0) | 7 (14.0) | 54 (27.6) |
| Mean | 57.3 | 55.6 | 56.4 | 40.8 | 52.4 |
| SD | 29.01 | 28.60 | 29.50 | 29.56 | 29.76 |
| Median | 62.0 | 55.5 | 63.0 | 29.5 | 55.0 |
| Minimum | 2 | 8 | 7 | 4 | 2 |
| Maximum | 91 | 89 | 93 | 91 | 93 |

## Attachment 11: Demographic and Baseline Characteristics (PAI-2006 OA Monotherapy)

Demographic and Baseline Characteristics
(Study 42160443-PAI2006 Interim Analysis: Intent-To-Treat Analysis Set)

| | ------ Placebo ----- (N=48) | Fulranumab 3mgQ4wk (N=48) | Fulranumab 9mgQ4wk (N=50) | - Oxycodone CR BID - (N=50) | ------- Total ------ (N=196) |
|---|---|---|---|---|---|
| **Sex, n (%)** | | | | | |
| N | 48 | 48 | 50 | 50 | 196 |
| Unknown | 0 | 0 | 1 ( 2.0) | 0 | 1 ( 0.5) |
| Female | 25 (52.1) | 30 (62.5) | 29 (58.0) | 25 (50.0) | 109 (55.6) |
| Male | 23 (47.9) | 18 (37.5) | 20 (40.0) | 25 (50.0) | 86 (43.9) |
| **Race, n (%)** | | | | | |
| N | 48 | 48 | 50 | 50 | 196 |
| White | 40 (83.3) | 34 (70.8) | 36 (72.0) | 38 (76.0) | 148 (75.5) |
| Black or African American | 8 (16.7) | 13 (27.1) | 14 (28.0) | 11 (22.0) | 46 (23.5) |
| Asian | 0 | 1 ( 2.1) | 0 | 1 ( 2.0) | 2 ( 1.0) |
| **Age** | | | | | |
| N | 48 | 48 | 50 | 50 | 196 |
| Category, n (%) | | | | | |
| <65 | 34 (70.8) | 37 (77.1) | 36 (72.0) | 35 (70.0) | 142 (72.4) |
| ≥ 65 | 14 (29.2) | 11 (22.9) | 14 (28.0) | 15 (30.0) | 54 (27.6) |
| Mean (SD) | 59.2 (9.25) | 58.8 (8.47) | 58.6 (10.06) | 60.9 (8.77) | 59.4 (9.14) |
| Median | 60.5 | 57.5 | 57.0 | 60.0 | 58.0 |
| Range | (43;78) | (41;79) | (40;80) | (47;78) | (40;80) |
| **Baseline weight (kg)** | | | | | |
| N | 48 | 48 | 50 | 50 | 196 |
| Mean (SD) | 91.4 (18.24) | 90.3 (17.87) | 90.2 (17.21) | 91.9 (18.51) | 90.9 (17.83) |
| Median | 92.7 | 88.3 | 89.0 | 90.5 | 90.5 |
| Range | (60;131) | (49;137) | (52;136) | (51;133) | (49;137) |
| **Baseline height (cm)** | | | | | |
| N | 48 | 48 | 50 | 50 | 196 |
| Mean (SD) | 169.9 (12.03) | 168.2 (10.29) | 170.0 (10.89) | 170.3 (10.30) | 169.6 (10.84) |
| Median | 167.0 | 169.5 | 169.4 | 168.3 | 169.0 |
| Range | (152;193) | (142;193) | (150;195) | (145;192) | (142;195) |
| **Baseline bmi (kg/m2)** | | | | | |
| N | 48 | 48 | 50 | 50 | 196 |
| Mean (SD) | 31.6 (5.13) | 31.8 (5.20) | 31.1 (4.67) | 31.5 (4.50) | 31.5 (4.85) |
| Median | 31.2 | 31.5 | 30.6 | 31.7 | 31.4 |
| Range | (24;41) | (19;44) | (22;40) | (18;39) | (18;44) |
| **Stratum 1 - baseline opioid use, n (%)** | | | | | |
| N | 48 | 48 | 50 | 50 | 196 |
| No opioids | 36 (75.0) | 32 (66.7) | 34 (68.0) | 36 (72.0) | 138 (70.4) |
| Use opioids | 12 (25.0) | 16 (33.3) | 16 (32.0) | 14 (28.0) | 58 (29.6) |
| **Stratum 2 - baseline body weight group, n (%)** | | | | | |
| N | 48 | 48 | 50 | 50 | 196 |
| <85kg | 19 (39.6) | 19 (39.6) | 20 (40.0) | 20 (40.0) | 78 (39.8) |
| ≥ 85kg | 29 (60.4) | 29 (60.4) | 30 (60.0) | 30 (60.0) | 118 (60.2) |

Stratum 1: baseline opioid use was assigned to subjects based on their medications reported at screening visit during the blinded review and it replaced the one used as the stratification factor 1 for randomization in IVRS.
Stratum 2: baseline body weight group was the stratification factor 2 for randomization in IVRS.

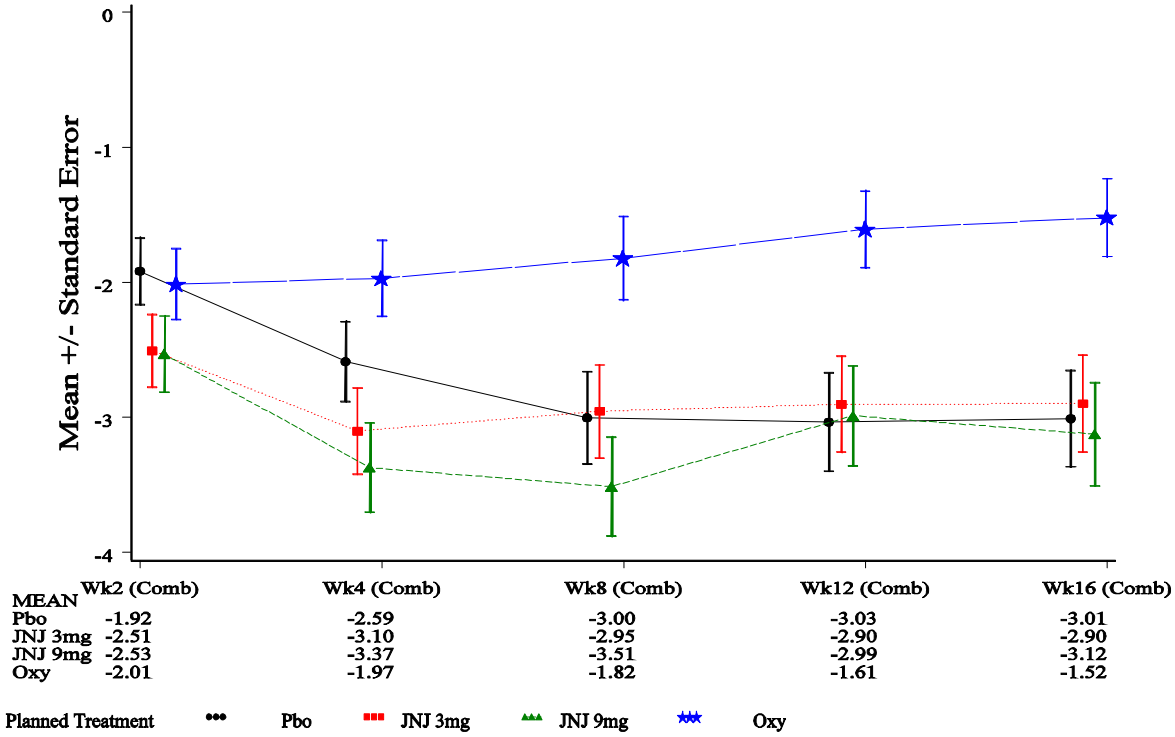
## Attachment 12: Study Completion/Withdrawal Information (PAI-2006 OA Monotherapy)

**Output TSIDS01B:** Study Completion/Withdrawal Information for the Double-Blind Phase
(Study 42160443-PAI2006 Interim Analysis - 28DEC2010: All Randomized Subjects Analysis Set)

| **Analysis Phase** Status Reason For Withdrawal/Termination | Placebo (N=48) n (%) | Fulranumab 3mgQ4wk (N=48) n (%) | Fulranumab 9mgQ4wk (N=50) n (%) | Oxycodone CR BID (N=50) n (%) | Total (N=196) n (%) |
|---|---|---|---|---|---|
| **Double-blind** | 48 | 48 | 50 | 50 | 196 |
| Ongoing on 28dec2010 | 29 ( 60) | 23 ( 48) | 33 ( 66) | 22 ( 44) | 107 ( 55) |
| Completed | 12 ( 25) | 12 ( 25) | 10 ( 20) | 5 ( 10) | 39 ( 20) |
| Withdrawn | 7 ( 15) | 13 ( 27) | 7 ( 14) | 23 ( 46) | 50 ( 26) |
| Adverse event | 2 ( 4) | 5 ( 10) | 1 ( 2) | 14 ( 28) | 22 ( 11) |
| Investigator decision | 0 | 0 | 1 ( 2) | 0 | 1 ( 1) |
| Lack of efficacy | 4 ( 8) | 2 ( 4) | 0 | 3 ( 6) | 9 ( 5) |
| Lost to follow up | 1 ( 2) | 0 | 0 | 0 | 1 ( 1) |
| Sponsor discontinued cohort/study | 0 | 1 ( 2) | 1 ( 2) | 0 | 2 ( 1) |
| Subject choice (subject withdrew consent) | 0 | 4 ( 8) | 4 ( 8) | 5 ( 10) | 13 ( 7) |
| Other | 0 | 1 ( 2) | 0 | 1 ( 2) | 2 ( 1) |

Note: Percentages calculated with the number of subjects per analysis phase as denominator.
tsids01b.rtf generated by rds.sas, 04NOV2011 08:23

**Attachment 13: Mean Change from Baseline in the Average Pain Intensity Score Over Time in the Double-Blind Phase (COMB) – Intent-to-Treat Analysis Set (PAI-2006 OA Monotherapy)**




Note: Combination (COMB) imputation used baseline observation carried forward (BOCF) for subjects who withdrew prior to clinical hold and last observation carried forward (LOCF) for subjects who were ongoing at clinical hold cutoff date of 28 December 2010.

## Attachment 14: Treatment-Emergent Adverse Events in at Least 5% of Subjects in any Treatment Group in PAI-2004 (OA Add-on)

**Table TAE01ALL_5P:** Treatment-Emergent Adverse Events in at Least 5% of Subjects in any Treatment Group for the All Combined Phases
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-To-Treat Analysis Set)

| **Body System Or Organ Class**<br>Dictionary-Derived Term | Placebo<br>(N=78)<br>n (%) | JNJ-42160443<br>1mgQ4wk<br>(N=77)<br>n (%) | JNJ-42160443<br>3mgQ8wk<br>(N=76)<br>n (%) | JNJ-42160443<br>3mgQ4wk<br>(N=79)<br>n (%) | JNJ-42160443<br>6mgQ8wk<br>(N=78)<br>n (%) | JNJ-42160443<br>10mgQ8wk<br>(N=78)<br>n (%) | Total<br>JNJ42160443<br>(N=388)<br>n (%) |
|---|---|---|---|---|---|---|---|
| **Total no. subjects WITH ADVERSE EVENTS** | 69 ( 88) | 66 ( 86) | 72 ( 95) | 74 ( 94) | 72 ( 92) | 68 ( 87) | 352 ( 91) |
| **Musculoskeletal and connective tissue disorders** | 37 ( 47) | 39 ( 51) | 43 ( 57) | 47 ( 59) | 49 ( 63) | 43 ( 55) | 221 ( 57) |
| Arthralgia | 12 ( 15) | 15 ( 19) | 14 ( 18) | 22 ( 28) | 17 ( 22) | 14 ( 18) | 82 ( 21) |
| Osteoarthritis | 11 ( 14) | 9 ( 12) | 9 ( 12) | 14 ( 18) | 17 ( 22) | 19 ( 24) | 68 ( 18) |
| Back pain | 8 ( 10) | 7 ( 9) | 8 ( 11) | 7 ( 9) | 9 ( 12) | 9 ( 12) | 40 ( 10) |
| Pain in extremity | 4 ( 5) | 6 ( 8) | 8 ( 11) | 5 ( 6) | 11 ( 14) | 9 ( 12) | 39 ( 10) |
| Joint swelling | 1 ( 1) | 4 ( 5) | 2 ( 3) | 7 ( 9) | 6 ( 8) | 5 ( 6) | 24 ( 6) |
| Musculoskeletal pain | 2 ( 3) | 7 ( 9) | 6 ( 8) | 1 ( 1) | 5 ( 6) | 4 ( 5) | 23 ( 6) |
| Muscle spasms | 1 ( 1) | 6 ( 8) | 3 ( 4) | 4 ( 5) | 5 ( 6) | 2 ( 3) | 20 ( 5) |
| Synovial cyst | 0 | 1 ( 1) | 1 ( 1) | 1 ( 1) | 3 ( 4) | 6 ( 8) | 12 ( 3) |
| Myalgia | 0 | 1 ( 1) | 3 ( 4) | 1 ( 1) | 1 ( 1) | 4 ( 5) | 10 ( 3) |
| Joint stiffness | 0 | 0 | 0 | 4 ( 5) | 1 ( 1) | 0 | 5 ( 1) |
| **Infections and infestations** | 32 ( 41) | 39 ( 51) | 35 ( 46) | 31 ( 39) | 30 ( 38) | 29 ( 37) | 164 ( 42) |
| Upper respiratory tract infection | 4 ( 5) | 8 ( 10) | 12 ( 16) | 12 ( 15) | 6 ( 8) | 11 ( 14) | 49 ( 13) |
| Nasopharyngitis | 6 ( 8) | 9 ( 12) | 9 ( 12) | 9 ( 11) | 4 ( 5) | 9 ( 12) | 40 ( 10) |
| Urinary tract infection | 2 ( 3) | 5 ( 6) | 3 ( 4) | 3 ( 4) | 4 ( 5) | 0 | 15 ( 4) |
| Bronchitis | 2 ( 3) | 1 ( 1) | 2 ( 3) | 5 ( 6) | 4 ( 5) | 1 ( 1) | 13 ( 3) |
| Sinusitis | 9 ( 12) | 4 ( 5) | 4 ( 5) | 2 ( 3) | 2 ( 3) | 1 ( 1) | 13 ( 3) |
| Cellulitis | 1 ( 1) | 5 ( 6) | 0 | 0 | 2 ( 3) | 1 ( 1) | 8 ( 2) |

