in-person instruction on at-home knee exercise. The primary outcome measure was a composite score on the Western Ontario McMaster University Osteoarthritis Index (WOMAC; 100 points), which assessed knee pain, function and stiffness on a per subject basis. The secondary outcome was the Knee Pain Scale (KPS) which assessed knee pain severity and frequency on a per knee basis; both were done at baseline, 5, 9, 12, 26 and 52 weeks. Procedure-related opioid medication use, subject satisfaction and adverse events were also assessed.

**Results:** Analysis was by intention to treat. No significant baseline differences existed between the groups in age, gender, pain duration, body mass index or WOMAC scores. 89 subjects (57±8.3 years old, 59 female) with moderate to severe KOA received an average of 4.3±0.7 prolotherapy injection sessions over a 17-week treatment period. All groups reported improved composite WOMAC scores compared to baseline status (p < 0.01) at 52 weeks. However, WOMAC scores for prolotherapy subjects, adjusted for gender, age and body mass index showed significantly greater improvement on WOMAC score at 52 weeks: 15.32±3.52 points for prolotherapy compared to 7.68±3.41 points for saline injection (p < 0.05) and 8.25±3.33 points for exercise (p < 0.05). The improvement by prolotherapy subjects exceeded minimal clinical important difference. KPS scores of prolotherapy subjects showed similar improvement per injected knee compared to baseline status (p < 0.001) and controls. Prescribed post-procedure opioid medication resulted in rapid diminution of prolotherapy injection pain. Satisfaction with prolotherapy was high and there were no adverse events.

**Conclusions:** Prolotherapy resulted in safe, significant, sustained improvement of pain, function and stiffness scores compared to blinded saline injections and at-home exercises in knee osteoarthritis.

### 309 A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY OF rhFGF18 ADMINISTERED INTRAARTICULARLY USING SINGLE OR MULTIPLE ASCENDING DOSES IN PATIENTS WITH PRIMARY KNEE OSTEARTHRITIS (OA), SCHEDULED FOR TOTAL KNEE REPLACEMENT

**L.E. Dahleberg,1 K. Flechsenhar2, D. Dreher2, S. Gouteux2, J.S. Jurvelin3.**
1Uund Univ, Malmö, Sweden; 2Merck Serono S.A. (an affiliate of Merck KGaA, Darmstadt, Germany), Geneva, Switzerland; 3Univ. of Eastern Finland, Kuopio, Finland

**Purpose:** No approved disease-modifying OA drugs (DMOAD) are available. Use of a chondrocyte-targeted growth factor is a promising approach with the potential to induce chondrocyte proliferation, increase matrix production and promote cartilage repair. This Phase I study evaluated the local and systemic acute safety of recombinant human fibroblast growth factor 18 (rhFGF18) intraarticular (i.a.) injection, after single ascending dose (SAD) and multiple ascending dose (MAD) regimens in candidates for total knee replacement (TKR) surgery. As secondary objectives, effects of rhFGF18 on systemic biomarkers and exposure were evaluated. Tertiary objectives were to assess: effect of rhFGF18 on knee cartilage in selected regions of interest by MRI and in-person instruction on at-home knee exercise. The primary outcome measure was a composite score on the Western Ontario McMaster University Osteoarthritis Index (WOMAC; 100 points), which assessed knee pain, function and stiffness on a per subject basis. The secondary outcome was the Knee Pain Scale (KPS) which assessed knee pain severity and frequency on a per knee basis; both were done at baseline, 5, 9, 12, 26 and 52 weeks. Procedure-related opioid medication use, subject satisfaction and adverse events were also assessed.

