ECGs and vital signs were unremarkable and similar across all treatments. Plasma TCA concentration across the FX006 doses were linear and dose-dependent. Peak plasma concentrations achieved with 40 mg TCA IR were 10X of those seen with FX006 40 mg.

**Conclusions:** It is demonstrated that sustained residency of TCA in the joint prolongs therapeutic effect. The 40 mg dose of FX006 produced an effect at Week 12 (−3.7) that was equivalent to the maximal effect of TCA IR at Week 4. Surprisingly, between Weeks 2 and 11, the anesthetic effect of the 40 mg dose of FX006 exceeded the maximal effect of TCA IR seen at Week 4. This observation suggests that prolonged occupation of the corticosteroid receptor may be associated with an enhanced anesthetic effect. Further, this amplification of effect may constitute a meaningful clinical improvement relative to TCA IR as indicated by the 20% responder analysis for the 40 mg dose of FX006. A study is underway to determine the TCA concentrations in the joint at varying time points, and subsequent studies against placebo will define effect size and duration of action.

**Methods:** MOST is a NIH-funded longitudinal study of persons with or at risk for symptomatic knee OA. Participant visits at 60, 72 and 84 months were used for this analysis. At the 60-month visit, participants underwent evaluation of unilateral isokinetic knee extensor strength and bilateral evaluation of vibratory perception threshold (VPT). VPT was evaluated using a biothesiometer. The applicator tip was placed on preselected anatomic bony prominences. The voltage was initially set at “0” and then increased by 1 volt/second until the participant acknowledged sensation and this was defined as the VPT. The mean VPT between the limbs was used for analyses. Quadriceps strength was evaluated as the maximum torque during active isokinetic extension. Strength measures were corrected for gravity by dividing the maximum torque by BMI. VPT and quadriceps strength were categorized into sex-specific groups based on ±1 SD of the mean of the sample.

At all visits, participants were asked about symptoms and frequency of knee instability in the past 3 months. Knee “buckling” was defined according to a question that asked if and how many times the participant noted their knee “giving way” and “slipping” was defined according to a question that asked if and how many times the knee “felt like it was shifting, slipping, or going to give way but didn’t actually do so”. Knee instability was defined as the occurrence of either symptom. Incident instability was defined as someone who answered “no” to experiencing either symptom at the 60 month visit but answered “yes” to one or both at the 72 or 84 month visit. Worsening of instability was defined as an increase in the level of instabilities frequency using the 3-level variable with 0–1 times, 2–5 times, and >5 episodes over 3 months. Subjects with >5 times instability at 60 M were excluded. An increase in one level or more of frequency was considered worsening. A person-based analyses using Poisson regression with robust error variance to estimate adjusted relative risk for the association of VPT and muscle strength with knee instability incidence and progression was performed. We adjusted in analyses for age, sex, BMI, race, clinic site, KL grade and WOMAC knee pain as well as for each predictor (muscle strength and VPT).

**Results:** We evaluated 2212 participants (60% women, mean [SD] age = 68 [8] years, and mean [SD] BMI = 31 [6]). 17% of participants reported buckling, 29% reported slipping and 37% reported instability (buckling and/or slipping) in the past 3 months at the 60-month visit. Over the follow-up period, 32% developed incident instability, and 20% had incident buckling. Similarly, 11% had worsening of instability, and 21% had worsening of buckling. Quadriceps weakness and impaired

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**Table 1** Secondary efficacy endpoints at Week 8; FX006 10 mg and 40 mg vs. TCA IR.