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

## Attachment 14: Treatment-Emergent Adverse Events in at Least 5% of Subjects in any Treatment Group in PAI-2004 (OA Add-on) (Continued)

**Table TAE01ALL_5P:** Treatment-Emergent Adverse Events in at Least 5% of Subjects in any Treatment Group for the All Combined Phases
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-To-Treat Analysis Set)

| Body System Or Organ Class<br>Dictionary-Derived Term | Placebo<br>(N=78)<br>n (%) | JNJ-42160443<br>1mgQ4wk<br>(N=77)<br>n (%) | JNJ-42160443<br>3mgQ8wk<br>(N=76)<br>n (%) | JNJ-42160443<br>3mgQ4wk<br>(N=79)<br>n (%) | JNJ-42160443<br>6mgQ8wk<br>(N=78)<br>n (%) | JNJ-42160443<br>10mgQ8wk<br>(N=78)<br>n (%) | Total<br>JNJ42160443<br>(N=388)<br>n (%) |
|---|---|---|---|---|---|---|---|
| **Nervous system disorders** | 22 ( 28) | 16 ( 21) | 34 ( 45) | 32 ( 41) | 34 ( 44) | 32 ( 41) | 148 ( 38) |
| Paraesthesia | 4 ( 5) | 3 ( 4) | 10 ( 13) | 12 ( 15) | 16 ( 21) | 10 ( 13) | 51 ( 13) |
| Headache | 7 ( 9) | 7 ( 9) | 14 ( 18) | 7 ( 9) | 5 ( 6) | 5 ( 6) | 38 ( 10) |
| Carpal tunnel syndrome | 1 ( 1) | 4 ( 5) | 3 ( 4) | 9 ( 11) | 6 ( 8) | 8 ( 10) | 30 ( 8) |
| Hypoaesthesia | 3 ( 4) | 4 ( 5) | 3 ( 4) | 7 ( 9) | 6 ( 8) | 9 ( 12) | 29 ( 7) |
| Dizziness | 1 ( 1) | 0 | 4 ( 5) | 1 ( 1) | 6 ( 8) | 6 ( 8) | 17 ( 4) |
| **Injury, poisoning and procedural complications** | 15 ( 19) | 20 ( 26) | 15 ( 20) | 23 ( 29) | 22 ( 28) | 26 ( 33) | 106 ( 27) |
| Muscle strain | 1 ( 1) | 5 ( 6) | 3 ( 4) | 3 ( 4) | 8 ( 10) | 6 ( 8) | 25 ( 6) |
| Contusion | 4 ( 5) | 4 ( 5) | 2 ( 3) | 3 ( 4) | 3 ( 4) | 3 ( 4) | 15 ( 4) |
| Joint sprain | 0 | 4 ( 5) | 1 ( 1) | 2 ( 3) | 1 ( 1) | 4 ( 5) | 12 ( 3) |
| Procedural pain | 2 ( 3) | 1 ( 1) | 0 | 3 ( 4) | 0 | 4 ( 5) | 8 ( 2) |
| **Gastrointestinal disorders** | 14 ( 18) | 21 ( 27) | 21 ( 28) | 23 ( 29) | 18 ( 23) | 21 ( 27) | 104 ( 27) |
| Nausea | 3 ( 4) | 3 ( 4) | 4 ( 5) | 5 ( 6) | 5 ( 6) | 5 ( 6) | 22 ( 6) |
| Diarrhoea | 3 ( 4) | 9 ( 12) | 4 ( 5) | 3 ( 4) | 3 ( 4) | 2 ( 3) | 21 ( 5) |
| Constipation | 3 ( 4) | 4 ( 5) | 6 ( 8) | 1 ( 1) | 3 ( 4) | 6 ( 8) | 20 ( 5) |
| **General disorders and administration site conditions** | 16 ( 21) | 16 ( 21) | 11 ( 14) | 22 ( 28) | 19 ( 24) | 18 ( 23) | 86 ( 22) |
| Oedema peripheral | 4 ( 5) | 6 ( 8) | 4 ( 5) | 10 ( 13) | 9 ( 12) | 8 ( 10) | 37 ( 10) |
| Fatigue | 4 ( 5) | 4 ( 5) | 2 ( 3) | 3 ( 4) | 3 ( 4) | 3 ( 4) | 15 ( 4) |

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.

## Attachment 14: Treatment-Emergent Adverse Events in at Least 5% of Subjects in any Treatment Group in PAI-2004 (OA Add-on) (Continued)

**Table TAE01ALL_5P:** Treatment-Emergent Adverse Events in at Least 5% of Subjects in any Treatment Group for the All Combined Phases
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-To-Treat Analysis Set)

| Body System Or Organ Class<br>Dictionary-Derived Term | Placebo<br>(N=78)<br>n (%) | JNJ-42160443<br>1mgQ4wk<br>(N=77)<br>n (%) | JNJ-42160443<br>3mgQ8wk<br>(N=76)<br>n (%) | JNJ-42160443<br>3mgQ4wk<br>(N=79)<br>n (%) | JNJ-42160443<br>6mgQ8wk<br>(N=78)<br>n (%) | JNJ-42160443<br>10mgQ8wk<br>(N=78)<br>n (%) | Total<br>JNJ42160443<br>(N=388)<br>n (%) |
|---|---|---|---|---|---|---|---|
| **Respiratory, thoracic and mediastinal disorders** | 6 ( 8) | 15 ( 19) | 20 ( 26) | 20 ( 25) | 12 ( 15) | 6 ( 8) | 73 ( 19) |
| Cough | 1 ( 1) | 5 ( 6) | 5 ( 7) | 3 ( 4) | 5 ( 6) | 2 ( 3) | 20 ( 5) |
| Oropharyngeal pain | 2 ( 3) | 3 ( 4) | 5 ( 7) | 2 ( 3) | 2 ( 3) | 2 ( 3) | 14 ( 4) |
| **Surgical and medical procedures** | 8 ( 10) | 8 ( 10) | 8 ( 11) | 19 ( 24) | 14 ( 18) | 19 ( 24) | 68 ( 18) |
| Knee arthroplasty | 3 ( 4) | 5 ( 6) | 4 ( 5) | 13 ( 16) | 6 ( 8) | 10 ( 13) | 38 ( 10) |
| Hip arthroplasty | 4 ( 5) | 3 ( 4) | 2 ( 3) | 5 ( 6) | 8 ( 10) | 8 ( 10) | 26 ( 7) |
| **Investigations** | 12 ( 15) | 12 ( 16) | 9 ( 12) | 10 ( 13) | 14 ( 18) | 14 ( 18) | 59 ( 15) |
| Blood pressure increased | 2 ( 3) | 2 ( 3) | 3 ( 4) | 1 ( 1) | 4 ( 5) | 1 ( 1) | 11 ( 3) |
| **Skin and subcutaneous tissue disorders** | 9 ( 12) | 11 ( 14) | 14 ( 18) | 13 ( 16) | 7 ( 9) | 8 ( 10) | 53 ( 14) |
| Rash | 1 ( 1) | 4 ( 5) | 4 ( 5) | 2 ( 3) | 2 ( 3) | 3 ( 4) | 15 ( 4) |
| Pruritus | 1 ( 1) | 2 ( 3) | 4 ( 5) | 2 ( 3) | 1 ( 1) | 1 ( 1) | 10 ( 3) |
| **Vascular disorders** | 7 ( 9) | 9 ( 12) | 7 ( 9) | 9 ( 11) | 9 ( 12) | 10 ( 13) | 44 ( 11) |
| Hypertension | 6 ( 8) | 5 ( 6) | 5 ( 7) | 3 ( 4) | 6 ( 8) | 6 ( 8) | 25 ( 6) |
| **Psychiatric disorders** | 3 ( 4) | 5 ( 6) | 8 ( 11) | 10 ( 13) | 10 ( 13) | 6 ( 8) | 39 ( 10) |
| Insomnia | 0 | 1 ( 1) | 3 ( 4) | 5 ( 6) | 3 ( 4) | 4 ( 5) | 16 ( 4) |
| Depression | 1 ( 1) | 1 ( 1) | 3 ( 4) | 2 ( 3) | 5 ( 6) | 0 | 11 ( 3) |
| **Ear and labyrinth disorders** | 4 ( 5) | 4 ( 5) | 1 ( 1) | 3 ( 4) | 5 ( 6) | 2 ( 3) | 15 ( 4) |
| Vertigo | 1 ( 1) | 3 ( 4) | 1 ( 1) | 1 ( 1) | 4 ( 5) | 0 | 9 ( 2) |

See footnotes on the first page of the table.
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**Attachment 15: Charcot of the Foot (NPP-2002 DPN)**

Subject 500267 received 2 doses of study drug and experienced an AE of arthritis of the right foot 36 days after the last dose of study drug (administered 09 November 2010). The subject reported no prior medical history of OA. The subject was seen by a rheumatologist and treated for arthritis of the right foot. This subject had a second AE of bilateral arthritis of feet and joints approximately 4 months after the last dose of study drug. An X-ray was performed following the second arthritis event and a preliminary assessment that the findings were compatible with Charcot arthropathy was provided by the radiologist. The radiograph of the involved foot showed a foreign body (described as possibly a broken needle) in the soft tissue of the foot. The AE is reported as ongoing. The subject had withdrawn from study 87 days after the last dose of study drug (on 03 February 2011) due to the clinical hold and was in the post-treatment/follow-up phase when the second AE occurred.

## Attachment 16: Adjudication of Joint Replacements Reported Between 08 July 2001 and 08 December 2011

Between 08 July 2011 and 08 December 2011, 10 subjects (involving 12 joints) had non-solicited post-study joint replacements or adverse events possibly related to joint destruction that were reported to the sponsor and were not previously adjudicated.

Of these, 6 subjects (involving 7 joints) provided informed consent for the collection of their joint replacement data and had sufficient radiologic images for adjudication. The 7 joint replacements were adjudicated on 08 December 2011. Three joint replacements were classified as RPOA (all 3 in fulranumab groups), 2 were classified as normal OA (1 placebo and 1 fulranumab), and 2 had insufficient information to assess (both fulranumab). The 3 cases of RPOA were considered either possibly related (2) or probably related (1) to blinded study therapy, 2 cases of normal progression of OA were considered not related to blinded study therapy, and 2 cases had insufficient data for assessment.

**Joint Replacements in Fulranumab Clinical Studies by Study Drug and Fulranumab Dose - Adjudicated Between 08 July 2011 to 08 December 2011**

| Treatment | Number of Adjudicated Joint Replacements[a] | Adjudicated Case Definitions | | | | | |
|---|---|---|---|---|---|---|---|
| | | ON | RPOA | RPOA With Features of ON | Normal Progression of OA | NA[b] | Insufficient Information |
| Placebo | 1 | 0 | 0 | 0 | 1 | 0 | 0 |
| Fulranumab | 6 | 0 | 3 | 0 | 1 | 0 | 2 |
| Oxycodone CR | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Total** | **7** | **0** | **3** | **0** | **2** | **0** | **2** |
| By fulranumab dose[c]: | | | | | | | |
| 3mgQ4wk | 1 | 0 | 1 | 0 | 0 | 0 | 0 |
| 6mgQ8wk | 4 | 0 | 1 | 0 | 1 | 0 | 2 |
| 10mgQ8wk | 1 | 0 | 1 | 0 | 0 | 0 | 0 |

NA=not applicable; OA=osteoarthritis; ON=osteonecrosis: Qxwk=every x weeks; RPOA=rapidly progressing osteoarthritis.

[a] Percentages are not calculated in this table as this table summarizes the number of joints replaced.

[b] Cases of joint replacements revisions and/or device failures were considered not applicable for adjudication.

[c] Arranged in increasing order based upon initial dose.