**Results:** Analysis was by intention to treat. No significant baseline differences existed between the groups in age, gender, pain duration, body mass index or WOMAC scores. 89 subjects (57±8.3 years old, 59 female) with moderate to severe KOA received an average of 4.3±0.7 prolotherapy injection sessions over a 17-week treatment period. All groups reported improved composite WOMAC scores compared to baseline status (p < 0.01) at 52 weeks. However, WOMAC scores for prolotherapy subjects, adjusted for gender, age and body mass index showed significantly greater improvement on WOMAC score at 52 weeks: 15.32±3.52 points for prolotherapy compared to 7.68±3.41 points for saline injection (p < 0.05) and 8.25±3.33 points for exercise (p < 0.05). The improvement by prolotherapy subjects exceeded minimal clinical important difference. KPS scores of prolotherapy subjects showed similar improvement per injected knee compared to baseline status (p < 0.001) and controls. Prescribed post-procedure opioid medication resulted in rapid diminution of prolotherapy injection pain. Satisfaction with prolotherapy was high and there were no adverse events.

**Conclusions:** Prolotherapy resulted in safe, significant, sustained improvement of pain, function and stiffness scores compared to blinded saline injections and at-home exercises in knee osteoarthritis.

### 309 A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY OF rhFGF18 ADMINISTERED INTRAARTICULARLY USING SINGLE OR MULTIPLE ASCENDING DOSES IN PATIENTS WITH PRIMARY KNEE OSTEARTHRITIS (OA), SCHEDULED FOR TOTAL KNEE REPLACEMENT

**L.E. Dahleberg,1 K. Flechsenhar2, D. Dreher2, S. Gouteux2, J.S. Jurvelin3.**
1Uund Univ, Malmö, Sweden; 2Merck Serono S.A. (an affiliate of Merck KGaA, Darmstadt, Germany), Geneva, Switzerland; 3Univ. of Eastern Finland, Kuopio, Finland

**Purpose:** No approved disease-modifying OA drugs (DMOAD) are available. Use of a chondrocyte-targeted growth factor is a promising approach with the potential to induce chondrocyte proliferation, increase matrix production and promote cartilage repair. This Phase I study evaluated the local and systemic acute safety of recombinant human fibroblast growth factor 18 (rhFGF18) intraarticular (i.a.) injection, after single ascending dose (SAD) and multiple ascending dose (MAD) regimens in candidates for total knee replacement (TKR) surgery. As secondary objectives, effects of rhFGF18 on systemic biomarkers and exposure were evaluated. Tertiary objectives were to assess: effect of rhFGF18 on knee cartilage in selected regions of interest by MRI and X-ray; cartilage structure and absence/presence of cartilage proliferation from samples taken during TKR surgery; effect of rhFGF18 on OA symptoms in the target knee. An exploratory objective was to evaluate biomechanical properties of cartilage taken during TKR surgery.

**Methods:** Eligible patients were ≥40 y with primary femorobial knee OA, who were candidates for TKR surgery (planned ≥2 weeks after anticipated last injection of study drug); stable oral OA treatment was permitted. Patients received rhFGF18 or placebo, randomized 3:1 per cohort, injected i.a. into the target knee once (SAD) or once weekly for 3 weeks (MAD). SAD cohorts received 3 μg, 10 μg, 30 μg, 100 μg or 300 μg; MAD cohorts received 10 μg, 30 μg, 100 μg, 300 μg or highest tolerated dose. Follow-up and safety reviews occurred before each dose escalation. All subjects had final review 24 weeks after first injection. Unconfined compression testing (dynamic and equilibrium modulus) and histological analysis (modified Mankin scoring) were conducted for cartilage taken during TKR surgery.

**Results:** In SAD cohorts, 25 patients received rhFGF18; 8 received placebo. In MAD cohorts, 30 patients received rhFGF18; 10 received placebo. Age range 48.5–87.1; BMI range 21.1–46.9 kg/m². No local/systemic acute safety concerns emerged, no subjects discontinued treatment prematurely, no adverse events (AE) led to discontinuation. Two deaths were reported: 1 patient (MAD 30 μg) died of pulmonary embolism 2 days after TKR surgery (considered likely to be unrelated to rhFGF18 as a potential DMOAD.

