and placebo was also significant ($p < 0.001$) with the shortest times observed with diclofenac-N. Treatment-emergent AEs were similar across treatment groups with similar rates in subjects treated with placebo (52.9%), diclofenac-N 35 mg (60.8%) and diclofenac-N 18 mg (55.1%).
Conclusions: An investigational, proprietary, nano-formulated, lower dose, oral diclofenac demonstrated good efficacy, onset of action, and tolerability. As suggested by this phase-2 clinical trial, use of this lower dose formulation could maintain efficacy, shorten onset of action, and possibly result in an improved tolerability profile for patients with acute arthritic pain.

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THE APPLICATION OF PLATELET-RICH PLASMA IN EARLY OSTEOARTHRITIS OF KNEE

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Purpose: Platelet-rich plasma (PRP) is a natural concentrate of autologous blood growth factors experimented in different fields of medicine in order to test its potential to enhance tissue regeneration, and so emerged as a treatment option for tendinopathies and chronic wounds. In addition to release of growth factors, PRP also promotes concentrated anti-inflammatory signals including interleukin-1a, which has been a focus of emerging treatments for osteoarthritis. The primary objective is to compare a single, intra-articular injection of platelet-rich plasma (PRP) with hyruan injection in patients with early osteoarthritis of knee and to assess the clinical efficacy and safety of intra-articular platelet-rich plasma (PRP) injection in patients with low degree osteoarthritis (OA) of the knee.
Methods: Between June 2008 and October 2010, we reviewed the results of 86 consecutive primary osteoarthritic patients underwent intra-articular injection of PRP.In a group of early osteoarthritis patients, inclusion criteria was set to those who were able to be followed up for at least 6 months and showed as Kellgren-Lawrence grade I on simple radiograph or MRI, and exclusion criteria was set as severe obesity, infection, immunosuppressed patients, advanced osteoarthritis(K-L grade I, II, III), and severe deformity. PRP was injected once, in principle. Also, to compare the effects of PRP, hyruan injection was performed in 21 cases during the same period in a same target group, and the effect was compared by perfoming 3 times in an interval of 1 week. Results were evaluated at 4, 8, 12, 18, 24 weeks post-injection using radiologic study, visual analogue scale (VAS) and international knee documentation committee (IKDC) score for functional score.
Results: According to VAS, the mean preoperative scale was 8.2 (range 7–10) and the mean postoperative scale was 3.2 (range 1–4) and 2.9 (range 0–4) at 12 and 24 weeks of follow-up. In IKDC score, the mean preoperative knee score was 57.5 points (range 32–77), and the mean postoperative knee score was 77.3 points (range 60–95) and 88.9 points (range 69–98) at 12 and 24 weeks of follow-up, respectively. Patients receiving PRP experienced statistically significantly greater improvements in VAS ($p = 0.032$), and IKDC score measures, than patients receiving hyruan injection. There was no different between the safety results of the two groups. No increased risk of local adverse events was observed in the follow-up periods.
Conclusions: According to VAS, the mean preoperative scale was 8.2 (range 7–10) and the mean postoperative scale was 3.2 (range 1–4) and 2.9 (range 0–4) at 12 and 24 weeks of follow-up. In IKDC score, the mean preoperative knee score was 57.5 points (range 32–77), and the mean postoperative knee score was 77.3 points (range 60–95) and 88.9 points (range 69–98) at 12 and 24 weeks of follow-up, respectively. Patients receiving PRP experienced statistically significantly greater improvements in VAS ($p = 0.032$), and IKDC score measures, than patients receiving hyruan injection. There was no different between the safety results of the two groups. No increased risk of local adverse events was observed in the follow-up periods.

