Background: In new draft guidance for OA drugs, the U.S. FDA notes the "well-recognized discordance" in clinical trials between structural imaging and patient benefit. In a randomized double-blind, placebo-controlled trial, IA TPX-100 was associated with statistically significant and clinically meaningful improvement in knee functions among subjects (n=93) recruited for mild-moderate (ICRS grades 2-3) bilateral patellofemoral OA. No treatment differences in PF cartilage were detected, consistent with FDA concerns. However, only 14% of knees had measurable PF cartilage change on follow-up MRIs, limiting power for analysis of treatment differences in PF cartilage (ACR/ACHP 2017).

Objectives: To conduct a subset analysis of knee function and cartilage thickness correlations among the 73% of subjects (n=68) who had, in addition to PFOA, bilateral tibiofemoral OA (TFOA).

Methods: Subjects received 4 weekly injections of IA TPX-100 in one knee and identical saline placebo in the contralateral knee, as randomly assigned. MRIs were obtained at baseline, 6 and 12 months; and patient-reported outcomes (KOOS/WOMAC) were obtained at baseline, 3, 6 and 12 months. Subjects, sites, sponsor and central readers were blind to treatment assignment. All subjects receiving 4 weekly injections of 200 mg TPX-100 with at least one follow-up MRI were included for efficacy. The database was locked prior to all analyses, and clinically meaningful differences in outcome measures were selected a priori, based on the literature (Roos 2003).

Results: Of 68 subjects with bilateral TFOA, 47% had ICRS grade 4 (severe) TFOA at baseline, and 43% had ICRS grade 3 (moderate) disease. Demographic data for the cohort was consistent with the U.S. THR OA population in mean age (60.8 years), BMI (30.6), and gender distribution (60% females). IA TPX-100 was safe and well tolerated, with no drug-related serious adverse events or safety concerns. The mean functional improvement of TPX-100-treated knees was significantly higher than that of placebo-exposed knees at 6 and 12 months (p<0.04 and p<0.02, respectively). Responder knees, defined a priori with ≥ 8 points increase in KOOS function, had mean improvements in function of 20.5 and 22.4 at 6 and 12 months, respectively. Pearson analysis revealed a significant positive 12-month correlation (p=0.05) between degree of functional improvement and cartilage thickness increase/stabilization in TF cartilage in TPX-100-treated knees (Table 1).

Abstract THU0441 –Table 1.

Cartilage Thickness vs. Knee Function (KOOS ADL)

<table>
<thead>
<tr>
<th>Month</th>
<th>Cartilage Thickness</th>
<th>Pearson Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Correlation p-value</td>
<td>Medial TF 0.242 0.048</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Entire TF 0.332 0.007</td>
</tr>
</tbody>
</table>

Conclusion: In subjects with bilateral TFOA, statistically significant and clinically meaningful, robust functional improvements in TPX-100-treated knees were seen at 6 and 12 months compared with placebo-exposed knees. Formal analysis revealed statistically significant correlations between functional improvement and increase or stabilization of lateral, medial and total TF cartilage thickness. To our knowledge, TPX-100 is the first candidate DMOAD to show improvement in critical knee function concordant with increase/stabilization of cartilage structure compared with placebo-exposed knees.

REFERENCE:

Acknowledgement: We thank Drs. Felix Eckstein and Ali Guermazi for central readings of MRIs.