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(360) Functional testing and pre-to post pain measure outcomes in chronic knee osteoarthritis pain with milnacipran: interim analysis of a randomized, double-blind, placebo-controlled trial

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Knee osteoarthritis is a chronic disease that affects twenty-seven million Americans and can cause significant stiffness and pain. Chronic pain is associated with structural changes and sensitization within the peripheral and central nervous systems. Serotonin norepinephrine reuptake inhibitors (SNRIs) are thought to modulate central sensitization. Milnacipran is a SNRI with greater selectivity for norepinephrine over serotonin reuptake inhibition. The hypothesis that functional testing would show improved performance and decreased pre-to posttest pain in subjects treated with milnacipran as compared to placebo was evaluated. Interim analysis of data collected during a single-site pilot phase IV randomized, double-blind placebo-controlled trial of milnacipran in a chronic knee osteoarthritis model was performed. Twenty-five subjects with a diagnosis of knee osteoarthritis were randomly assigned to milnacipran 200mg (n=17) or placebo (n=8) in a 2:1 ratio. Subjects were interviewed and tested at their visits during enrollment, completion of placebo lead-in phase, and at conclusion of the eleven week study. Functional testing included stair climb, treadmill, sit-to-stand, and finger-to-floor testing. Pain was assessed using a numeric rating scale (NRS) before and after each functional test. Milnacipran did not show statistically significant differences from placebo in treadmill, sit-to-stand, and finger-to-floor testing throughout all three visits. A statistically significant decrease in pre-to posttest pain (p=0.026) was found with subjects taking placebo as compared to milnacipran during stair climb testing at the concluding visit; all other stair climb pain ratings showed no statistically significant differences between placebo and milnacipran. These preliminary findings suggest that milnacipran does not significantly affect functional performance or pre-to posttest pain in a chronic knee osteoarthritis model. Further study is needed on the methodology of pain ratings during functional testing and the effects of milnacipran on chronic pain conditions. Supported by a grant from Forest Research Institute.

(361) The impact of prior opioid use on the response to pregabalin in fibromyalgia clinical trials

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Fibromyalgia (FM) is a chronic pain disorder for which pregabalin is an approved treatment. While not a recommended treatment option, opioids are used by many FM patients. The impact of prior opioid use on the response to pregabalin treatment in FM has not been assessed. A pooled analysis of four large clinical trials of pregabalin in FM patients was conducted to assess the effect of prior opioid use on the response to treatment. Patients were divided into those using opioids prior to the trial and those who were not. Change in least squares (LS) mean pain score (assessed by 0-10 numeric rating scale, controlled for baseline pain score) in the pregabalin and placebo groups was assessed. There were 2053 patients in the analysis set, including 368 with prior opioid use, with equal numbers treated with placebo, pregabalin 300mg/day and pregabalin 450mg/day. Median duration of opioid use was 1.1 years. Patients ceased opioid use a median of 15.0 days prior to the start of the trial. The LS mean (SE) change in pain score for the placebo group was −0.73 (0.18) with prior opioid use vs. −1.22 (0.08) without, −1.57 (0.18) vs. −1.61 (0.08) with pregabalin 300mg/day, and −1.72 (0.18) vs. −1.89 (0.08) with pregabalin 450mg/day. The treatment effect (LS mean difference from placebo [95% CI]) in patients with and without prior opioid use was 0.85 (0.35-1.35) and 0.39 (0.16-0.63), respectively for pregabalin 300mg/day and 1.00 (0.50-1.50) and 0.66 (0.43-0.90) for pregabalin 450mg/day. Adverse events and discontinuations were also assessed. FM patients with prior opioid use had a greater treatment response to pregabalin compared with placebo. These findings may inform the design of future trials.