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A PHASE 2 STUDY EVALUATING THE EFFICACY AND SAFETY OF A NOVEL, PROPRIETARY, NANO-FORMULATED ORAL INDOMETHACIN

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Purpose: Nonsteroidal anti-inflammatory drugs (NSAIDs) are a common medication taken for acute pain relief. Indomethacin has a long-established efficacy and safety profile yet can have a variable and somewhat slow onset of action. Indomethacin also has the potential for gastrointestinal adverse events (AEs), suggesting the need for a new formulation which can safely provide fast onset of acute pain relief. Our objective was to evaluate the analgesic efficacy and safety of an investigational, proprietary, nano-formulated, oral indomethacin compared with placebo in subjects with acute dental pain.
Methods: This was a phase-2, multicenter, randomized, double-blind, single-dose, parallel-group, placebo-controlled study. In total, 203 subjects were enrolled who: were 18–50 years of age, had extraction of ≥2 third molars, and experienced moderate to severe pain intensity within 6 hours after surgery. Subjects received either nano-formulated indomethacin 20 mg, 40 mg, or placebo. The primary efficacy variable was the sum of total pain relief (TOTPAR) over 8 hours (TOTPAR-8). Higher scores indicated better pain relief.
Results: Nano-formulated indomethacin was significantly ($p < 0.001$) better than placebo for TOTPAR-8 (mean; 95% CI): 40 mg (12.56; 2.64); 20 mg (10.79; 2.66); placebo (3.02; 2.64). Nano-formulated indomethacin was also significantly ($p < 0.001$) better than placebo for TOTPAR-4 (mean; 95% CI): 40 mg (6.16; 4.78); 20 mg (5.47; 4.61); placebo (1.63; 2.83). The difference in time to onset of analgesia between each treatment and placebo was also significant ($p < 0.001$). Treatment-emergent AEs occurred less often in subjects treated with nano-formulated indomethacin 20 mg (38.0%) than those treated with nano-formulated indomethacin 40 mg (51.0%) or placebo (56.9%).
Conclusions: A proprietary, nano-formulated, lower dose, oral indomethacin demonstrated good efficacy, onset of action, and tolerability. The ability to utilize a lower dose and maintain efficacy could result in an improved tolerability and safety profile and is in line with the FDA directive to use the lowest effective dose for the shortest duration.

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CLINICAL EVALUATION OF A HERBAL FORMULATION, RHULIEF™, IN THE MANAGEMENT OF KNEE OSTEOARTHRITIS

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Purpose: The study was conducted to evaluate the efficacy, safety and tolerability of Rhulief™, a unique mixture of acetyl boswellic acids with acetyl 11-keto beta boswellic acid (AKBA) content of 10% w/w and BCM 95®, a composition of curcumin which is about 7 times more bioavailable than conventional curcumin, compared with non steroidal anti-inflammatory drug, Celecoxib in the management of knee Osteoarthritis.
Methods: Fifty four subjects were screened, 30 subjects were enrolled and 28 completed the study. Subjects of both sexes aged 18 to 65 years who were medically stable with moderate form of osteoarthritis evidenced by narrowing of the medial joint space with swelling were randomized into two groups and were treated for a period of 12 weeks.
Gr I: Oral administration of Rhulief™ 500 mg capsule twice daily
Gr II: Oral administration of Celecoxib 100 mg capsule twice daily
Subjects with long standing and severe form of osteoarthritis, persons with history of rheumatoid or reactive arthritis and significant systemic diseases were excluded from the study. Symptom scoring and clinical examination were done during their each visit to find out the efficacy of the drug. Safety of the drug was assessed by recording the liver function test, renal function test and haemogram.
Results: The results of the symptom scoring revealed that there was a significant ($p < 0.05$) improvement in pain scores within the groups over a period of 12 weeks and the improvement was more with Gr I. Significant ($p < 0.05$) improvement in walking distance and joint line tenderness were also observed within the groups and the effects were greater with Gr I. Statistically significant difference between range of movements were observed within both the groups ($p < 0.05$). The differences in range of movements were comparable in both groups and there was no significant change between the two groups. Vital signs, haemogram, liver function test and renal function test were not adversely modified by Rhulief™. The results of the present study concluded that the treatment was well-tolerated and did not produce any adverse effect in patients.
Conclusions: Rhulief™ at 500 mg twice a day was better than Celecoxib 100 mg twice daily in symptom scoring and clinical examination. It was equally effective as Celecoxib in alleviating crepitus and range of joint movements. The drug was well tolerated and no dose-related toxicity was found. Efficacy and tolerability of Rhulief™ used in the current

study was shown to be superior to those of Celecoxib for treating active osteoarthritis.

