Structural Severity in Knee Osteoarthritis Impacts Treatment Response: A Post Hoc Pooled Analysis of Lorecivivint Clinical Trials

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Background

- Disease heterogeneity and difficulty assessing pain and joint structure in clinical trials are challenges to developing effective treatments options for osteoarthritis (OA).
- This post hoc analysis of lorecivivint (LOR), an intra-articular CLK/DYRK inhibitor thought to modulate Wnt and inflammatory pathways, examined the structural heterogeneity of participants enrolled in Phase 2 and 3 trials and the impact on LOR treatment effect.
- The purpose of this analysis was to identify potential associations between OA pain reporting and knee joint structure which may aid future clinical trial design.

Methods

- Data was analyzed from two Phase 2 (OA-02, NCT02536833; OA-04, NCT03122860), and two Phase 3 (OA-10, NCT04385303; OA-11, NCT03928184) trials.
- In all trials, participants had ACR-defined (clinical and radiographic) knee OA, Kellgren-Lawrence (KL) grades 2-3.
- For OA-04, OA-10 and OA-11, additional criteria included Pain Numeric Rating Scale (NRS) [0-10] ≥4 and ≤8 in the target knee and <4 in the contralateral knee.
- Baseline JSW for each study was compared using baseline-adjusted ANCOVA at each timepoint.

Results

Table. Medial JSN by KL Grade

<table>
<thead>
<tr>
<th>KL Grade</th>
<th>Grade 0 n (%)</th>
<th>Grade 1 n (%)</th>
<th>Grade 2 n (%)</th>
<th>Grade 3 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>OA-04 76</td>
<td>23 (30.2%)</td>
<td>48 (63.2%)</td>
<td>5 (6.6%)</td>
</tr>
<tr>
<td></td>
<td>OA-10 201</td>
<td>54 (26.9%)</td>
<td>118 (58.7%)</td>
<td>29 (14.4%)</td>
</tr>
<tr>
<td></td>
<td>OA-11 260</td>
<td>1 (0.4%)</td>
<td>229 (88.1%)</td>
<td>30 (11.5%)</td>
</tr>
<tr>
<td>3</td>
<td>OA-04 133</td>
<td>14 (10.5%)</td>
<td>87 (65.4%)</td>
<td>32 (24.1%)</td>
</tr>
<tr>
<td></td>
<td>OA-10 212</td>
<td>2 (0.9%)</td>
<td>59 (27.8%)</td>
<td>128 (60.4%)</td>
</tr>
<tr>
<td></td>
<td>OA-11 245</td>
<td>0</td>
<td>116 (47.4%)</td>
<td>129 (52.6%)</td>
</tr>
</tbody>
</table>

Conclusions

- In this post hoc analysis, there was substantial heterogeneity in baseline mJSW across LOR clinical trials within the KL 2-3 grade inclusion criteria.
- Phase 3 LOR trials had more advanced knee OA relative to Phase 2 LOR trials, particularly all participants in OA-11 and KL 3 participants in OA-10.
- Participants with less structurally advanced knee OA showed greater pain treatment responses to 0.07 mg LOR compared to those with more advanced disease.
- These data support the hypothesis that the amount of OA structural damage is associated with the pain of knee OA and that earlier intervention may improve outcomes.


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