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(368) Long-term safety and efficacy of tanezumab as treatment for chronic low back pain (NCT00924664)

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This randomized, parallel-group, multicenter study evaluated long-term safety and efficacy of tanezumab in patients with chronic low back pain (CLBP). Patients from the parent study (NCT00876187) were eligible for this safety extension study within 12 weeks after last dose of parent study medication or upon discontinuation due to lack of efficacy. Patients received 3 intravenous then 4 subcutaneous administrations of tanezumab 10mg (n=321) or 20mg (n=527) at 8-week intervals. Safety assessments included adverse event documentation, physical and neurological examinations, and laboratory tests. Efficacy analyses included change from parent study Baseline in Brief Pain Inventory-short form, Roland-Morris Disability Questionnaire, and Patient's Global Assessment of CLBP. The study discontinued prematurely due to an FDA-imposed clinical hold. Mean extension study treatment duration was 194 and 202 days for tanezumab 10 and 20mg, respectively. The most frequently reported treatment-related adverse events were paresthesia, arthralgia, and hypoesthesia. Osteonecrosis was reported in 6 patients (tanezumab 10mg: n=2 [0.6%]; tanezumab 20mg: n=4 [0.8%]); 9 additional patients (tanezumab 10mg: n=7 [2.2%]; tanezumab 20mg: n=2 [0.4%]) underwent total joint replacement (TJR). Of these, all 6 patients with reported osteonecrosis and 4/9 undergoing TJR were evaluated by a blinded expert Adjudication Committee. Adjudication outcomes were: osteonecrosis (n=0); worsening osteoarthritis (OA; n=5); another diagnosis or indeterminate (n=5). Of the 5 patients adjudicated to worsening OA, 2 were adjudicated to normal progression, 1 was adjudicated to rapid progression of OA and in 2 patients the rate of OA progression was indeterminable. Improvements in efficacy observed in the parent study (at Week 16) were maintained through Week 32 in this study. Both tanezumab doses significantly improved all efficacy outcomes from parent study Baseline to Week 32 in this extension study. In conclusion, long-term tanezumab was generally safe and provided durable efficacy in patients with CLBP. Supported by Pfizer, Inc.

(369) Oxycodone DETERx, an extended-release, tamper-resistant formulation for management of chronic pain

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Oxycodone DETERx is a multiparticulate, extended-release (ER), tamper-resistant formulation, designed to retain its time-release mechanism following common tampering methods such as crushing, chewing, and preparation for IV injection. The formulation was developed to be administered as an intact capsule, but has the potential to be administered by sprinkling or feeding tube, benefiting patients with dysphagia/odynophagia as well as special populations such as infants/toddlers and the elderly. A single-dose, open-label, cross-over pharmacokinetic study was conducted in healthy volunteers to evaluate safety and pharmacokinetics of oxycodone DETERx compared to a reference (OxyContin®OP) in the fed state. The following in vitro studies were conducted to assess tamper-resistant characteristics: 1) Effect of ten common household crushing methods (e.g., hammer, coffee grinder, mortar and pestle) on particle size reduction for both oxycodone DETERx and the reference; 2) Extraction studies using several commonly available ingestible solvents and beverages; and 3) Syringability of oxycodone DETERx by drawing melted DETERx beads into a syringe. In the pharmacokinetic study, the safety profile of oxycodone DETERx was similar to reference; Oxycodone DETERx was bioequivalent to reference based on extent-of-absorption (AUClast and AUCINF). Microscopy and particle size measurement with laser diffraction showed relatively minor changes in particle size compared with controls for 6 of 10 tampering methods used; 4 tampering methods had no effect on particle size. Dissolution studies demonstrated that crushed beads retained ER properties for all tools tested. The DETERx formulation prevented drug from "dose dumping" upon exposure to different ingestible solvents and beverages. Due to the high melting point, the formulation solidified while drawing up into a syringe, demonstrating the resistance of the formulation to direct injection. Oxycodone DETERx may provide various patient populations with analgesia for chronic pain while mitigating the risk of abuse and diversion due to its tamper-resistant characteristics. Supported by Collegium Pharmaceutical.