## Attachment 17: Demographic and Baseline Characteristics by Joint Replacement Status as of 08 July 2011 (PAI-2004 OA Add-on)

**Table TSUB02B_JRJUL8:** Demographic and Baseline Characteristics by Joint Replacement Status
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-to-Treat Analysis Set)

| | Placebo (N=78) | | Fulranumab 1mgQ4wk (N=77) | | Fulranumab 3mgQ8wk (N=76) | | Fulranumab 3mgQ4wk (N=79) | | Fulranumab 6mgQ8wk (N=78) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | JR=NO | JR=YES | JR=NO | JR=YES | JR=NO | JR=YES | JR=NO | JR=YES | JR=NO | JR=YES |
| **Age** | | | | | | | | | | |
| N | 70 | 8 | 68 | 9 | 68 | 8 | 62 | 17 | 66 | 12 |
| Category, n (%) | | | | | | | | | | |
| < 65 | 47 (67.1) | 3 (37.5) | 41 (60.3) | 8 (88.9) | 45 (66.2) | 4 (50.0) | 41 (66.1) | 8 (47.1) | 45 (68.2) | 8 (66.7) |
| ≥ 65 | 23 (32.9) | 5 (62.5) | 27 (39.7) | 1 (11.1) | 23 (33.8) | 4 (50.0) | 21 (33.9) | 9 (52.9) | 21 (31.8) | 4 (33.3) |
| Mean | 61.0 | 64.3 | 61.0 | 62.4 | 60.4 | 61.5 | 59.6 | 65.2 | 60.5 | 61.8 |
| SD | 8.16 | 9.11 | 9.53 | 6.75 | 8.94 | 8.64 | 9.38 | 8.43 | 8.88 | 9.69 |
| Median | 61.0 | 67.0 | 62.0 | 63.0 | 60.5 | 62.5 | 59.0 | 65.0 | 59.5 | 59.0 |
| Minimum | 42 | 45 | 42 | 51 | 42 | 46 | 40 | 49 | 41 | 52 |
| Maximum | 80 | 73 | 78 | 77 | 78 | 71 | 79 | 80 | 77 | 80 |
| **SEX, n (%)** | | | | | | | | | | |
| N | 70 | 8 | 68 | 9 | 68 | 8 | 62 | 17 | 66 | 12 |
| Female | 38 (54.3) | 5 (62.5) | 39 (57.4) | 6 (66.7) | 40 (58.8) | 5 (62.5) | 33 (53.2) | 13 (76.5) | 39 (59.1) | 8 (66.7) |
| Male | 32 (45.7) | 3 (37.5) | 29 (42.6) | 3 (33.3) | 28 (41.2) | 3 (37.5) | 29 (46.8) | 4 (23.5) | 27 (40.9) | 4 (33.3) |
| **Race, n (%)** | | | | | | | | | | |
| N | 70 | 8 | 68 | 9 | 68 | 8 | 62 | 17 | 66 | 12 |
| White | 60 (85.7) | 7 (87.5) | 56 (82.4) | 9 (100) | 62 (91.2) | 6 (75.0) | 51 (82.3) | 16 (94.1) | 53 (80.3) | 12 (100) |
| Black | 6 ( 8.6) | 1 (12.5) | 7 (10.3) | 0 | 5 ( 7.4) | 1 (12.5) | 10 (16.1) | 1 ( 5.9) | 9 (13.6) | 0 |
| Asian | 3 ( 4.3) | 0 | 3 ( 4.4) | 0 | 1 ( 1.5) | 1 (12.5) | 1 ( 1.6) | 0 | 2 ( 3.0) | 0 |
| Other | 1 ( 1.4) | 0 | 2 ( 2.9) | 0 | 0 | 0 | 0 | 0 | 2 ( 3.0) | 0 |
| **Baseline BMI (kg/m2), n (%)** | | | | | | | | | | |
| N | 70 | 8 | 68 | 9 | 68 | 8 | 62 | 17 | 66 | 12 |
| < 30 | 30 (42.9) | 3 (37.5) | 35 (51.5) | 5 (55.6) | 25 (36.8) | 3 (37.5) | 26 (41.9) | 8 (47.1) | 26 (39.4) | 3 (25.0) |
| 30 to <40 | 35 (50.0) | 5 (62.5) | 31 (45.6) | 4 (44.4) | 41 (60.3) | 5 (62.5) | 33 (53.2) | 8 (47.1) | 34 (51.5) | 6 (50.0) |
| ≥ 40 | 5 ( 7.1) | 0 | 2 ( 2.9) | 0 | 2 ( 2.9) | 0 | 3 ( 4.8) | 1 ( 5.9) | 6 ( 9.1) | 3 (25.0) |

## Attachment 17: Demographic and Baseline Characteristics by Joint Replacement Status as of 08 July 2011 (PAI-2004 OA Add-on) (Continued)

**Table TSUB02B_JRJUL8:** Demographic and Baseline Characteristics by Joint Replacement Status
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-to-Treat Analysis Set)

| | Fulranumab 10mgQ8wk (N=78) | | Total Fulranumab (N=388) | | Total (N=466) | |
|---|---|---|---|---|---|---|
| | JR=NO | JR=YES | JR=NO | JR=YES | JR=NO | JR=YES |
| **Age** | | | | | | |
| N | 61 | 17 | 325 | 63 | 395 | 71 |
| Category, n (%) | | | | | | |
| < 65 | 40 (65.6) | 8 (47.1) | 212 (65.2) | 36 (57.1) | 259 (65.6) | 39 (54.9) |
| ≥ 65 | 21 (34.4) | 9 (52.9) | 113 (34.8) | 27 (42.9) | 136 (34.4) | 32 (45.1) |
| Mean | 60.5 | 64.6 | 60.4 | 63.5 | 60.5 | 63.6 |
| SD | 9.48 | 9.12 | 9.19 | 8.56 | 9.01 | 8.56 |
| Median | 62.0 | 65.0 | 60.0 | 63.0 | 61.0 | 63.0 |
| Minimum | 40 | 47 | 40 | 46 | 40 | 45 |
| Maximum | 79 | 77 | 79 | 80 | 80 | 80 |
| **SEX, n (%)** | | | | | | |
| N | 61 | 17 | 325 | 63 | 395 | 71 |
| Female | 31 (50.8) | 11 (64.7) | 182 (56.0) | 43 (68.3) | 220 (55.7) | 48 (67.6) |
| Male | 30 (49.2) | 6 (35.3) | 143 (44.0) | 20 (31.7) | 175 (44.3) | 23 (32.4) |
| **Race, n (%)** | | | | | | |
| N | 61 | 17 | 325 | 63 | 395 | 71 |
| White | 50 (82.0) | 16 (94.1) | 272 (83.7) | 59 (93.7) | 332 (84.1) | 66 (93.0) |
| Black | 6 ( 9.8) | 1 ( 5.9) | 37 (11.4) | 3 ( 4.8) | 43 (10.9) | 4 ( 5.6) |
| Asian | 4 ( 6.6) | 0 | 11 ( 3.4) | 1 ( 1.6) | 14 ( 3.5) | 1 ( 1.4) |
| Other | 1 ( 1.6) | 0 | 5 ( 1.5) | 0 | 6 ( 1.5) | 0 |
| **Baseline BMI (kg/m2), n (%)** | | | | | | |
| N | 61 | 17 | 325 | 63 | 395 | 71 |
| < 30 | 28 (45.9) | 8 (47.1) | 140 (43.1) | 27 (42.9) | 170 (43.0) | 30 (42.3) |
| 30 to <40 | 31 (50.8) | 8 (47.1) | 170 (52.3) | 31 (49.2) | 205 (51.9) | 36 (50.7) |
| ≥ 40 | 2 ( 3.3) | 1 ( 5.9) | 15 ( 4.6) | 5 ( 7.9) | 20 ( 5.1) | 5 ( 7.0) |

## Attachment 17: Demographic and Baseline Characteristics by Joint Replacement Status as of 08 July 2011 (PAI-2004 OA Add-on) (Continued)

**Table TSUB02B_JRJUL8:** Demographic and Baseline Characteristics by Joint Replacement Status
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-to-Treat Analysis Set)

| | Placebo (N=78) | | Fulranumab 1mgQ4wk (N=77) | | Fulranumab 3mgQ8wk (N=76) | | Fulranumab 3mgQ4wk (N=79) | | Fulranumab 6mgQ8wk (N=78) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | JR=NO | JR=YES | JR=NO | JR=YES | JR=NO | JR=YES | JR=NO | JR=YES | JR=NO | JR=YES |
| **Strata 2 - baseline body weight group, n (%)** | | | | | | | | | | |
| N | 70 | 8 | 68 | 9 | 68 | 8 | 62 | 17 | 66 | 12 |
| <85kg | 27 (38.6) | 4 (50.0) | 26 (38.2) | 5 (55.6) | 26 (38.2) | 4 (50.0) | 24 (38.7) | 7 (41.2) | 26 (39.4) | 5 (41.7) |
| ≥ 85kg | 43 (61.4) | 4 (50.0) | 42 (61.8) | 4 (44.4) | 42 (61.8) | 4 (50.0) | 38 (61.3) | 10 (58.8) | 40 (60.6) | 7 (58.3) |
| **Strata 1 - baseline opioid use, n (%)** | | | | | | | | | | |
| N | 70 | 8 | 68 | 9 | 68 | 8 | 62 | 17 | 66 | 12 |
| No opioids | 46 (65.7) | 7 (87.5) | 46 (67.6) | 6 (66.7) | 48 (70.6) | 5 (62.5) | 40 (64.5) | 13 (76.5) | 46 (69.7) | 7 (58.3) |
| USe opioids | 24 (34.3) | 1 (12.5) | 22 (32.4) | 3 (33.3) | 20 (29.4) | 3 (37.5) | 22 (35.5) | 4 (23.5) | 20 (30.3) | 5 (41.7) |
| **Nsaid use in prior and DB EFf phase, n (%)** | | | | | | | | | | |
| N | 70 | 8 | 68 | 9 | 68 | 8 | 62 | 17 | 66 | 12 |
| Yes | 56 (80.0) | 6 (75.0) | 50 (73.5) | 8 (88.9) | 51 (75.0) | 7 (87.5) | 52 (83.9) | 15 (88.2) | 54 (81.8) | 11 (91.7) |
| No | 14 (20.0) | 2 (25.0) | 18 (26.5) | 1 (11.1) | 17 (25.0) | 1 (12.5) | 10 (16.1) | 2 (11.8) | 12 (18.2) | 1 ( 8.3) |
| **Opioid use in prior and DB EFf phase, n (%)** | | | | | | | | | | |
| N | 70 | 8 | 68 | 9 | 68 | 8 | 62 | 17 | 66 | 12 |
| Yes | 25 (35.7) | 3 (37.5) | 22 (32.4) | 3 (33.3) | 23 (33.8) | 3 (37.5) | 24 (38.7) | 5 (29.4) | 22 (33.3) | 6 (50.0) |
| No | 45 (64.3) | 5 (62.5) | 46 (67.6) | 6 (66.7) | 45 (66.2) | 5 (62.5) | 38 (61.3) | 12 (70.6) | 44 (66.7) | 6 (50.0) |
| **Type of study joint, n (%)** | | | | | | | | | | |
| N | 70 | 8 | 68 | 9 | 68 | 8 | 62 | 17 | 66 | 12 |
| Hip | 9 (12.9) | 4 (50.0) | 13 (19.1) | 4 (44.4) | 18 (26.5) | 3 (37.5) | 15 (24.2) | 4 (23.5) | 16 (24.2) | 6 (50.0) |
| Knee | 61 (87.1) | 4 (50.0) | 55 (80.9) | 5 (55.6) | 50 (73.5) | 5 (62.5) | 47 (75.8) | 13 (76.5) | 50 (75.8) | 6 (50.0) |

## Attachment 17: Demographic and Baseline Characteristics by Joint Replacement Status as of 08 July 2011 (PAI-2004 OA Add-on) (Continued)

**Table TSUB02B_JRJUL8:** Demographic and Baseline Characteristics by Joint Replacement Status
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-to-Treat Analysis Set)

| | Fulranumab 10mgQ8wk (N=78) | | Total Fulranumab (N=388) | | Total (N=466) | |
|---|---|---|---|---|---|---|
| | JR=NO | JR=YES | JR=NO | JR=YES | JR=NO | JR=YES |
| **Strata 2 - baseline body weight group, n (%)** | | | | | | |
| N | 61 | 17 | 325 | 63 | 395 | 71 |
| <85kg | 25 (41.0) | 6 (35.3) | 127 (39.1) | 27 (42.9) | 154 (39.0) | 31 (43.7) |
| ≥ 85kg | 36 (59.0) | 11 (64.7) | 198 (60.9) | 36 (57.1) | 241 (61.0) | 40 (56.3) |
| **Strata 1 - baseline opioid use, n (%)** | | | | | | |
| N | 61 | 17 | 325 | 63 | 395 | 71 |
| No opioids | 41 (67.2) | 12 (70.6) | 221 (68.0) | 43 (68.3) | 267 (67.6) | 50 (70.4) |
| USe opioids | 20 (32.8) | 5 (29.4) | 104 (32.0) | 20 (31.7) | 128 (32.4) | 21 (29.6) |
| **Nsaid use in prior and DB EFf phase, n (%)** | | | | | | |
| N | 61 | 17 | 325 | 63 | 395 | 71 |
| Yes | 50 (82.0) | 15 (88.2) | 257 (79.1) | 56 (88.9) | 313 (79.2) | 62 (87.3) |
| No | 11 (18.0) | 2 (11.8) | 68 (20.9) | 7 (11.1) | 82 (20.8) | 9 (12.7) |
| **Opioid use in prior and DB EFf phase, n (%)** | | | | | | |
| N | 61 | 17 | 325 | 63 | 395 | 71 |
| Yes | 19 (31.1) | 5 (29.4) | 110 (33.8) | 22 (34.9) | 135 (34.2) | 25 (35.2) |
| No | 42 (68.9) | 12 (70.6) | 215 (66.2) | 41 (65.1) | 260 (65.8) | 46 (64.8) |
| **Type of study joint, n (%)** | | | | | | |
| N | 61 | 17 | 325 | 63 | 395 | 71 |
| Hip | 11 (18.0) | 5 (29.4) | 73 (22.5) | 22 (34.9) | 82 (20.8) | 26 (36.6) |
| Knee | 50 (82.0) | 12 (70.6) | 252 (77.5) | 41 (65.1) | 313 (79.2) | 45 (63.4) |

## Attachment 17: Demographic and Baseline Characteristics by Joint Replacement Status as of 08 July 2011 (PAI-2004 OA Add-on) (Continued)

