Conclusions: A single IA administration of 40 mg of FX006 maintained pharmacologically active synovial fluid concentrations of TCA for at least 12 weeks, while TCA IR produced levels that are below the lower limit of quantitation by 6 weeks. These data underpin the differentiation of FX006 from TCA IR and provide pharmacokinetic basis for previously demonstrated prolongation and amplification of pain relief compared to TCA IR in OA patients following a single IA injection. FX006 also has the potential for an improved systemic safety profile as evidenced by peak plasma concentrations that are 40-fold lower than TCA IR at the same dose, seen in the aggregate of clinical studies with FX006 to date.

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GASTROINTESTINAL SAFETY AND TOLERABILITY OF LONG-TERM GCSB-5 OF DRIED EXTRACTS OF SIX HERBS IN PATIENTS WITH OSTEOARTHRITIS: A 24 WEEKS, MULTI-CENTERS, SINGLE ARM PHASE IV STUDY

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Purpose: A previous study on GCSB-5 was shown to be non-inferior to Celecoxib in efficacy and safety in treating osteoarthritis, but its safety information on the gastrointestinal (GI) safety is limited to only 12 weeks. A longer term (24 weeks) study with a larger number of patients is necessary to establish the GI safety of GCSB-5. The primary goal of this study was to determine the incidence of GI disorders associated with GCSB-5. The secondary goal was to collect 24-week safety data of GCSB-5.
Methods: A single arm safety study on 24-week GCSB-5 was conducted. Additionally, the results of this study were compared with Historical Data of Celecoxib. This study was performed in 19 academic institutions between May 2012 and June 2013. Two GCSB-5 capsules (300 mg per capsule) were prescribed two times per day for 24 weeks. Incidence of GI disorders was the primary outcome. Incidence of GI perforation, ulcer obstruction and bleeding (PUB), gastroduodenal ulcer, and dropout due to GI complications were the major secondary outcome variables.
Results: A total of 761 patients with osteoarthritis were enrolled and 756 patients took at least one dose of study drug. A total of 629 patients (82.7%) completed the 24 weeks follow-up visit. The incidence of GI disorders among the 756 patients with or without aspirin exposure was 23.7%. Aspirin use did not show any significant difference in GI disorders. The annualized incidence rate of PUB was 0.0%. The annualized incidence rate of gastroduodenal ulcer was 0.0%. The drop-out rate due to GI disorders in GCSB-5 was 4.8%. As the results compared with Historical Data of Celecoxib, the incidence of GI disorders (29.9%), annualized rate of PUB and gastroduodenal ulcer (2.2%), and drop-out rate (8.7%) due to GI disorders for Celecoxib were significantly higher than GCSB-5.
Conclusions: This study indicated GCSB-5 was safe for patients with osteoarthritis during long-term treatment. Furthermore, the safety results of GCSB-5 associated with GI disorder were comparable to Celecoxib.

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THE EFFECT OF PREOPERATIVE PAIN TREATMENT BY MEANS OF DULOXETINE ON POSTOPERATIVE OUTCOME AFTER TOTAL HIP OR KNEE ARTHROPLASTY: DESIGN OF A PRAGMATIC RANDOMIZED CONTROLLED TRIAL

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Purpose: Total joint replacement (TJR) is considered to be one of the most safe, successful, and cost-effective treatments for advanced osteoarthritis (OA). However, residual pain seems to be a major factor of patient's dissatisfaction following Total Hip Arthroplasty/Total Knee Arthroplasty (THA/TKA). The proportion of patients suffering from unfavourable long-term residual pain is relatively high, proportions ranging from 10 to 34% after knee and 7 to 23% after hip replacement surgery. Changes within the central nervous system are presumably accountable for accessory pain amplification and sensitization. Currently there are studies indicating that a preoperative degree of central sensitisation (CS) is associated with poorer postoperative outcomes and residual pain. Thus, it could be hypothesized that preoperative treatment of CS could enhance postoperative outcomes. Duloxetine, a combined serotonin and norepinephrine reuptake inhibitor (SNRI), has shown to be effective in several chronic pain syndromes, including knee-OA, in which CS is likely one of the underlying pain mechanisms. This study aims to evaluate the postoperative effects of preoperative screening and targeted duloxetine treatment of CS on residual pain, compared to care as usual.
Methods: This multi-centre, pragmatic, prospective, open-label, randomized controlled trial (RCT) includes adults which are on the waiting list for primary THA/TKA, with a possible or likely neuropathic pain (NP) phenotype at screening (defined by a score >12 point on the modified-painDETECT questionnaire), hence this will probably identify patients who are more likely to experience CS. Patients will be randomly allocated to the preoperative "duloxetine treatment group" (1 week initiation 30 mg/d, 7 weeks 60 mg/d, 2 weeks taper-phase 30 mg/d) or the "care as usual group" (no specific preoperative intervention). The primary endpoint is the degree of postoperative pain 6 months after THA/TKA, assessed with the pain subscale of the Hip disability/Knee injury and Osteoarthritis Outcome Score (HOOS/KOOS). Secondary endpoints, at multiple pre- and postoperative time points (up to 12 months postoperative) will be; pain, neuropathic pain (NP), sensitisation (pressure pain thresholds, temporal summation), quality of life and depressive/anxiety symptoms. Furthermore, factors such as perceived satisfaction and arthroplasty related expectations will be analyzed. Based on a minimally clinical important difference of 10 points on the HOOS/KOOS; a total of 118 patients are anticipated to be randomized to detect a clinical relevant difference (80% power, 20% protocol violators and/or dropout included).
Results: Data analysis will be conducted on an intention-to-treat basis. In case of the primary endpoint a Student's t-test (or a non-parametric equivalent in case of a skewed distribution) will be used to determine if there is a difference in pain on the HOOS/KOOS at 6 months postoperative between the two groups. GEE (Generalized Estimating Equation) analysis will be used to determine whether there is a difference on pain between the two groups over time, adjusted for relevant covariates. The same principles will be used to asses the secondary time points. A P-value of < 0.05 is considered statistically significant.
Conclusions: This study is, as far as we know, the first pragmatic RCT assessing the postoperative effects of a preoperative targeted duloxetine treatment in OA-patients suffering from a degree of preoperative CS (indicated by a possible or likely NP-phenotype). We believe a pragmatic trial design is valid; hence it mimics the "real life status", with a "care as usual" control group, as much as possible. Furthermore, the endpoints are, unlike placebo controlled explanatory trials, more focused on the relevancy to everyday life; like hip and knee specific pain, function and quality of life. Knowledge gained with this study can potentially improve postoperative pain relief and rehabilitation after TJR.

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DIFFERENTIAL PROFILING OF SECRETOMES FROM HUMAN CARTILAGE TO IDENTIFY POTENTIAL EARLY SPECIFIC PROTEIN BIOMARKERS IN OSTEOARTHRITIS

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Purpose: Osteoarthritis (OA) is characterized by the progressive loss of cartilage structural extracellular matrix (ECM) components. The release of these proteins from the tissue can vary according to the stage of the disease and the specific joint affected. The aim of this study was to