### 110 IRON OVERLOAD AND HEMOCHROMATOSIS (HFE) MUTATION CORRELATE WITH CLINICAL OUTCOMES IN AN OSTEOARTHRITIS COHORT

**L. Kennish1, M. Attur1, X. Huang1, Y. Lai2, C. Liu3, S. Krasnokutsky1, J. Samuels3, S.B. Abramson1.**
1NYU Hosp for Joint Diseases-Rheumatology, New York, NY, USA; 2NYU Hosp for Joint Diseases-Orthopedics, New York, NY, USA

**Purpose:** Iron may be a contributing risk factor for osteoarthritis (OA) development – increased iron is found in OA synovial fluid and is cytotoxic towards chondrocytes. Additionally, patients with hereditary hemochromatosis develop an OA phenotype that is associated with higher ferritin levels. We examined the hypothesis that serum ferritin is elevated in patients with knee OA and that levels of ferritin correlate with OA severity.

**Methods:** The study included 150 patients with symptomatic knee OA (patients were diagnosed by aCR criteria with a WOMAC score >125) and 21 controls who were enrolled in a 2 year longitudinal study. Exclusion criteria were steroid use, inflammatory arthritis, infection, diabetes, hepatic/renal disease, or heart failure. Baseline clinical (age, gender, BMI, WOMAC pain score) and radiographic characteristics (KL score) were obtained. Cross sectional peripheral blood samples were analyzed for serum ferritin by ELISA. Plasma PGE2 and COMP fragments were measured by ELISA and PCR based HFE genotyping performed on patients and controls. Statistical analysis included ANOVA and student’s t-test.

**Results:** Ferritin was measured in 129 OA patients with mean age 65 years (35% men), BMI 26.5 and, in those who had radiographic scoring, KL score 0–2 (48) and 3–4 (48), and 20 controls with mean age 56 years (55% men), and BMI 26.5. Men and women with OA had higher average ferritin than those without OA (one way ANOVA, p = 0.008; men: 71.06 vs. 40.42 ng/ml, p < 0.01; women: 42.57 vs. 32.98 ng/ml, p=ns). Ferritin levels greater than 100 ng/ml were observed in 13% of patients with OA, and in 0% of controls. OA patients had higher frequency of homozygous HFE gene mutation C282Y/C282Y (2.29%) compared to controls (0%) and in those with higher ferritin (p=0.05). Similarly, COMP fragments was also elevated in OA patients (286.7 vs. 145.7 ng/ml, p = 0.03) and in those with higher ferritin (p = 0.05).

**Conclusions:** Selected patients with symptomatic knee OA have increased ferritin compared to controls, as well as an increased incidence of the C282Y/C282Y HFE gene mutation. Higher levels of ferritin in OA are...
independently associated with OA severity (KL score), WOMAC pain and elevations of biomarkers – PGE2 and COMP fragments. Our data suggest that increased iron (ferritin levels) may promote cartilage damage in patients with knee OA and merits further investigation as a biomarker of disease severity and progression.

311 SAFETY AND EFFICACY OF NSAIDs IN ELDERLY ARTHRITIS PATIENTS: A SUBGROUP ANALYSIS

H. Kellner1, M. Essex2, C. Li3,1. Div. of Rheumatology, Ctr. for Inflammatory Joint Diseases, Munich, Germany; 1Pfizer Inc, New York, NY, USA; 2Pfizer Inc., New York, NY, USA

Purpose: As increasing age is a well-known risk factor for gastrointestinal (GI) adverse events and may contribute to reduced compliance and discontinuation of therapy, we set out to compare the safety and efficacy of celecoxib vs diclofenac slow release (SR) plus omeprazole in elderly patients with arthritis.