**Table TSUB02B_JRJUL8:** Demographic and Baseline Characteristics by Joint Replacement Status
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-to-Treat Analysis Set)

| | Placebo (N=78) | | Fulranumab 1mgQ4wk (N=77) | | Fulranumab 3mgQ8wk (N=76) | | Fulranumab 3mgQ4wk (N=79) | | Fulranumab 6mgQ8wk (N=78) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | JR=NO | JR=YES | JR=NO | JR=YES | JR=NO | JR=YES | JR=NO | JR=YES | JR=NO | JR=YES |
| **Womac baseline pain category, n (%)** | | | | | | | | | | |
| N | 70 | 8 | 68 | 9 | 68 | 8 | 61 | 17 | 66 | 12 |
| None to mild | 2 ( 2.9) | 0 | 10 (14.7) | 0 | 3 ( 4.4) | 0 | 8 (13.1) | 1 ( 5.9) | 3 ( 4.5) | 0 |
| Moderate | 45 (64.3) | 6 (75.0) | 37 (54.4) | 4 (44.4) | 42 (61.8) | 6 (75.0) | 38 (62.3) | 9 (52.9) | 39 (59.1) | 7 (58.3) |
| Severe | 23 (32.9) | 2 (25.0) | 21 (30.9) | 5 (55.6) | 23 (33.8) | 2 (25.0) | 15 (24.6) | 7 (41.2) | 24 (36.4) | 5 (41.7) |
| **Kl grade at screening, n (%)** | | | | | | | | | | |
| N | 70 | 8 | 68 | 9 | 68 | 8 | 61 | 17 | 66 | 12 |
| 2 | 33 (47.1) | 2 (25.0) | 25 (36.8) | 1 (11.1) | 31 (45.6) | 2 (25.0) | 35 (57.4) | 3 (17.6) | 32 (48.5) | 1 ( 8.3) |
| 3 | 30 (42.9) | 2 (25.0) | 34 (50.0) | 5 (55.6) | 27 (39.7) | 4 (50.0) | 20 (32.8) | 7 (41.2) | 21 (31.8) | 8 (66.7) |
| 4 | 7 (10.0) | 4 (50.0) | 9 (13.2) | 3 (33.3) | 10 (14.7) | 2 (25.0) | 6 ( 9.8) | 7 (41.2) | 13 (19.7) | 3 (25.0) |
| **Baseline average nrs pain score** | | | | | | | | | | |
| N | 70 | 8 | 68 | 9 | 68 | 8 | 62 | 17 | 66 | 12 |
| Mean | 7.1 | 6.7 | 6.9 | 7.5 | 6.7 | 6.7 | 6.6 | 6.9 | 6.8 | 6.9 |
| SD | 1.10 | 1.15 | 1.40 | 2.05 | 1.23 | 0.82 | 1.00 | 1.31 | 1.11 | 0.91 |
| Median | 7.0 | 6.5 | 6.7 | 7.6 | 6.5 | 6.5 | 6.6 | 7.0 | 7.0 | 7.0 |
| Minimum | 5 | 5 | 5 | 5 | 5 | 6 | 5 | 5 | 5 | 5 |
| Maximum | 10 | 9 | 10 | 10 | 10 | 8 | 9 | 10 | 10 | 8 |
| **Womac baseline pain score** | | | | | | | | | | |
| N | 70 | 8 | 68 | 9 | 68 | 8 | 61 | 17 | 66 | 12 |
| Mean | 6.6 | 6.5 | 6.1 | 7.6 | 6.4 | 6.4 | 5.9 | 6.7 | 6.3 | 6.6 |
| SD | 1.45 | 1.59 | 1.74 | 2.10 | 1.50 | 1.09 | 1.41 | 1.61 | 1.63 | 1.31 |
| Median | 6.5 | 6.1 | 6.2 | 8.4 | 6.5 | 6.3 | 6.0 | 6.4 | 6.2 | 6.7 |
| Minimum | 3 | 5 | 1 | 5 | 3 | 5 | 2 | 4 | 1 | 5 |
| Maximum | 10 | 10 | 9 | 10 | 10 | 8 | 9 | 9 | 10 | 8 |

## Attachment 17: Demographic and Baseline Characteristics by Joint Replacement Status as of 08 July 2011 (PAI-2004 OA Add-on) (Continued)

**Table TSUB02B_JRJUL8:** Demographic and Baseline Characteristics by Joint Replacement Status
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-to-Treat Analysis Set)

| | Fulranumab 10mgQ8wk (N=78) | | Total Fulranumab (N=388) | | Total (N=466) | |
|---|---|---|---|---|---|---|
| | JR=NO | JR=YES | JR=NO | JR=YES | JR=NO | JR=YES |
| **Womac baseline pain category, n (%)** | | | | | | |
| N | 61 | 17 | 324 | 63 | 394 | 71 |
| None to mild | 5 ( 8.2) | 1 ( 5.9) | 29 ( 9.0) | 2 ( 3.2) | 31 ( 7.9) | 2 ( 2.8) |
| Moderate | 35 (57.4) | 10 (58.8) | 191 (59.0) | 36 (57.1) | 236 (59.9) | 42 (59.2) |
| Severe | 21 (34.4) | 6 (35.3) | 104 (32.1) | 25 (39.7) | 127 (32.2) | 27 (38.0) |
| **Kl grade at screening, n (%)** | | | | | | |
| N | 61 | 17 | 324 | 63 | 394 | 71 |
| 2 | 27 (44.3) | 8 (47.1) | 150 (46.3) | 15 (23.8) | 183 (46.4) | 17 (23.9) |
| 3 | 22 (36.1) | 7 (41.2) | 124 (38.3) | 31 (49.2) | 154 (39.1) | 33 (46.5) |
| 4 | 12 (19.7) | 2 (11.8) | 50 (15.4) | 17 (27.0) | 57 (14.5) | 21 (29.6) |
| **Baseline average nrs pain score** | | | | | | |
| N | 61 | 17 | 325 | 63 | 395 | 71 |
| Mean | 6.8 | 7.2 | 6.8 | 7.0 | 6.8 | 7.0 |
| SD | 1.13 | 1.15 | 1.18 | 1.27 | 1.17 | 1.25 |
| Median | 6.5 | 7.5 | 6.7 | 7.0 | 6.8 | 7.0 |
| Minimum | 5 | 5 | 5 | 5 | 5 | 5 |
| Maximum | 9 | 9 | 10 | 10 | 10 | 10 |
| **Womac baseline pain score** | | | | | | |
| N | 61 | 17 | 324 | 63 | 394 | 71 |
| Mean | 6.4 | 6.5 | 6.2 | 6.7 | 6.3 | 6.7 |
| SD | 1.41 | 1.46 | 1.55 | 1.54 | 1.54 | 1.54 |
| Median | 6.2 | 6.4 | 6.2 | 6.6 | 6.2 | 6.6 |
| Minimum | 3 | 3 | 1 | 3 | 1 | 3 |
| Maximum | 10 | 9 | 10 | 10 | 10 | 10 |

## Attachment 17: Demographic and Baseline Characteristics by Joint Replacement Status as of 08 July 2011 (PAI-2004 OA Add-on) (Continued)

**Table TSUB02B_JRJUL8:** Demographic and Baseline Characteristics by Joint Replacement Status
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-to-Treat Analysis Set)

| | Placebo (N=78) | | Fulranumab 1mgQ4wk (N=77) | | Fulranumab 3mgQ8wk (N=76) | | Fulranumab 3mgQ4wk (N=79) | | Fulranumab 6mgQ8wk (N=78) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | JR=NO | JR=YES | JR=NO | JR=YES | JR=NO | JR=YES | JR=NO | JR=YES | JR=NO | JR=YES |
| **Womac baseline physical function** | | | | | | | | | | |
| N | 70 | 8 | 68 | 9 | 68 | 8 | 61 | 17 | 66 | 12 |
| Mean | 6.6 | 6.3 | 6.1 | 7.3 | 6.5 | 6.6 | 6.0 | 6.9 | 6.2 | 6.1 |
| SD | 1.54 | 1.40 | 1.96 | 2.18 | 1.40 | 0.84 | 1.60 | 1.32 | 1.83 | 1.49 |
| Median | 6.5 | 6.2 | 6.0 | 7.8 | 6.6 | 6.3 | 5.9 | 6.9 | 6.3 | 6.3 |
| Minimum | 3 | 5 | 0 | 4 | 2 | 6 | 1 | 5 | 1 | 3 |
| Maximum | 10 | 9 | 10 | 10 | 9 | 8 | 9 | 9 | 10 | 8 |
| **Womac baseline stiffness score** | | | | | | | | | | |
| N | 70 | 8 | 68 | 9 | 68 | 8 | 61 | 17 | 66 | 12 |
| Mean | 6.9 | 7.4 | 6.5 | 7.5 | 7.0 | 6.9 | 7.0 | 6.9 | 6.8 | 6.9 |
| SD | 1.81 | 1.12 | 1.77 | 2.03 | 1.44 | 1.27 | 1.39 | 1.95 | 1.85 | 1.13 |
| Median | 7.0 | 7.5 | 6.5 | 8.0 | 7.0 | 6.8 | 7.0 | 6.5 | 7.0 | 7.0 |
| Minimum | 1 | 5 | 2 | 5 | 4 | 5 | 4 | 3 | 2 | 5 |
| Maximum | 10 | 9 | 10 | 10 | 10 | 9 | 10 | 10 | 10 | 9 |

## Attachment 17: Demographic and Baseline Characteristics by Joint Replacement Status as of 08 July 2011 (PAI-2004 OA Add-on) (Continued)

**Table TSUB02B_JRJUL8:** Demographic and Baseline Characteristics by Joint Replacement Status
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-to-Treat Analysis Set)

| | Fulranumab 10mgQ8wk (N=78) | | Total Fulranumab (N=388) | | Total (N=466) | |
|---|---|---|---|---|---|---|
| | JR=NO | JR=YES | JR=NO | JR=YES | JR=NO | JR=YES |
| **Womac baseline physical function** | | | | | | |
| N | 61 | 17 | 324 | 63 | 394 | 71 |
| Mean | 6.3 | 6.7 | 6.2 | 6.7 | 6.3 | 6.7 |
| SD | 1.46 | 1.62 | 1.67 | 1.53 | 1.65 | 1.51 |
| Median | 6.2 | 6.9 | 6.2 | 6.8 | 6.4 | 6.7 |
| Minimum | 1 | 2 | 0 | 2 | 0 | 2 |
| Maximum | 9 | 9 | 10 | 10 | 10 | 10 |
| **Womac baseline stiffness score** | | | | | | |
| N | 61 | 17 | 324 | 63 | 394 | 71 |
| Mean | 6.8 | 6.5 | 6.8 | 6.9 | 6.8 | 6.9 |
| SD | 1.50 | 2.04 | 1.61 | 1.76 | 1.64 | 1.70 |
| Median | 7.0 | 7.0 | 7.0 | 7.0 | 7.0 | 7.0 |
| Minimum | 1 | 2 | 1 | 2 | 1 | 2 |
| Maximum | 10 | 9 | 10 | 10 | 10 | 10 |

tsub02b_jrjul8.rtf generated by rdm02b.sas, 28JAN2012 21:11

## Attachment 18: Prior Medications Containing Corticosteroids by Joint Replacement Status (PAI-2004 OA Add-on)

**Table TSUB14_JUL8:** Previous Pain Medications Containing Corticosteroids
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-to-Treat Analysis Set)

Joint replacement: No
Note: Pain medications in the last year that are not part of baseline pain treatment

| Standardized Medication Name | Placebo (N=70) n (%) | Fulranumab 1mgQ4wk (N=68) n (%) | Fulranumab 3mgQ8wk (N=68) n (%) | Fulranumab 3mgQ4wk (N=62) n (%) | Fulranumab 6mgQ8wk (N=66) n (%) | Fulranumab 10mgQ8wk (N=61) n (%) | Total (N=395) n (%) |
|---|---|---|---|---|---|---|---|
| **Total no. subjects WITH PREVIOUS MEDICATION** | 3 ( 4) | 2 ( 3) | 3 ( 4) | 3 ( 5) | 2 ( 3) | 1 ( 2) | 14 ( 4) |
| Cortisone | 1 ( 1) | 2 ( 3) | 1 ( 1) | 1 ( 2) | 1 ( 2) | 0 | 6 ( 2) |
| Corticosteroid nos | 1 ( 1) | 0 | 1 ( 1) | 0 | 0 | 0 | 2 ( 1) |
| Methylprednisolone acetate | 0 | 0 | 0 | 1 ( 2) | 1 ( 2) | 0 | 2 ( 1) |
| Betamethasone | 0 | 0 | 1 ( 1) | 0 | 0 | 0 | 1 (<1) |
| Methylprednisolone | 0 | 0 | 0 | 0 | 0 | 1 ( 2) | 1 (<1) |
| Triamcinolone | 0 | 0 | 0 | 1 ( 2) | 0 | 0 | 1 (<1) |
| Triamcinolone acetonide | 1 ( 1) | 0 | 0 | 0 | 0 | 0 | 1 (<1) |

Note: Percentages calculated with the number of subjects in each group as denominator.

**Table TSUB14_JUL8:** Previous Pain Medications Containing Corticosteroids
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-to-Treat Analysis Set)

Joint replacement: Yes
Note: Pain medications in the last year that are not part of baseline pain treatment

| Standardized Medication Name | Placebo (N=8) n (%) | Fulranumab 1mgQ4wk (N=9) n (%) | Fulranumab 3mgQ8wk (N=8) n (%) | Fulranumab 3mgQ4wk (N=17) n (%) | Fulranumab 6mgQ8wk (N=12) n (%) | Fulranumab 10mgQ8wk (N=17) n (%) | Total (N=71) n (%) |
|---|---|---|---|---|---|---|---|
| **Total no. subjects WITH PREVIOUS MEDICATION** | 1 ( 13) | 1 ( 11) | 1 ( 13) | 1 ( 6) | 0 | 0 | 4 ( 6) |
| Methylprednisolone acetate | 1 ( 13) | 1 ( 11) | 0 | 0 | 0 | 0 | 2 ( 3) |
| Cortisone | 0 | 0 | 1 ( 13) | 0 | 0 | 0 | 1 ( 1) |
| Triamcinolone acetonide | 0 | 0 | 0 | 1 ( 6) | 0 | 0 | 1 ( 1) |

See footnotes on the first page of the table.
tsub14_jrjul8.rtf generated by rcm.sas, 28JAN2012 21:26

## Attachment 19: Prior Medications Containing Corticosteroids Continued Into the Double-Blind Efficacy Phase by Joint Replacement Status (PAI-2004 OA Add-on)

**Table TSUB15_JRJUL8:** Prior Medications Containing Corticosteroids Continued Into Double Blind Efficacy Phase by Joint Replacement Status
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-to-Treat Analysis Set)

**Joint replacement: No**

| Standardized Medication Name | Placebo (N=70) n (%) | Fulranumab 1mgQ4wk (N=68) n (%) | Fulranumab 3mgQ8wk (N=68) n (%) | Fulranumab 3mgQ4wk (N=62) n (%) | Fulranumab 6mgQ8wk (N=66) n (%) | Fulranumab 10mgQ8wk (N=61) n (%) | Total (N=395) n (%) |
|---|---|---|---|---|---|---|---|
| **Total no. subjects WITH CONCOMITANT MEDICATION** | 9 ( 13) | 5 ( 7) | 2 ( 3) | 4 ( 6) | 5 ( 8) | 2 ( 3) | 27 ( 7) |
| Fluticasone propionate | 5 ( 7) | 2 ( 3) | 0 | 1 ( 2) | 2 ( 3) | 1 ( 2) | 11 ( 3) |
| Mometasone furoate | 0 | 1 ( 1) | 1 ( 1) | 1 ( 2) | 1 ( 2) | 0 | 4 ( 1) |
| Triamcinolone acetonide | 2 ( 3) | 0 | 0 | 0 | 0 | 1 ( 2) | 3 ( 1) |
| Budesonide | 1 ( 1) | 0 | 1 ( 1) | 0 | 0 | 0 | 2 ( 1) |
| Budesonide w/formoterol fumarate | 1 ( 1) | 0 | 0 | 0 | 1 ( 2) | 0 | 2 ( 1) |
| Fluticasone | 0 | 1 ( 1) | 0 | 0 | 1 ( 2) | 0 | 2 ( 1) |
| Beclometasone dipropionate | 1 ( 1) | 0 | 0 | 0 | 0 | 0 | 1 ( <1) |
| Betamethasone | 0 | 0 | 1 ( 1) | 0 | 0 | 0 | 1 ( <1) |
| Ciclesonide | 0 | 0 | 0 | 1 ( 2) | 0 | 0 | 1 ( <1) |
| Clobetasol propionate | 0 | 0 | 0 | 0 | 1 ( 2) | 0 | 1 ( <1) |
| Flunisolide | 0 | 0 | 0 | 1 ( 2) | 0 | 0 | 1 ( <1) |
| Hydrocortisone | 0 | 0 | 0 | 0 | 1 ( 2) | 0 | 1 ( <1) |
| Lotrisone | 0 | 1 ( 1) | 0 | 0 | 0 | 0 | 1 ( <1) |
| Prednisolone | 1 ( 1) | 0 | 0 | 0 | 0 | 0 | 1 ( <1) |

Note: Percentages calculated with the number of subjects in each group as denominator.