(370) Efficacy and safety of subcutaneous tanezumab in patients with pain related to diabetic peripheral neuropathy (NCT01087203)

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This randomized, double-blind, placebo-controlled, parallel-group, multicenter study evaluated efficacy, safety, and tolerability of tanezumab in patients with diabetic peripheral neuropathy (DPN) pain. Patients received two subcutaneous injections of placebo or tanezumab (20 mg) at 8-week intervals. Efficacy was evaluated by change from baseline in average DPN pain and Patient's Global Assessment (PGA) of DPN. Safety evaluations included adverse event reports, physical and neurological examinations, and laboratory tests. Protein gene product (PGP) 9.5-positive intraepidermal nerve fiber (IENF) density was assessed from skin biopsy sites in the thigh and distal leg. Quantitative Sensory Testing including heat-as-pain thresholds and stimulus response slopes at the thigh and foot were also performed. The study was terminated early with only 46% of planned enrollment (tanezumab n=38; placebo: n=35) and most patients receiving a single dose of study medication due to a partial clinical hold placed on most tanezumab clinical studies by the FDA. At Week 8, tanezumab treatment resulted in significantly greater mean pain reduction (least squares mean difference versus placebo: -1.32; p=0.009), but no significant improvement or worsening in PGA of DPN (p>0.05). The most frequently reported adverse events with tanezumab treatment were arthralgia, pain in extremity, back pain, and myalgia. More tanezumab-treated patients reported adverse events of abnormal peripheral sensation. Nearly all patients (97%) treated with tanezumab had final neurological examinations that were either unchanged from their baseline assessment or exhibited small, clinically insignificant changes. A small decline in IENF density was evident with tanezumab at both locations while a small increase in IENF density occurred with placebo treatment; changes in IENF were not statistically significant. For the heat-as-pain evaluation, no significant thermal hyperalgesia was demonstrated. In this initial study for DPN-related pain, tanezumab was generally safe and efficacious with significantly improved pain relief versus placebo treatment. Supported by Pfizer Inc.

(371) Pulsed Radio Frequency Energy (PRFE) fields in the treatment of post-operative pain: a randomized, double-blind, sham-controlled pivotal study in the human bunion model

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The post-bunionectomy pain model is a well-established post-operative analgesic pain model in the evaluation of analgesic pharmaceuticals. The assay sensitivity of the model makes this a generalizable model that is well suited for the evaluation of novel therapeutics. Over 50 pharmaceutical research protocols using this model have been submitted to FDA. The model has not, however, been applied previously to Medical Devices. We describe the first study of a medical device using the post-operative bunionectomy model and highlight the modifications to the traditional model that are necessary for device trials. Ours is a multi-center, randomized, double-blind, sham-controlled, prospective study of the efficacy of Pulsed Radio Frequency Energy (PRFE) in treatment of acute post-operative pain. PRFE is an adjunctive FDA-cleared biophysical modality that is thought to provide analgesia through incitement of the endogenous peripheral opioid pathway and reduction of post-operative inflammation. Treatment involves the local application of radio frequency electromagnetic fields to the surgical site in a non-contact, non-thermal fashion. Treatment is administered twice-daily by the patient at home through intact dressings. Side effects are rare and minor. In contrast to opioid therapy, there is no sedation or systemic side effects. In this trial, patients with moderate-severe post-operative pain are enrolled and self-report pain intensity every one-half to two hours over the 72-hour efficacy analysis period. The primary endpoint is the sum of time-weighted pain intensity differences (SPID) from the time of initiation of first postoperative treatment with the test device to 72 hours thereafter. Secondary outcome measures include total pain relief (TOTPAR), cumulative opioid consumption and time to first supplemental analgesic medication. Rescue analgesia with IV morphine and PO oxycodone are permitted, with data imputed to minimize confounding of the device effect by opioid consumption. The application of this widely accepted model to medical devices demonstrates its versatility.