<table>
<thead>
<tr>
<th>Condition</th>
<th>LSMO vs TCA IR (90% CI) 2 sided p-value</th>
<th>LSMMD vs TCA IR (90% CI) 2 sided p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOMAC A (pain) 0–4 Likert scale</td>
<td>−0.27 (−0.51, −0.03) 0.0654</td>
<td>−0.37 (−0.61, −0.13) 0.0116</td>
</tr>
<tr>
<td>WOMAC A1 (pain on walking) 0–4 Likert scale</td>
<td>−0.3 (−0.6, −0.01) 0.0496</td>
<td>−0.34 (−0.67, −0.01) 0.0496</td>
</tr>
<tr>
<td>WOMAC B (stiffness) 0–4 Likert scale</td>
<td>−0.38 (−0.65, −0.10) 0.0252</td>
<td>−0.49 (−0.77, −0.22) 0.0036</td>
</tr>
<tr>
<td>WOMAC C (function) 0–4 Likert scale</td>
<td>−0.28 (−0.52, −0.04) 0.0518</td>
<td>−0.37 (−0.61, −0.14) 0.0098</td>
</tr>
<tr>
<td>OMERACT-OARSI Responders n(%) p-value (vs. TCA IR)</td>
<td>52 (91.2%) 0.0076</td>
<td>53 (89.8%) 0.0118</td>
</tr>
<tr>
<td>PGIC1–7 Likert scale</td>
<td>−0.6 (−1.0, −0.2) 0.0116</td>
<td>−0.7 (−1.1, −0.3) 0.0026</td>
</tr>
<tr>
<td>MGIC1–7 Likert scale</td>
<td>−0.6 (−1.0, −0.2) 0.0116</td>
<td>−0.7 (−1.1, −0.3) 0.0026</td>
</tr>
</tbody>
</table>

LSMD = Least square mean difference.

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**Figure 1.** Weekly Mean of Average Daily Pain Score (ADP)

**Figure 2.** Proportion of Responders, >20% Improvement
vibratory sense were each associated with the risk of incident knee instability, and impaired vibratory sense predicted worsening of both outcomes (see Table).

**Conclusions:** In this large cohort of participants, impaired vibratory sense and quadriceps weakness were each associated with a range of knee instability outcomes. Thus, vibratory sense and muscle strength may be important risk factors for knee instability in persons with or at risk for knee OA.

### **Methods:**

- **Comorbidities evaluated:** Included hypertension requiring medication, diabetes, and metabolic syndrome (defined as BMI of 30 kg/m² or greater as well as the presence of hypertension and diabetes). Met criteria for metabolic syndrome (3.5% vs 1.7%; p < 0.001).
- **Risk factors and morbidity data:** From the Osteoarthritis (OA) Research Network (2001–2012) database, including 8,221 patients with knee OA (55.7% women; mean age 65.7 years; 62.7% vs 56.4%; p < 0.001) compared to hip OA patients. A significantly greater proportion of knee OA patients were being treated for hypertension (66.8% vs 58.2%; p < 0.001), had diabetes (17.7% vs 8.8%; p < 0.001), and met criteria for metabolic syndrome (3.5% vs 1.7%; p < 0.001). Controlling for age, gender, class of obesity, smoking, and chronic systemic steroid use, knee OA patients had significantly greater odds of a diagnosis of hypertension (OR 1.11; 95% CI [1.06–1.16]) and diabetes (OR 1.35; 95% CI [1.27–1.42]), and of meeting the criteria for metabolic syndrome (OR 1.35; 95% CI [1.18–1.54]).

### **Purpose:**

Osteoarthritis (OA) of the knee has been reported to be independently associated with a higher prevalence of medical comorbidities marked by systemic inflammation when compared to end-stage hip osteoarthritis.

### **Method:**

- **Comorbidities:** Marked by systemic inflammation.
- **Potential interactions:** Between OA and other medical conditions.
- **Purpose:** To understand the nature of these associations, as well as to investigate potential interactions between these conditions, each of which has been reported to be independently associated with a systemic inflammatory state.

### **Conclusions:**

While arthroplasty patients with knee OA are marked by differences in demographic profile compared to those with hip OA, the results of the present study demonstrate that these variations alone fail to explain observed discrepancies in the prevalence of associated patient comorbidities. Even when controlled for demographic profile, smoking, and chronic steroid use, patients with knee OA continued to have significantly greater odds of an associated diagnosis of hypertension, diabetes, or the presence of metabolic syndrome. These findings further support the notion that knee OA is marked by unique associations with systemic disease. Further work is needed to better understand the nature of these associations, as well as to investigate potential interactions between these conditions, each of which has been reported to be independently associated with a systemic inflammatory state.