## Attachment 19: Prior Medications Containing Corticosteroids Continued Into the Double-Blind Efficacy Phase by Joint Replacement Status (PAI-2004 OA Add-on) (Continued)

**Table TSUB15_JRJUL8:** Prior Medications Containing Corticosteroids Continued Into Double Blind Efficacy Phase by Joint Replacement Status
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-to-Treat Analysis Set)

**Joint replacement: Yes**

| Standardized Medication Name | Placebo (N=8) n (%) | Fulranumab 1mgQ4wk (N=9) n (%) | Fulranumab 3mgQ8wk (N=8) n (%) | Fulranumab 3mgQ4wk (N=17) n (%) | Fulranumab 6mgQ8wk (N=12) n (%) | Fulranumab 10mgQ8wk (N=17) n (%) | Total (N=71) n (%) |
|---|---|---|---|---|---|---|---|
| **Total no. subjects WITH CONCOMITANT MEDICATION** | 2 ( 25) | 1 ( 11) | 1 ( 13) | 2 ( 12) | 3 ( 25) | 2 ( 12) | 11 ( 15) |
| Mometasone furoate | 1 ( 13) | 0 | 0 | 0 | 2 ( 17) | 0 | 3 ( 4) |
| Fluticasone propionate | 0 | 0 | 0 | 1 ( 6) | 1 ( 8) | 0 | 2 ( 3) |
| Betamethasone valerate | 1 ( 13) | 0 | 0 | 0 | 0 | 0 | 1 ( 1) |
| Budesonide | 0 | 0 | 1 ( 13) | 0 | 0 | 0 | 1 ( 1) |
| Clobetasol propionate | 0 | 1 ( 11) | 0 | 0 | 0 | 0 | 1 ( 1) |
| Fluocinonide | 0 | 0 | 0 | 1 ( 6) | 0 | 0 | 1 ( 1) |
| Prednisone | 0 | 0 | 0 | 0 | 0 | 1 ( 6) | 1 ( 1) |
| Triamcinolone acetonide | 0 | 0 | 0 | 0 | 0 | 1 ( 6) | 1 ( 1) |

See footnotes on the first page of the table.
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## Attachment 20: Concomitant Medications Containing Corticosteroids by Joint Replacement Status (PAI-2004 OA Add-on)

**Table TSUB13C_JRJUL8:** Concomitant Medications Containing Corticosteroids for the Combined DB Efficacy, DB Extension and Post-treatment Phases by Joint Replacement Status (Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-to-Treat Analysis Set)

Joint replacement: No

| Standardized Medication Name | Placebo (N=70) n (%) | Fulranumab 1mgQ4wk (N=68) n (%) | Fulranumab 3mgQ8wk (N=68) n (%) | Fulranumab 3mgQ4wk (N=62) n (%) | Fulranumab 6mgQ8wk (N=66) n (%) | Fulranumab 10mgQ8wk (N=61) n (%) | Total (N=395) n (%) |
|---|---|---|---|---|---|---|---|
| **Total no. subjects WITH CONCOMITANT MEDICATION** | 19 ( 27) | 17 ( 25) | 22 ( 32) | 21 ( 34) | 23 ( 35) | 15 ( 25) | 117 ( 30) |
| Cortisone | 3 ( 4) | 3 ( 4) | 4 ( 6) | 5 ( 8) | 7 ( 11) | 1 ( 2) | 23 ( 6) |
| Prednisone | 0 | 2 ( 3) | 4 ( 6) | 5 ( 8) | 4 ( 6) | 5 ( 8) | 20 ( 5) |
| Methylprednisolone | 1 ( 1) | 5 ( 7) | 4 ( 6) | 4 ( 6) | 1 ( 2) | 2 ( 3) | 17 ( 4) |
| Fluticasone propionate | 7 ( 10) | 2 ( 3) | 2 ( 3) | 1 ( 2) | 2 ( 3) | 1 ( 2) | 15 ( 4) |
| Methylprednisolone acetate | 4 ( 6) | 1 ( 1) | 4 ( 6) | 2 ( 3) | 1 ( 2) | 1 ( 2) | 13 ( 3) |
| Mometasone furoate | 1 ( 1) | 3 ( 4) | 3 ( 4) | 1 ( 2) | 3 ( 5) | 0 | 11 ( 3) |
| DEXamethasone | 0 | 0 | 4 ( 6) | 1 ( 2) | 2 ( 3) | 3 ( 5) | 10 ( 3) |
| Triamcinolone acetonide | 5 ( 7) | 0 | 1 ( 1) | 1 ( 2) | 1 ( 2) | 2 ( 3) | 10 ( 3) |
| Triamcinolone | 0 | 2 ( 3) | 0 | 1 ( 2) | 2 ( 3) | 2 ( 3) | 7 ( 2) |
| Budesonide | 3 ( 4) | 0 | 2 ( 3) | 0 | 0 | 0 | 5 ( 1) |
| Betamethasone | 0 | 1 ( 1) | 1 ( 1) | 2 ( 3) | 0 | 0 | 4 ( 1) |
| Budesonide w/formoterol fumarate | 2 ( 3) | 1 ( 1) | 0 | 0 | 1 ( 2) | 0 | 4 ( 1) |
| Ciclesonide | 0 | 0 | 0 | 2 ( 3) | 2 ( 3) | 0 | 4 ( 1) |
| Fluticasone | 0 | 1 ( 1) | 0 | 2 ( 3) | 1 ( 2) | 0 | 4 ( 1) |
| Hydrocortisone | 0 | 0 | 0 | 1 ( 2) | 3 ( 5) | 0 | 4 ( 1) |
| Clobetasol propionate | 0 | 0 | 0 | 0 | 2 ( 3) | 1 ( 2) | 3 ( 1) |
| Corticosteroids for systemic use | 0 | 0 | 0 | 1 ( 2) | 1 ( 2) | 0 | 2 ( 1) |
| Beclometasone dipropionate | 1 ( 1) | 0 | 0 | 0 | 0 | 0 | 1 ( <1) |
| Betamethasone valerate | 0 | 1 ( 1) | 0 | 0 | 0 | 0 | 1 ( <1) |
| Ciclosporin | 1 ( 1) | 0 | 0 | 0 | 0 | 0 | 1 ( <1) |
| Clocortolone pivalate | 0 | 0 | 0 | 0 | 1 ( 2) | 0 | 1 ( <1) |
| Corticosteroid nos | 0 | 0 | 0 | 0 | 1 ( 2) | 0 | 1 ( <1) |
| Corticosteroids | 0 | 0 | 0 | 1 ( 2) | 0 | 0 | 1 ( <1) |
| Diprospan | 1 ( 1) | 0 | 0 | 0 | 0 | 0 | 1 ( <1) |

Note: Percentages calculated with the number of subjects in each group as denominator.

## Attachment 20: Concomitant Medications Containing Corticosteroids by Joint Replacement Status (PAI-2004 OA Add-on) (Continued)

**Table TSUB13C_JRJUL8:** Concomitant Medications Containing Corticosteroids for the Combined DB Efficacy, DB Extension and Post-treatment Phases by Joint Replacement Status (Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-to-Treat Analysis Set)

Joint replacement: No

| Standardized Medication Name | Placebo (N=70) n (%) | Fulranumab 1mgQ4wk (N=68) n (%) | Fulranumab 3mgQ8wk (N=68) n (%) | Fulranumab 3mgQ4wk (N=62) n (%) | Fulranumab 6mgQ8wk (N=66) n (%) | Fulranumab 10mgQ8wk (N=61) n (%) | Total (N=395) n (%) |
|---|---|---|---|---|---|---|---|
| Flunisolide | 0 | 0 | 0 | 1 ( 2) | 0 | 0 | 1 (<1) |
| Fluocinonide | 0 | 0 | 1 ( 1) | 0 | 0 | 0 | 1 (<1) |
| Garasone | 0 | 0 | 0 | 0 | 1 ( 2) | 0 | 1 (<1) |
| Halcinonide | 0 | 0 | 0 | 0 | 1 ( 2) | 0 | 1 (<1) |
| Hydrocortisone valerate | 0 | 0 | 0 | 0 | 1 ( 2) | 0 | 1 (<1) |
| Lotrisone | 0 | 1 ( 1) | 0 | 0 | 0 | 0 | 1 (<1) |
| Methylprednisolone sodium succinate | 0 | 0 | 1 ( 1) | 0 | 0 | 0 | 1 (<1) |
| Ophthalmologicals | 0 | 0 | 0 | 0 | 0 | 1 ( 2) | 1 (<1) |
| Prednisolone | 1 ( 1) | 0 | 0 | 0 | 0 | 0 | 1 (<1) |
| Prednisone acetate | 0 | 0 | 0 | 0 | 1 ( 2) | 0 | 1 (<1) |
| Triamcinolone hEXacetonide | 0 | 0 | 0 | 0 | 1 ( 2) | 0 | 1 (<1) |

See footnotes on the first page of the table.

## Attachment 20: Concomitant Medications Containing Corticosteroids by Joint Replacement Status (PAI-2004 OA Add-on) (Continued)

**Table TSUB13C_JRJUL8:** Concomitant Medications Containing Corticosteroids for the Combined DB Efficacy, DB Extension and Post-treatment Phases by Joint Replacement Status (Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-to-Treat Analysis Set)

Joint replacement: Yes

| Standardized Medication Name | Placebo (N=8) n (%) | Fulranumab 1mgQ4wk (N=9) n (%) | Fulranumab 3mgQ8wk (N=8) n (%) | Fulranumab 3mgQ4wk (N=17) n (%) | Fulranumab 6mgQ8wk (N=12) n (%) | Fulranumab 10mgQ8wk (N=17) n (%) | Total (N=71) n (%) |
|---|---|---|---|---|---|---|---|
| **Total no. subjects WITH CONCOMITANT MEDICATION** | 4 ( 50) | 6 ( 67) | 2 ( 25) | 8 ( 47) | 7 ( 58) | 6 ( 35) | 33 ( 46) |
| Prednisone | 1 ( 13) | 1 ( 11) | 0 | 2 ( 12) | 1 ( 8) | 2 ( 12) | 7 ( 10) |
| Mometasone furoate | 2 ( 25) | 1 ( 11) | 0 | 1 ( 6) | 2 ( 17) | 0 | 6 ( 8) |
| Methylprednisolone acetate | 0 | 2 ( 22) | 0 | 1 ( 6) | 0 | 2 ( 12) | 5 ( 7) |
| Triamcinolone acetonide | 1 ( 13) | 0 | 0 | 1 ( 6) | 1 ( 8) | 2 ( 12) | 5 ( 7) |
| Cortisone | 0 | 0 | 0 | 2 ( 12) | 1 ( 8) | 1 ( 6) | 4 ( 6) |
| DEXamethasone | 0 | 2 ( 22) | 0 | 1 ( 6) | 0 | 1 ( 6) | 4 ( 6) |
| Fluocinonide | 0 | 1 ( 11) | 0 | 1 ( 6) | 0 | 0 | 2 ( 3) |
| Fluticasone propionate | 0 | 0 | 0 | 1 ( 6) | 1 ( 8) | 0 | 2 ( 3) |
| Lotrisone | 0 | 1 ( 11) | 0 | 0 | 0 | 1 ( 6) | 2 ( 3) |
| Methylprednisolone | 0 | 0 | 0 | 0 | 1 ( 8) | 1 ( 6) | 2 ( 3) |
| Methylprednisolone sodium succinate | 0 | 1 ( 11) | 0 | 0 | 0 | 1 ( 6) | 2 ( 3) |
| Betamethasone | 0 | 0 | 0 | 1 ( 6) | 0 | 0 | 1 ( 1) |
| Betamethasone valerate | 1 ( 13) | 0 | 0 | 0 | 0 | 0 | 1 ( 1) |
| Budesonide | 0 | 0 | 1 ( 13) | 0 | 0 | 0 | 1 ( 1) |
| Clobetasol propionate | 0 | 1 ( 11) | 0 | 0 | 0 | 0 | 1 ( 1) |
| Fluticasone | 0 | 0 | 1 ( 13) | 0 | 0 | 0 | 1 ( 1) |
| Fluticasone furoate | 0 | 0 | 0 | 1 ( 6) | 0 | 0 | 1 ( 1) |
| Hydrocortisone | 0 | 0 | 0 | 0 | 0 | 1 ( 6) | 1 ( 1) |
| Mykoproct n | 0 | 0 | 0 | 0 | 0 | 1 ( 6) | 1 ( 1) |
| Otosporin | 0 | 0 | 0 | 0 | 0 | 1 ( 6) | 1 ( 1) |
| Prednisolone | 0 | 0 | 0 | 0 | 1 ( 8) | 0 | 1 ( 1) |
| Triamcinolone | 0 | 0 | 1 ( 13) | 0 | 0 | 0 | 1 ( 1) |

See footnotes on the first page of the table.