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A PILOT STUDY OF THE USE OF A TRUFIT PLUG FOR CARTILAGE REPAIR IN THE KNEE AND HOW TO DEAL WITH EARLY CLINICAL FAILURES?

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Purpose: The purpose of this pilot study is to present our short-term experience with the TruFit plug (Smith & Nephew, Andover, MA) for cartilage repair in the knee and to discuss our approach to treat early clinical failures.
Methods: Twenty patients were consecutively treated for their cartilage lesion with this plug technique. These patients were prospectively clinically evaluated at 6 and 12 months of follow-up. Magnetic resonance imaging (MRI) was used for morphological analysis of the cartilage repair. Biopsy samples were taken from 3 cases during revision surgery, allowing histological assesment of the repair tissue.
Results: The short-term clinical and MRI outcome of this pilot study are mediocre. No signs of deterioration of the repair tissue were observed. Three of the 15 patients (20.0%) displayed persistent or even more clinical symptoms after insertion of the plug. These patients were considered as failures and therefore eligible for revision surgery. During revision surgery the repair tissue was carefully removed. The remaining osteochondral defect was filled with autologous bone grafts. Immediate and persistent relieve of symptoms was observed in all 3 patients. Histological assessment of biopsy specimens taken during revision surgery of these 3 patients revealed fibrous vascularized repair tissue with the presence of foreign-body giant cells.
Conclusion: The overall short term clinical and MRI outcome of a TruFit plug for cartilage repair in the knee is mediocre. In this pilot study a modest clinical improvement became apparent at 12 months of follow-up. MRI data showed no deterioration of the repair tissue. Remarkably, 3 of the 15 patients (20%) had persistent clinical symptoms after surgery. These patients were succesfully treated with the removal of the osteochondral plug remnants and the application of autologous bone grafts. Longer follow-up studies and randomised controlled trials are mandatory to confirm the findings of this pilot study.

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MID-TERM RESULTS OF THE TREATMENT OF CARTILAGE DEFECTS IN THE KNEE USING ALGINATE BEADS CONTAINING HUMAN MATURE ALLOGENIC CHONDROCYTES

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Purpose: The purpose of this paper was to present our mid-term experience with the implantation of alginate beads containing human mature allogenic chondrocytes for the treatment of cartilage lesions in the knee.
Methods: A biodegradable, alginate-based biocompatible scaffold containing human mature allogenic chondrocytes was used for cartilage lesions in the knee. Twenty-one patients were clinically prospectively evaluated with use of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and a Visual Analogue Scale (VAS). The mean follow-up time was 6.3 years (5–8 years). MRI data were analyzed based on the MOCART (Magnetic Resonance Observation of Cartilage Repair Tissue) system, allowing morphological assessment of the repair tissue. MRI images were taken at one year of follow-up and at a mean follow-up of 6.1 years (5–7 years).
Results: During the follow-up period the WOMAC and VAS scores improved significantly. No signs of clinical deterioration or adverse reactions to the alginate beads/allogenic chondrocyte implantation were observed. Four failures occured during the follow-up period in this study (19.05%). The MOCART scoring methods indicated that the condition of the repair tissue deteriorated on MRI.
Conclusions: This investigation provided useful information on the efficacy of this new treatment in chondral lesions of the knee. The mid-term clinical outcome of the presented technique was promising. However, these results were not confirmed by the MRI findings. Moreover, the MRI data indicated a deterioration of the repair tissue. These results inspire us to search for further improvements of this technique.