(362) Effect of food and dose on pregabalin controlled release pharmacokinetics in healthy volunteers

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Pregabalin is indicated in the US for several conditions, including the management of neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia or spinal cord injury, and fibromyalgia. It is currently approved as an immediate-release (IR) formulation with twice (BID) or three-times (TID) daily administration depending on indication. We report the pharmacokinetic results of seven Phase I open-label crossover studies (18-28 subjects/study) using a controlled-release (CR) once-daily formulation of pregabalin in healthy volunteers. Four multiple-dose studies analyzed the pharmacokinetics of 82.5, 165, 330 and 660mg (2x330mg) pregabalin CR taken once-daily following a medium-fat evening meal, compared with 25mg TID, 75mg BID, 150mg BID and 300mg BID pregabalin IR (fasted), respectively. For all CR doses, total pregabalin exposures (AUC24 [μg•h/mL]) were equivalent to the corresponding IR dose (as the ratio [CR/IR] of adjusted geometric means ranged from 93-97% and all the 90% CIs for AUC24 ratios fell entirely within the 80-125% acceptance range). Pregabalin CR pharmacokinetics were dose-proportional following administration of 82.5-660mg/day pregabalin CR. Three single-dose studies analyzed the effect of food on 330mg pregabalin CR pharmacokinetics compared with 300mg pregabalin IR. Neither fat nor calorie content of the preceding evening meal affected pregabalin CR pharmacokinetics compared with pregabalin IR. With food, total pregabalin exposures for 330mg CR were equivalent to 300mg IR (as the ratio [CR/IR] of adjusted geometric means ranged from 88-103% and the 90% CIs for AUCinf ratios fell entirely within 80-125%). Total exposure decreased by approximately 30% when pregabalin CR was administered under a fasting state in the evening or at bedtime. Pregabalin CR was well tolerated with no serious adverse events. Collectively, these seven studies demonstrate that, when administered following an evening meal, total daily exposure with pregabalin CR is equivalent to the corresponding pregabalin IR dose. Sponsored by Pfizer Inc.

F13 Novel Therapeutic Agents

(363) Efficacy of MAP0004 evaluated by combined relief from migraine pain and freedom from nausea, photophobia and phonophobia in subjects with episodic migraines

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Migraine is a disabling condition affecting approximately 30 million people in the USA. Most clinical trials evaluating the efficacy of the acute treatment of migraine use endpoints measuring relief of pain over time. Associated symptoms, such as nausea, photophobia and phonophobia are included in the International Headache Society diagnostic criteria for migraine and relief of these symptoms are usually also included as clinical trial endpoints. MAP0004, an investigational product which delivers dihydroergotamine via a breath-synchronized metered dose inhaler (TEMPO®), was shown to be superior to placebo in effectively relieving migraine pain at 30 minutes, 2, 4, 24 and 48 hours in a large randomized double-blind placebo-controlled Phase 3 trial. In an effort to evaluate a more robust measure of efficacy, this post-hoc analysis assessed the combined relief from migraine pain (defined as pain reduction from moderate or severe to mild or none) and freedom from nausea, photophobia and phonophobia at several time points post-treatment without the use of rescue medication prior to those time points. Additionally, the sustainability of this effect 2-24 hours without the use of rescue medication was assessed. 794 subjects treated a qualifying migraine and had at least one post-dose efficacy assessment. Significantly higher percentage of MAP0004-treated subjects achieved combined relief from migraine pain and freedom from associated symptoms compared to placebo at: 1 hour (20.9% vs. 14.1%; p=0.0131), 2 hours (36.8% vs. 19.4%, p<0.0001), 4 hours (45.8% vs. 23.9%, p<0.0001), 24 hours (49.6% vs. 31.7%, p<0.0001) and 48 hours (41.1% vs. 28.5%, p=0.0002) post-treatment. This combined efficacy endpoint was sustained 2-24 hours in a significantly higher percentage of subjects treated with MAP004 than with placebo (28% vs. 11.3%, p<0.0001). The most common adverse events during the double-blind period in ≥ 2% of MAP0004-treated subjects and > placebo were medication aftertaste (6.1%), nausea (4.4%) and cough (2.4%).