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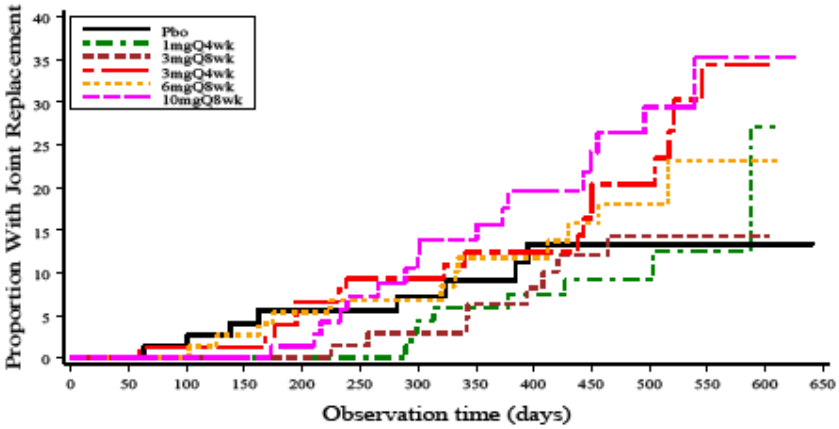
**Attachment 21: Time to Joint Replacement Surgery (PAI-2004 OA Add-on)**

**Figure FJREP01B_UP: Kaplan-Meier Plot of Time to Joint Replacement Surgery**
( 42160443-PAI2004-08July2011 : ITT Analysis Set)




No. Subjects With Specified Observation Time

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pbo | 78 | 77 | 72 | 65 | 63 | 56 | 50 | 46 | 39 | 37 | 19 | 9 | 1 | 0 |
| 1mgQ4wk | 77 | 77 | 73 | 73 | 73 | 70 | 65 | 61 | 56 | 50 | 29 | 14 | 3 | 0 |
| 3mgQ8wk | 76 | 76 | 75 | 73 | 72 | 66 | 61 | 54 | 48 | 43 | 24 | 10 | 2 | 0 |
| 3mgQ4wk | 79 | 79 | 77 | 75 | 70 | 63 | 61 | 56 | 49 | 40 | 28 | 10 | 3 | 0 |
| 6mgQ8wk | 78 | 78 | 76 | 72 | 67 | 63 | 59 | 52 | 46 | 38 | 21 | 7 | 2 | 0 |
| 10mgQ8wk | 78 | 77 | 76 | 74 | 71 | 61 | 52 | 49 | 39 | 33 | 23 | 9 | 2 | 0 |

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## Attachment 22: Fracture-Related Adverse Events

**Table TAE01ALL_FRACT_E2:** Etiology and Fracture Type for Fracture Related AEs
(Study: JNJ42160443: Intent-To-Treat Analysis Set)

Includes studies PAI-2003, PAI-2004, PAI-2005, PAI-2006, NPP-2001, NPP-2002

| **Etiology** Fracture Type | Placebo (N=285) n (%) | Fulranumab (N=931) n (%) | Oxycodone (N=50) n (%) |
|---|---|---|---|
| **Total no. subjects with fractures** | 4 ( 1) | 34 ( 4) | 0 |
| **Unspecified/unknown** | 2 ( 1) | 15 ( 2) | 0 |
| Lower extremity | 1 ( <1) | 9 ( 1) | 0 |
| Upper extremity + other | 2 ( 1) | 8 ( 1) | 0 |
| **Traumatic** | 2 ( 1) | 14 ( 2) | 0 |
| Lower extremity | 2 ( 1) | 10 ( 1) | 0 |
| Upper extremity + other | 0 | 4 ( <1) | 0 |
| **Osteoporotic** | 0 | 4 ( <1) | 0 |
| Lower extremity | 0 | 3 ( <1) | 0 |
| Upper extremity + other | 0 | 2 ( <1) | 0 |
| **Pathologic** | 0 | 2 ( <1) | 0 |
| Lower extremity | 0 | 2 ( <1) | 0 |

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Excludes open-label and post-treatment events for the 4 NPP-2001 subjects who were assigned to Placebo in DB and also received OL Fulranumab.
Includes events with FRACTURE as part of the preferred term or verbatim
tae01all_fract_e2.rtf generated by rae01_xstudy.sas, 20JAN2012 11:51

**Table TAE01ALL_FRACT_E3:** Fracture Type and Etiology for Fracture Related AEs
(Study: JNJ42160443: Intent-To-Treat Analysis Set)

Includes studies PAI-2003, PAI-2004, PAI-2005, PAI-2006, NPP-2001, NPP-2002

| **Fracture Type** Etiology | Placebo (N=285) n (%) | Fulranumab (N=931) n (%) | Oxycodone (N=50) n (%) |
|---|---|---|---|
| **Total no. subjects with fractures** | 4 ( 1) | 34 ( 4) | 0 |
| **Lower extremity** | 3 ( 1) | 23 ( 2) | 0 |
| Unspecified/unknown | 1 ( <1) | 11 ( 1) | 0 |
| Traumatic | 2 ( 1) | 10 ( 1) | 0 |
| Osteoporotic | 0 | 3 ( <1) | 0 |
| **Upper extremity + other** | 2 ( 1) | 14 ( 2) | 0 |
| Unspecified/unknown | 2 ( 1) | 8 ( 1) | 0 |
| Traumatic | 0 | 4 ( <1) | 0 |
| Osteoporotic | 0 | 2 ( <1) | 0 |

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
Excludes open-label and post-treatment events for the 4 NPP-2001 subjects who were assigned to Placebo in DB and also received OL Fulranumab.
Includes events with FRACTURE as part of the preferred term or verbatim
tae01all_fract_e3.rtf generated by rae01_xstudy.sas, 26JAN2012 11:02

## Attachment 23: Adverse Event Preferred Terms Possibly Related to Joint Destruction

| Musculoskeletal Soc Relevant Adverse Event Preferred Terms |
|---|
| Advanced OA |
| Avascular Necrosis |
| Degenerative Joint Disease |
| Exacerbated OA Pain |
| Groin Pain |
| Increased Knee or Hip Pain |
| Intermittent Increase in Knee / Hip Pain |
| Knee Effusion |
| Knee Swelling |
| Normal Progression of OA/ OA/End Stage Osteoarthritis |
| Osteonecrosis of Hip / Knee |
| Osteopenia of Femoral Neck |
| Rapid Progression of OA |
| Severe OA |
| Sharp Pain Hip/ Knee |
| Worsening of Knee / Hip / Shoulder Pain |
| Worsening of OA |

| Musculoskeletal SOC Preferred Term Requiring Further Review |
|---|
| Arthralgia |
| Arthritis |
| Back Pain |
| Groin Pain |
| Joint Swelling |
| Musculoskeletal Pain |
| Osteoarthritis |
| Osteonecrosis |
| Osteopenia |

| Injury SOC Relevant Adverse Event Preferred Terms |
|---|
| Dislocated Hip |
| Epicondylitis |
| Hip Pain Secondary to Hip Collapse |
| Injury to Knees |
| Medial Meniscus Tear |
| Shoulder Bicep Rupture |
| Torn Ligament |

| Injury SOC Preferred Terms Requiring Further Review |
|---|
| Meniscus Lesion |
| Joint Dislocation |
| Muscle Rupture |
| Epicondylitis |
| Ligament Rupture |
| Joint Injury |

**Attachment 24: Adjudication Results as of 08 July 2011**

| SUBJECT ID | STUDY | DIAGNOSIS | ATTRIBUTION | JOINT INVOLVED |
|---|---|---|---|---|
| 00130903 | PAI2003 | NA | NA | Left Knee [a] |
| 00131105 | PAI2003 | NP OA | Not Related | Left Hip |
| **00131107** [b] | **PAI2003** | **RPOA** | **Possibly Related** | **Left Hip** |
| 00131208 | PAI2003 | NP OA | Not Related | Right Knee |
| 00131607 | PAI2003 | NA | Not Related | Lumbar [c] |
| 00132302 | PAI2003 | NP OA | Not Related | Right Knee |
| 00132609 | PAI2003 | NP OA | Not Related | Right Knee |
| 00132609 | PAI2003 | Insufficient | Insufficient | Left Knee |
| 00134023 | PAI2003 | NP OA | Not Related | Left Hip |
| 00134301 | PAI2003 | NP OA | Not Related | Right Shoulder |
| 00140402 | PAI2004 | NP OA | Not Related | Right Knee |
| 00140602 | PAI2004 | Insufficient | Insufficient | Right Knee |
| 00141311 | PAI2004 | NP OA | Not Related | Left Knee |
| **00141318** [b] | PAI2004 | NP OA | Not Related | Left Hip |
| 00141404 | PAI2004 | RPOA | Tie: Possibly Related or Insufficient | Right Knee |
| 00141405 | PAI2004 | NP OA | Not Related | Left Knee |
| 00141406 | PAI2004 | NP OA | Not Related | Right Knee |
| 00141410 | PAI2004 | NP OA | Not Related | Right Hip |
| 00141501 | PAI2004 | NP OA | Not Related | Right Knee |
| 00141501 | PAI2004 | NP OA | Not Related | Left Knee |
| 00141513 | PAI2004 | NP OA | Not Related | Non JR Right Knee |
| 00141707 | PAI2004 | NP OA | Not Related | Left Hip |
| 00142309 [d] | PAI2004 | NP OA | Not Related | Right Hip |
| 00142309 [d] | PAI2004 | Insufficient | Insufficient | Left Hip |
| 00142503 | PAI2004 | NL OA | Not Related | Right Knee |
| 00142505 | PAI2004 | Insufficient | Insufficient | Right Knee |
| **00142914** [b] | **PAI2004** | **RPOA** | **Possibly Related** | **Right Hip** |
| 00142919 | PAI2004 | NP OA | Not Related | Right Shoulder |
| 00143302 | PAI2004 | Insufficient | Insufficient | Left Knee |
| 00143309 | PAI2004 | RPOA | Possibly Related | Right Hip |
| 00143406 [d] | PAI2004 | NP OA | Not Related | Right Knee |
| 00143905 | PAI2004 | NP OA | Not Related | Right Knee |
| **00143915** [b] | **PAI2004** | **NP OA** | **Not Related** | **Left Hip** |
| **00143915** [b] | **PAI2004** | **NP OA** | **Not Related** | **Right Hip** |
| **00143918** [b] | **PAI2004** | **RPOA** | **Possibly Related** | **Right Knee** |
| 00144003 [d] | PAI2004 | RPOA | Possibly Related | Left Knee |
| 00144015 | PAI2004 | NA | NA | Right Knee[a] |

**Attachment 24: Adjudication Results as of 08 July 2011 (Continued)**

| SUBJECT ID | STUDY | DIAGNOSIS | ATTRIBUTION | JOINT INVOLVED |
|---|---|---|---|---|
| **00144205**[e] | **PAI2004** | **NP OA** | **Not Related** | **Non JR Right Hip** |
| 00144301 | PAI2004 | NA | NA | Left Knee [a] |
| 00144302 | PAI2004 | NP OA | Not Related | Left Knee |
| 00144403 | PAI2004 | NP OA | Not Related | Non JR Right Hip |
| **00144409** [b] | **PAI2004** | **RPOA** | **Not Related** | **Right Hip** |
| 00144602 | PAI2004 | NP OA | Not Related | Left Knee |
| **00144901** [b] | **PAI2004** | **RPOA** | **Possibly Related** | **Right Hip** |
| 00144902 | PAI2004 | RPOA | Possibly Related | Left Knee |
| 00144902 | PAI2004 | RPOA | Possibly Related | Right Knee |
| 00144904 | PAI2004 | NP OA | Not Related | Left Hip |
| 00144910 [d] | PAI2004 | NP OA | Not Related | Left Hip |
| 00144911 | PAI2004 | NP OA | Not Related | Right Hip |
| 00145002 [d] | PAI2004 | NP OA | Not Related | Right Knee |
| 00145009 | PAI2004 | NP OA | Not Related | Right Knee |
| 00145009 | PAI2004 | NP OA | Not Related | Left Knee |
| **00145014** [b] | **PAI2004** | **NP OA** | **Not Related** | **Left Hip** |
| 00145705 | PAI2004 | NP OA | Not Related | Right Knee |
| 00145712 | PAI2004 | NP OA | Not Related | Right Knee |
| 00146001 | PAI2004 | NP OA | Not Related | Left Knee |
| 00146002 | PAI2004 | RPOA | Possibly Related | Left Hip |
| 00146016 | PAI2004 | NP OA | Not Related | Left Knee |
| 00146016 | PAI2004 | NP OA | Not Related | Right Knee |
| 00146603 [d] | PAI2004 | NP OA | Not Related | Right Hip |
| 00146812 | PAI2004 | NP OA | Not Related | Left Knee |
| 00146817 | PAI2004 | NP OA | Not Related | Left Knee |
| 00146818 | PAI2004 | Insufficient | Insufficient | Left Shoulder |
| 00146901 | PAI2004 | Insufficient | Insufficient | Left Knee |
| 00146901 | PAI2004 | NP OA | Not Related | Right Knee |
| 00146902 | PAI2004 | NP OA | Not Related | Left Knee |
| 00147411 | PAI2004 | NP OA | Not Related | Left Hip |
| 00147509 | PAI2004 | NP OA | Not Related | Left Knee |
| 00147510 | PAI2004 | Insufficient | Insufficient | Right Hip |
| 00147510 | PAI2004 | NP OA | Not Related | Left Knee |
| 00148003 | PAI2004 | NA | NA | Right Hip[a] |
| 00148114 | PAI2004 | NP OA | Not Related | Left Hip |
| 00148301 | PAI2004 | NP OA | Not Related | Right Hip |
| 01140101 | PAI2004 | NP OA | Not Related | Right Hip |
| **01140203**[b] | **PAI2004** | **NP OA** | **Not Related** | **Left Hip** |
| 01140301 | PAI2004 | NP OA | Not Related | Left Knee |