Methods: Patients aged ≥65 years, with osteoarthritis and/or rheumatoid arthritis at increased GI risk who participated in the CONDOR trial (Celecoxib vs Omeprazole and Diclofenac in Patients With Osteoarthritis and Rheumatoid Arthritis) were included in this subgroup analysis. The CONDOR trial was a 6-month, prospective, double-blind, randomized clinical trial of celecoxib vs omeprazole and diclofenac SR. Eligible patients were expected to need nonsteroidal anti-inflammatory drugs (NSAID) therapy for at least 6 months; aspirin or antplatelet users were excluded. Patients were Helicobacter pylori negative. The primary end point was a composite of clinically significant upper and lower GI events adjudicated by an independent blinded expert committee and analyzed using a life-table method. Patients were randomized to either celecoxib 200 mg bid or diclofenac SR 75 mg bid plus omeprazole 20 mg qd. Follow up visits were at 1, 2, 4, and 6 months from baseline. Efficacy was determined by Patients’ Global Assessment of Arthritis at each visit.

Results: 2446 patients aged ≥65 years comprised the intent-to-treat population (n = 1219 celecoxib; n = 1227 diclofenac SR). Mean (SD) age was 70.4 (4.5) years for both arms; 83.0% of celecoxib and 80.8% of diclofenac SR patients were female. The majority of patients were white (54.1% celecoxib; 52.2% diclofenac SR). The difference between the 2 incidence proportions of adjudicated primary GI end points in patients aged ≥65 years, controlling for region, history of gastroduodenal ulceration, and time-block was statistically significant (odds ratio, 6.27; P < 0.0001 favoring celecoxib). 76.9% of celecoxib and 72.0% of diclofenac SR patients completed the study. Among those treated, 9.5% and 14.3% of patients, respectively, discontinued treatment for reasons related to study drug, and there were 2 deaths in the celecoxib arm and 1 in the diclofenac SR arm. Patients’ Global Assessment of Arthritis was 3.2±0.7 at baseline and 2.4±0.8 at Month 6 for both celecoxib and diclofenac SR, respectively. Similar percentages of patients rated efficacy at good/very good at baseline and Month 6 for celecoxib (10.5%, 55.9%) and diclofenac SR (10.6%, 56.4%). Least squares mean (SE) at Month 6 (last observation carried forward) was 2.521 (0.053) for celecoxib and diclofenac SR (P=NS), respectively.

Conclusions: The results of the CONDOR trial, in which celecoxib was superior to diclofenac SR plus omeprazole in reducing the risk of clinical outcomes across the entire GI tract, were confirmed in a subgroup analysis of patients ≥65 years. The safety and efficacy of both treatments was comparable in this population. These data may help physicians make more informed decisions in treating elderly patients with arthritis.

312 SAFETY AND EFFICACY OF RETREATMENT WITH A BIOENGINEERED HYALURONATE FOR PAINFUL OSTEOARTHRITIS OF THE KNEE: RESULTS OF THE OPEN-LABEL EXTENSION STUDY OF THE FLEXX TRIAL

R.D. Altman1, J.E. Rosen2, D.A. Bloch3, H.T. Hatoum4. 1UCLA, Agua Dulce, CA, USA; 2New York Hosp., Queens, NY, USA; 3Stanford Univ, Stanford, CA, USA; 4Univ. of Illinois, Chicago, IL, USA

Purpose: Intrarticular (IA) injection of hyaluronate (HA) has been shown to be safe and effective for relieving pain in patients with osteoarthritis (OA) of the knee and is recommended for patients who cannot be treated (OA) managed with non-pharmacologic interventions or simple analgesics. Although many studies support the safety and efficacy of single course IA-HA injections, fewer trials have evaluated the risks and benefits of repeated series of injections. This 26 week Extension Study of the FLEXX Trial was conducted to evaluate the safety of repeated intra-articular (IA) injections of Euflexxa® (1% sodium hyaluronate; IA-BioHA) for painful knee osteoarthritis (OA).

Methods: Participants who completed the randomized, double-blind, 26-week FLEXX Trial and who elected to participate in the Extension Study received asecon series of 3 weekly IA-BioHA injections and were followed for an additional 26 weeks. Adverse events (AEs) were recorded and the effect of treatment on knee pain was measured following a 50-foot walk test using a 100 mm visual analog scale (VAS). The 3 subscales of WOMAC, OARSI responder rate, Patient Global Assessment, SF-36, and intake of rescue medication was also evaluated.