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DULOXETINE AS TREATMENT FOR KNEE PAIN IN PATIENTS WITH OSTEOARTHRITIS WHO REGULARLY USE NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs): A POST HOC ANALYSIS OF TWO RANDOMIZED, PLACEBO-CONTROLLED TRIALS

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Purpose: To examine whether treatment with duloxetine has similar efficacy in patients with symptomatic knee osteoarthritis (OA) who regularly use NSAIDs as compared with those who do not.
Methods: We conducted a post hoc analysis of data from 2 randomized, placebo-controlled trials of duloxetine in patients with symptomatic knee OA. In each trial, patients were randomized to 13 weeks of treatment with duloxetine 60–120 mg once daily or placebo, and stratified according to concomitant NSAID use at baseline. NSAID users were identified as those patients who were taking a therapeutic dose of NSAID or acetaminophen for ≥14 days per month for 3 months immediately preceding the study. Efficacy measures were the Brief Pain Inventory (BPI) 24-h average pain severity score (0–10), and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC;0–96). Missing data were imputed using last-observation-carried-forward method. Differences in treatment effect of duloxetine versus placebo between subgroups were analyzed with an ANCOVA model that included therapy, study, baseline value, concomitant NSAID use, and therapy-by-NSAID subgroup interaction. Safety and tolerability were assessed with spontaneously reported treatment-emergent adverse events (TEAEs).
Results: There were a total of 105 duloxetine NSAID users, 112 placebo NSAID users, 134 duloxetine non-NSAID users, and 136 placebo non-NSAID users. Overall mean baseline ratings were BPI average pain=6.15, and WOMAC total=51.37, and there were no significant differences between NSAID subgroups on these measures. Mean changes from baseline are summarized in Figure 1. Treatment-by-NSAID use interactions were not significant for either of the outcome measures, which suggests that the effect of duloxetine treatment was not affected by concomitant NSAID use. Nausea was the most common TEAE reported in patients treated with duloxetine vs. placebo that was significantly ($p < 0.05$) more frequent regardless of concomitant NSAID use. In addition among NSAID users, patients treated with duloxetine vs. placebo reported significantly more hyperhidrosis ($p < 0.05$); and constipation ($p < 0.01$) was reported significantly more frequently among the non-NSAID users.

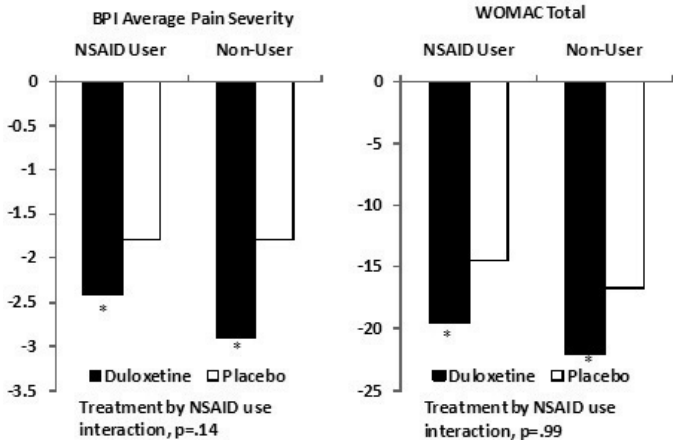

Fig. 1. Mean changes from baseline in BPI average pain severity and WOMAC total.

Conclusions: There were a total of 105 duloxetine NSAID users, 112 placebo NSAID users, 134 duloxetine non-NSAID users, and 136 placebo non-NSAID users. Overall mean baseline ratings were BPI average pain=6.15, and WOMAC total=51.37, and there were no significant differences between NSAID subgroups on these measures. Mean changes from baseline are summarized in Figure 1. Treatment-by-NSAID use interactions were not significant for either of the outcome measures, which suggests that the effect of duloxetine treatment was not affected by concomitant NSAID use. Nausea was the most common TEAE reported