**Attachment 24: Adjudication Results as of 08 July 2011 (Continued)**

| SUBJECT ID | STUDY | DIAGNOSIS | ATTRIBUTION | JOINT INVOLVED |
|---|---|---|---|---|
| 01140312 | PAI2004 | NP OA | Not Related | Right Hip |
| 01140314 | PAI2004 | RPOA | Possibly Related | Right Knee |
| **01140317** [b] | **PAI2004** | **NP OA** | **Not Related** | **Right Knee** |
| 01140503 | PAI2004 | NP OA | Not Related | Right Knee |
| 01140805 | PAI2004 | RPOA | Possibly Related | Right Knee |
| **01140809** [b] | **PAI2004** | **RPOA** | **Possibly Related** | **Right Hip** |
| 01140901 | PAI2004 | NP OA | Not Related | Non JR Right Knee |
| 01140901 | PAI2004 | NP OA | Not Related | Non JR Left Knee |
| 01140902 [d] | PAI2004 | NP OA | Not Related | Left Hip |
| 01140902 | PAI2004 | NP OA | Not Related | Right Knee |
| **01140908** [b] | **PAI2004** | **RPOA** | **Possibly Related** | **Right Hip** |
| **01141402** [b] | **PAI2004** | **Insufficient** | **Insufficient** | **Right Hip** |
| 01141405 | PAI2004 | NP OA | Not Related | Left Knee |
| 01141407 | PAI2004 | NP OA | Not Related | Right Knee |
| 01141714 | PAI2004 | RPOA | Possibly Related | Right Hip |
| 01141717 | PAI2004 | NP OA | Not Related | Left Hip |
| 01141802 | PAI2004 | NP OA | Not Related | Right Hip |
| 01142201 | PAI2004 | NP OA | Not Related | Right Knee |
| **08240304** [b] | **PAI2004** | **RPOA** | **Possibly Related** | **Right Knee** |
| 80010201 | PAI2006 | NP OA | Not Related | Right Knee |
| 80010201 | PAI2006 | NP OA | Not Related | Left Knee |
| 80011908 | PAI2006 | Insufficient | Insufficient | Left Knee |
| 80013708 | PAI2006 | NP OA | Not Related | Non JR Right Hip |
| 80013708 | PAI2006 | NP OA | Not Related | Non JR Left Hip |
| 80112601 | PAI2006 | Insufficient | Insufficient | Right Knee |
| 200002 | NPP2001 | NP OA | Not Related | Left Knee |
| 200050 | NPP2001 | NP OA | Not Related | Right Knee |
| **200079**[b] | **NPP2001** | **NP OA** | **Not Related** | **Right Hip** |
| 200108 | NPP2001 | Insufficient | Insufficient | Right Hip |
| 200126 | NPP2001 | NP OA | Not Related | Left Hip |
| **200126**[b] | **NPP2001** | **RPOA** | **Possibly Related** | **Right Hip** |

**Attachment 24: Adjudication Results as of 08 July 2011 (Continued)**

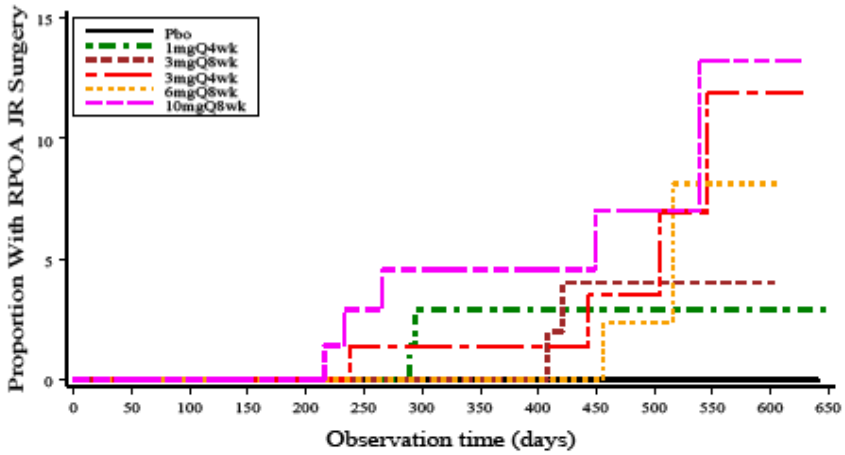
| SUBJECT ID | STUDY | DIAGNOSIS | ATTRIBUTION | JOINT INVOLVED |
|---|---|---|---|---|
| 145004012 | AMGEN403-145 | Insufficient | Insufficient | Right Knee |
| 145004012 | AMGEN403-145 | Insufficient | Insufficient | Left Knee |

[a] Case was a lumbar revision of a prior joint replacement.
[b] Cases had a previous diagnosis of AVN or ON from radiology or pathology reports.
[c] Case was a repair of a device failure.
[d] Cases that were previously considered as RPOA by the sponsor, investigator, and/or FDA.
[e] Case initially reported as ON based on radiology report was adjudicated as normal progression of OA; joint replacement information was received after the case was adjudicated.

Notes: RPOA=rapidly progressing osteoarthritis; NP of OA=normal progression of osteoarthritis;
Insufficient = information was insufficient for adjudication; NA=case not applicable for adjudication (ie, The case was a revision of a previous joint replacement or a repair of a device failure.) Non JR= non joint replacement, ie, a case that had an adverse event possibly indicative of joint destruction.

**Attachment 25: Time to Joint Replacement Surgery for Subjects with RPOA (PAI-2004 OA Add-on)**

**Figure FRPOA01B_UP: Kaplan-Meier Plot of Time to JR Surgery for RPOA Subjects**
( 42160443-PAI2004-08July2011 : ITT Analysis Set)




No. Subjects With Specified Observation Time

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pbo | 78 | 76 | 73 | 67 | 66 | 57 | 51 | 48 | 43 | 40 | 20 | 9 | 1 | 0 |
| 1mgQ4wk | 77 | 77 | 73 | 73 | 73 | 70 | 66 | 62 | 58 | 53 | 30 | 14 | 4 | 0 |
| 3mgQ8wk | 76 | 76 | 75 | 73 | 72 | 67 | 62 | 57 | 51 | 45 | 25 | 10 | 2 | 0 |
| 3mgQ4wk | 79 | 79 | 78 | 75 | 74 | 68 | 65 | 60 | 51 | 45 | 30 | 12 | 4 | 0 |
| 6mgQ8wk | 78 | 78 | 76 | 74 | 71 | 67 | 61 | 55 | 48 | 42 | 22 | 7 | 2 | 0 |
| 10mgQ8wk | 78 | 77 | 76 | 74 | 72 | 63 | 56 | 54 | 46 | 38 | 27 | 11 | 2 | 0 |

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## Attachment 26: Demographic and Baseline Characteristics for Subjects With RPOA, by Fulranumab Dose Group as of 08 July 2011 (PAI-2004 OA Add-on

**Table TSUB02D_JUL8:** Demographic and Baseline Characteristics for RPOA Cases
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-to-Treat Analysis Set)

| | Fulranumab 1mgQ4wk (N=2) | Fulranumab 3mgQ8wk (N=2) | Fulranumab 3mgQ4wk (N=4) | Fulranumab 6mgQ8wk (N=2) | Fulranumab 10mgQ8wk (N=5) | Total (N=15) |
|---|---|---|---|---|---|---|
| **Age** | | | | | | |
| N | 2 | 2 | 4 | 2 | 5 | 15 |
| Category, n (%) | | | | | | |
| < 65 | 2 (100) | 1 (50.0) | 2 (50.0) | 1 (50.0) | 0 | 6 (40.0) |
| ≥ 65 | 0 | 1 (50.0) | 2 (50.0) | 1 (50.0) | 5 (100) | 9 (60.0) |
| Mean (SD) | 55.0 (5.66) | 60.5 (7.78) | 63.3 (10.90) | 71.0 (12.73) | 70.0 (5.10) | 65.1 (9.12) |
| Median | 55.0 | 60.5 | 64.5 | 71.0 | 67.0 | 66.0 |
| Range | (51;59) | (55;66) | (49;75) | (62;80) | (65;76) | (49;80) |
| **SEX, n (%)** | | | | | | |
| N | 2 | 2 | 4 | 2 | 5 | 15 |
| Female | 1 (50.0) | 1 (50.0) | 4 (100) | 2 (100) | 3 (60.0) | 11 (73.3) |
| Male | 1 (50.0) | 1 (50.0) | 0 | 0 | 2 (40.0) | 4 (26.7) |
| **Race, n (%)** | | | | | | |
| N | 2 | 2 | 4 | 2 | 5 | 15 |
| White | 2 (100) | 1 (50.0) | 4 (100) | 2 (100) | 5 (100) | 14 (93.3) |
| Asian | 0 | 1 (50.0) | 0 | 0 | 0 | 1 ( 6.7) |
| **Baseline BMI (kg/m2), n (%)** | | | | | | |
| N | 2 | 2 | 4 | 2 | 5 | 15 |
| < 30 | 2 (100) | 1 (50.0) | 1 (25.0) | 1 (50.0) | 3 (60.0) | 8 (53.3) |
| 30 to <40 | 0 | 1 (50.0) | 2 (50.0) | 1 (50.0) | 2 (40.0) | 6 (40.0) |
| ≥ 40 | 0 | 0 | 1 (25.0) | 0 | 0 | 1 ( 6.7) |
| **Strata 2 - baseline body weight group, n (%)** | | | | | | |
| N | 2 | 2 | 4 | 2 | 5 | 15 |
| <85kg | 2 (100) | 1 (50.0) | 1 (25.0) | 2 (100) | 1 (20.0) | 7 (46.7) |
| ≥ 85kg | 0 | 1 (50.0) | 3 (75.0) | 0 | 4 (80.0) | 8 (53.3) |

## Attachment 26: Demographic and Baseline Characteristics for Subjects With RPOA, by Fulranumab Dose Group as of 08 July 2011 (PAI-2004 OA Add-on) (Continued)

**Table TSUB02D_JUL8:** Demographic and Baseline Characteristics for RPOA Cases
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-to-Treat Analysis Set)

| | Fulranumab 1mgQ4wk (N=2) | Fulranumab 3mgQ8wk (N=2) | Fulranumab 3mgQ4wk (N=4) | Fulranumab 6mgQ8wk (N=2) | Fulranumab 10mgQ8wk (N=5) | Total (N=15) |
|---|---|---|---|---|---|---|
| **Strata 1 - baseline opioid use, n (%)** | | | | | | |
| N | 2 | 2 | 4 | 2 | 5 | 15 |
| No opioids | 1 (50.0) | 0 | 4 (100) | 0 | 5 (100) | 10 (66.7) |
| USe opioids | 1 (50.0) | 2 (100) | 0 | 2 (100) | 0 | 5 (33.3) |
| **Nsaid use in prior and DB EFf phase, n (%)** | | | | | | |
| N | 2 | 2 | 4 | 2 | 5 | 15 |
| Yes | 2 (100) | 2 (100) | 4 (100) | 2 (100) | 5 (100) | 15 (100) |
| **Opioid use in prior and DB EFf phase, n (%)** | | | | | | |
| N | 2 | 2 | 4 | 2 | 5 | 15 |
| Yes | 1 (50.0) | 1 (50.0) | 0 | 2 (100) | 0 | 4 (26.7) |
| No | 1 (50.0) | 1 (50.0) | 4 (100) | 0 | 5 (100) | 11 (73.3) |
| **Type of study joint, n (%)** | | | | | | |
| N | 2 | 2 | 4 | 2 | 5 | 15 |
| Hip | 1 (50.0) | 0 | 2 (50.0) | 1 (50.0) | 2 (40.0) | 6 (40.0) |
| Knee | 1 (50.0) | 2 (100) | 2 (50.0) | 1 (50.0) | 3 (60.0) | 9 (60.0) |
| **Womac baseline pain category, n (%)** | | | | | | |
| N | 2 | 2 | 4 | 2 | 5 | 15 |
| Moderate | 1 (50.0) | 2 (100) | 2 (50.0) | 1 (50.0) | 4 (80.0) | 10 (66.7) |
| Severe | 1 (50.0) | 0 | 2 (50.0) | 1 (50.0) | 1 (20.0) | 5 (33.3) |
| **Kl grade at screening, n (%)** | | | | | | |
| N | 2 | 2 | 4 | 2 | 5 | 15 |
| 2 | 0 | 2 (100) | 2 (50.0) | 0 | 4 (80.0) | 8 (53.3) |
| 3 | 2 (100) | 0 | 1 (25.0) | 1 (50.0) | 0 | 4 (26.7) |
| 4 | 0 | 0 | 1 (25.0) | 1 (50.0) | 1 (20.0) | 3 (20.0) |

## Attachment 26: Demographic and Baseline Characteristics for Subjects With RPOA, by Fulranumab Dose Group as of 08 July 2011 (PAI-2004 OA Add-on) (Continued)

**Table TSUB02D_JUL8:** Demographic and Baseline Characteristics for RPOA Cases
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-to-Treat Analysis Set)

| | Fulranumab 1mgQ4wk (N=2) | Fulranumab 3mgQ8wk (N=2) | Fulranumab 3mgQ4wk (N=4) | Fulranumab 6mgQ8wk (N=2) | Fulranumab 10mgQ8wk (N=5) | Total (N=15) |
|---|---|---|---|---|---|---|
| **Baseline average nrs pain score** | | | | | | |
| N | 2 | 2 | 4 | 2 | 5 | 15 |
| Mean (SD) | 7.4 (2.24) | 6.6 (0.31) | 7.3 (2.03) | 7.4 (0.57) | 7.0 (1.12) | 7.1 (1.30) |
| Median | 7.4 | 6.6 | 7.2 | 7.4 | 7.5 | 7.0 |
| Range | (6;9) | (6;7) | (5;10) | (7;8) | (6;8) | (5;10) |
| **Womac baseline pain score** | | | | | | |
| N | 2 | 2 | 4 | 2 | 5 | 15 |
| Mean (SD) | 7.3 (2.97) | 6.2 (0.57) | 7.1 (2.17) | 6.5 (1.84) | 6.3 (1.10) | 6.6 (1.56) |
| Median | 7.3 | 6.2 | 7.1 | 6.5 | 6.2 | 6.2 |
| Range | (5;9) | (6;7) | (5;9) | (5;8) | (5;8) | (5;9) |
| **Womac baseline physical function** | | | | | | |
| N | 2 | 2 | 4 | 2 | 5 | 15 |
| Mean (SD) | 7.4 (3.24) | 6.0 (0.71) | 7.2 (1.34) | 6.4 (1.83) | 6.8 (1.29) | 6.8 (1.44) |
| Median | 7.4 | 6.0 | 7.4 | 6.4 | 6.8 | 6.5 |
| Range | (5;10) | (6;7) | (6;8) | (5;8) | (6;9) | (5;10) |
| **Womac baseline stiffness score** | | | | | | |
| N | 2 | 2 | 4 | 2 | 5 | 15 |
| Mean (SD) | 8.0 (2.83) | 6.3 (0.35) | 7.0 (3.03) | 6.5 (2.12) | 6.5 (1.46) | 6.8 (1.94) |
| Median | 8.0 | 6.3 | 8.3 | 6.5 | 7.0 | 7.0 |
| Range | (6;10) | (6;7) | (3;9) | (5;8) | (5;8) | (3;10) |