Results: The FLEXX Trial included 588 subjects with painful knee OA who received 3 weekly IA injections of either BioHA or buffered saline (IA-SA). Results from the FLEXX Trial showed that IA-BioHA decreased mean pain (VAS) scores decreased by 47.2%, 42.5%, and 44.1%, respectively, following a 50-foot walk test by −25.7 mm versus −18.5 mm for the IA-SA group. Both treatments were well tolerated with about 1% of subjects in each group reporting injection site reactions.

The Extension Study included 433 subjects, 219 who received IA-BioHA and 214 who received IA-SA during the FLEXX Trial. Safety results from the Extension Study indicate that 43.4% (188/433) of subjects had AEs, of which 4.8% (21/433) were deemed treatment-related AEs. Two AEs in the Extension study led to discontinuation, and no joint effusion was reported. Patients who continued with IA-BioHA in the Extension Study maintained their improvement from baseline, with an average further reduction in pain VAS score of −3.5 mm. Patients initially treated with IA-SA in the FLEXX Trial also had a reduction in pain VAS score of −9.0 mm. The OMERACT-OARSI responder rate for all subjects was 75.3% at the completion of the Extension Study. WOMAC Pain, Stiffness, and Disability scores decreased by 47.2%, 42.5%, and 44.1%, respectively. The Patient’s Global Assessment improved an additional −8.1 mm and there were 15.2% and 15.7% improvements for SF-36 physical functioning and bodily pain scores, respectively, from the beginning of the FLEXX Trial to the end of the Extension Study. Acetaminophen use was reduced from 14.6 to 9.5 tablets per week, representing an overall 34.9% reduction from the beginning of the FLEXX Trial.

Conclusions: Repeated intra-articular injection of IA-BioHA were effective, safe, and well-tolerated, and were not associated with an increase in AEs such as synovial effusions. Additional symptom improvements during the Extension Study were noted for subjects who received either IA-BioHA or IA-SA during the FLEXX Trial.

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

S. Daniels1, G. Manvelian1, A. Gibofsky3, 1Premier Res. Group, Austin, TX, USA; 2Independent Clinical Res. Consultant, Poway, CA, USA; 3Hosp. for Special Surgery, New York, NY, USA

Purpose: Nonsteroidal anti-inflammatory drugs (NSAIDs) are a common class of medication taken for acute arthritic pain. However, associated adverse events (AE) have prompted the development of new formulations that minimize AE’s and maintain efficacy. The purpose of this clinical study was to evaluate the analgesic efficacy and safety of an investigational, proprietary, nano-formulated, oral diclofenac (diclofenac-N) compared with placebo in subjects with acute dental pain.

Methods: This was a phase-2, multisite, randomized, double-blind, single-dose, parallel-group, active- and placebo-controlled study. In total, 200 subjects who were 18–50 years of age, had extraction of ≥2 third molars (at least one of which had to be a fully or partially impacted mandibular third molar), and experienced moderate to severe pain intensity within 6 hours after surgery were enrolled. Subjects received either diclofenac-N 35 mg or 18 mg, celecoxib 400 mg, or placebo. The primary efficacy variable was the sum of total pain relief (TOTPAR) over 0–12 hours (TOTPAR-12) after Time 0. Higher scores indicated better pain relief. TOTPAR-8 and TOTPAR-4 were also evaluated.

Results: Diclofenac-N was significantly (p < 0.001) better than placebo for TOTPAR-12. Mean ±SD TOTPAR-12 values for diclofenac-N 35 mg, diclofenac-N 18 mg, celecoxib 400 mg, and placebo were 16.81 ± 12.76, 17.76 ± 13.76, 14.61 ± 15.05, and 5.65 ± 11.33, respectively. TOTPAR-4 and TOTPAR-8 values for diclofenac-N 35 mg and diclofenac-N 18 mg demonstrated comparable results when compared to placebo. The difference in time-to-onset of analgesia between each treatment