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## Attachment 27: Characteristics for Subjects with RPOA (PAI-2004 OA Add-on)

**Table TSUB02E_RPOA:** Characteristics for Joint Replacement RPOA Surgeries
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-to-Treat Analysis Set)

| | Fulranumab 1mgQ4wk (N=2) | Fulranumab 3mgQ8wk (N=2) | Fulranumab 3mgQ4wk (N=4) | Fulranumab 6mgQ8wk (N=2) | Fulranumab 10mgQ8wk (N=5) | Total (N=15) |
|---|---|---|---|---|---|---|
| **RPOA type, n (%)** | | | | | | |
| N | 2 | 2 | 4 | 2 | 5 | 15 |
| Type 1 | 2 (100) | 2 (100) | 1 (25.0) | 0 | 1 (20.0) | 6 (40.0) |
| Type 2a | 0 | 0 | 1 (25.0) | 1 (50.0) | 1 (20.0) | 3 (20.0) |
| Type 2b | 0 | 0 | 2 (50.0) | 1 (50.0) | 3 (60.0) | 6 (40.0) |
| **Surgery joint, n (%)** | | | | | | |
| N | 2 | 2 | 4 | 2 | 5 | 15 |
| Left hip | 0 | 0 | 0 | 0 | 1 (20.0) | 1 ( 6.7) |
| Left knee | 0 | 1 (50.0) | 0 | 0 | 0 | 1 ( 6.7) |
| Right hip | 1 (50.0) | 0 | 3 (75.0) | 1 (50.0) | 2 (40.0) | 7 (46.7) |
| Right knee | 1 (50.0) | 1 (50.0) | 1 (25.0) | 1 (50.0) | 2 (40.0) | 6 (40.0) |
| **Diagnosis day** | | | | | | |
| N | 2 | 2 | 4 | 2 | 5 | 15 |
| Mean (SD) | 237.5 (14.85) | 358.5 (70.00) | 388.8 (136.86) | 367.0 (2.83) | 274.8 (159.14) | 323.7 (123.21) |
| Median | 237.5 | 358.5 | 419.0 | 367.0 | 204.0 | 365.0 |
| Range | (227;248) | (309;408) | (205;512) | (365;369) | (125;505) | (125;512) |
| **Diagnosis day, n (%)** | | | | | | |
| N | 2 | 2 | 4 | 2 | 5 | 15 |
| 121 - 150 days | 0 | 0 | 0 | 0 | 1 (20.0) | 1 ( 6.7) |
| 151 - 180 days | 0 | 0 | 0 | 0 | 1 (20.0) | 1 ( 6.7) |
| 181 - 210 days | 0 | 0 | 1 (25.0) | 0 | 1 (20.0) | 2 (13.3) |
| 211 - 240 days | 1 (50.0) | 0 | 0 | 0 | 0 | 1 ( 6.7) |
| 241 - 270 days | 1 (50.0) | 0 | 0 | 0 | 0 | 1 ( 6.7) |
| 301 - 330 days | 0 | 1 (50.0) | 0 | 0 | 0 | 1 ( 6.7) |
| 361 - 390 days | 0 | 0 | 1 (25.0) | 2 (100) | 1 (20.0) | 4 (26.7) |
| 391 - 420 days | 0 | 1 (50.0) | 0 | 0 | 0 | 1 ( 6.7) |
| 451 - 480 days | 0 | 0 | 1 (25.0) | 0 | 0 | 1 ( 6.7) |
| 481 - 510 days | 0 | 0 | 0 | 0 | 1 (20.0) | 1 ( 6.7) |
| 511 - 540 days | 0 | 0 | 1 (25.0) | 0 | 0 | 1 ( 6.7) |

N: Number of Joint-Replacement RPOA Surgeries

## Attachment 27: Characteristics for Subjects with RPOA (PAI-2004 OA Add-on) (Continued)

**Table TSUB02E_RPOA:** Characteristics for Joint Replacement RPOA Surgeries
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-to-Treat Analysis Set)

| | Fulranumab 1mgQ4wk (N=2) | Fulranumab 3mgQ8wk (N=2) | Fulranumab 3mgQ4wk (N=4) | Fulranumab 6mgQ8wk (N=2) | Fulranumab 10mgQ8wk (N=5) | Total (N=15) |
|---|---|---|---|---|---|---|
| **Surgery day** | | | | | | |
| N | 2 | 2 | 4 | 2 | 5 | 15 |
| Mean (SD) | 291.5 (3.54) | 414.5 (9.19) | 434.0 (137.83) | 486.0 (42.43) | 340.6 (144.72) | 388.2 (120.00) |
| Median | 291.5 | 414.5 | 474.0 | 486.0 | 266.0 | 421.0 |
| Range | (289;294) | (408;421) | (238;550) | (456;516) | (216;539) | (216;550) |
| **Surgery day, n (%)** | | | | | | |
| N | 2 | 2 | 4 | 2 | 5 | 15 |
| 211 - 240 days | 0 | 0 | 1 (25.0) | 0 | 2 (40.0) | 3 (20.0) |
| 241 - 270 days | 0 | 0 | 0 | 0 | 1 (20.0) | 1 ( 6.7) |
| 271 - 300 days | 2 (100) | 0 | 0 | 0 | 0 | 2 (13.3) |
| 391 - 420 days | 0 | 1 (50.0) | 0 | 0 | 0 | 1 ( 6.7) |
| 421 - 450 days | 0 | 1 (50.0) | 1 (25.0) | 0 | 1 (20.0) | 3 (20.0) |
| 451 - 480 days | 0 | 0 | 0 | 1 (50.0) | 0 | 1 ( 6.7) |
| 481 - 510 days | 0 | 0 | 1 (25.0) | 0 | 0 | 1 ( 6.7) |
| 511 - 540 days | 0 | 0 | 0 | 1 (50.0) | 1 (20.0) | 2 (13.3) |
| 541 - 570 days | 0 | 0 | 1 (25.0) | 0 | 0 | 1 ( 6.7) |
| **# inj before surgery** | | | | | | |
| N | 2 | 2 | 4 | 2 | 5 | 15 |
| Mean (SD) | 9.0 (0.00) | 11.0 (0.00) | 11.0 (3.74) | 13.5 (2.12) | 9.2 (4.21) | 10.5 (3.27) |
| Median | 9.0 | 11.0 | 11.5 | 13.5 | 8.0 | 11.0 |
| Range | (9;9) | (11;11) | (6;15) | (12;15) | (5;15) | (5;15) |
| **Days after last dose** | | | | | | |
| N | 2 | 2 | 4 | 2 | 5 | 15 |
| Mean (SD) | 67.5 (0.71) | 134.0 (8.49) | 152.3 (40.67) | 130.0 (94.75) | 104.4 (41.61) | 119.6 (48.12) |
| Median | 67.5 | 134.0 | 158.5 | 130.0 | 107.0 | 128.0 |
| Range | (67;68) | (128;140) | (97;195) | (63;197) | (38;141) | (38;197) |

See footnotes on the first page of the table.

## Attachment 27: Characteristics for Subjects with RPOA (PAI-2004 OA Add-on) (Continued)

**Table TSUB02E_RPOA:** Characteristics for Joint Replacement RPOA Surgeries
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-to-Treat Analysis Set)

| | Fulranumab 1mgQ4wk (N=2) | Fulranumab 3mgQ8wk (N=2) | Fulranumab 3mgQ4wk (N=4) | Fulranumab 6mgQ8wk (N=2) | Fulranumab 10mgQ8wk (N=5) | Total (N=15) |
|---|---|---|---|---|---|---|
| **Days after last dose, n (%)** | | | | | | |
| N | 2 | 2 | 4 | 2 | 5 | 15 |
| 31 - 60 days | 0 | 0 | 0 | 0 | 1 (20.0) | 1 ( 6.7) |
| 61 - 90 days | 2 (100) | 0 | 0 | 1 (50.0) | 0 | 3 (20.0) |
| 91 - 120 days | 0 | 0 | 1 (25.0) | 0 | 2 (40.0) | 3 (20.0) |
| 121 - 150 days | 0 | 2 (100) | 0 | 0 | 2 (40.0) | 4 (26.7) |
| 151 - 180 days | 0 | 0 | 2 (50.0) | 0 | 0 | 2 (13.3) |
| 181 - 210 days | 0 | 0 | 1 (25.0) | 1 (50.0) | 0 | 2 (13.3) |

See footnotes on the first page of the table.
tsub02e_rpoa.rtf generated by rdsub02e_rpoa.sas, 13JAN2012 14:32

## Attachment 28: Subjects with TEAEs included in the Peripheral Neuropathy SMQ by Joint Replacement Status as of 08 July 2011 (PAI-2004 OA Add-on)

**Output TAE_PNSMQB_JRJUL8B:** Peripheral Neurologic Related Treatment-Emergent AEs (Based on the Peripheral Neuropathy SMQ - Broad) for All Combined Phases
by RPOA and Joint Replacement Status and Treatment Group
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-To-Treat Analysis Set)

| | RPOA | | | JR minus RPOA | | | Non-JR | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total | Treatment, n (%) | | Total | Treatment, n (%) | | Total | Treatment, n (%) | |
| | (N=15) | Placebo | Fulranumab | (N=56) | Placebo | Fulranumab | (N=395) | Placebo | Fulranumab |
| Dictionary-Derived Term | n (%) | (N=0) | (N=15) | n (%) | (N=8) | (N=48) | n (%) | (N=70) | (N=325) |
| **Total no. subjects With TE Peripheral Neuro AEs** | 2 ( 13) | | 2 ( 13) | 9 ( 16) | 0 | 9 ( 19) | 80 ( 20) | 11 ( 16) | 69 ( 21) |
| Burning sensation | 0 | 0 | 0 | 0 | 0 | 0 | 6 ( 2) | 1 ( 1) | 5 ( 2) |
| Dysaesthesia | 0 | 0 | 0 | 0 | 0 | 0 | 2 ( 1) | 0 | 2 ( 1) |
| Hypoaesthesia | 1 ( 7) | 0 | 1 ( 7) | 2 ( 4) | 0 | 2 ( 4) | 29 ( 7) | 3 ( 4) | 26 ( 8) |
| Hyporeflexia | 0 | 0 | 0 | 0 | 0 | 0 | 4 ( 1) | 1 ( 1) | 3 ( 1) |
| Motor dysfunction | 0 | 0 | 0 | 0 | 0 | 0 | 1 ( <1) | 0 | 1 ( <1) |
| Muscular weakness | 0 | 0 | 0 | 2 ( 4) | 0 | 2 ( 4) | 4 ( 1) | 0 | 4 ( 1) |
| Neuropathy peripheral | 0 | 0 | 0 | 1 ( 2) | 0 | 1 ( 2) | 1 ( <1) | 1 ( 1) | 0 |
| Paraesthesia | 1 ( 7) | 0 | 1 ( 7) | 7 ( 13) | 0 | 7 ( 15) | 47 ( 12) | 4 ( 6) | 43 ( 13) |
| Sensory disturbance | 0 | 0 | 0 | 0 | 0 | 0 | 1 ( <1) | 1 ( 1) | 0 |

Note: Percentages in 'Total' column for each group calculated with the number of subjects in each group as denominator.
Percentages of treatment sub-groups calculated with number of subjects per sub-group as denominator.

## Attachment 28: Subjects with TEAEs included in the Peripheral Neuropathy SMQ by Joint Replacement Status as of 08 July 2011 (PAI-2004 OA Add-on) (Continued)

**Output TAE_PNSMQB_JRJUL8B:** Peripheral Neurologic Related Treatment-Emergent AEs (Based on the Peripheral Neuropathy SMQ - Broad) for All Combined Phases
by RPOA and Joint Replacement Status and Treatment Group (continued)
(Study 42160443-PAI-2004 - Database Lock August 30, 2011: Intent-To-Treat Analysis Set)

| | ---------- Total ---------- | | |
|---|---|---|---|
| | Total | --- Treatment, n (%) --- | |
| | (N=466) | Placebo | Fulranumab |
| Dictionary-Derived Term | n (%) | (N=78) | (N=388) |
| **Total no. subjects With TE Peripheral Neuro AEs** | 91 ( 20) | 11 ( 14) | 80 ( 21) |
| Burning sensation | 6 ( 1) | 1 ( 1) | 5 ( 1) |
| Dysaesthesia | 2 ( <1) | 0 | 2 ( 1) |
| Hypoaesthesia | 32 ( 7) | 3 ( 4) | 29 ( 7) |
| Hyporeflexia | 4 ( 1) | 1 ( 1) | 3 ( 1) |
| Motor dysfunction | 1 ( <1) | 0 | 1 ( <1) |
| Muscular weakness | 6 ( 1) | 0 | 6 ( 2) |
| Neuropathy peripheral | 2 ( <1) | 1 ( 1) | 1 ( <1) |
| Paraesthesia | 55 ( 12) | 4 ( 5) | 51 ( 13) |
| Sensory disturbance | 1 ( <1) | 1 ( 1) | 0 |

See footnotes on the first page of the table.
tae_pnsmqb_jrjul8b.rtf generated by rae_smq.sas, 14NOV2011 17:32