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 cumulative frequency distribution plots by KL grade.
- Percentage of participants with JSW < 3mm, an estimate of advanced OA, were summarized for each study.[1]
- Participant radiographs were categorized for OARSI joint space narrowing (JSN) estimated from joint space width.[2]
- For trials which captured Pain NRS, treatment responses were assessed according to KL grade and by trial.
- For all treatment-related outcomes, change from baseline was estimated using baseline-adjusted ANCOVA at each timepoint.

Results

Figure 1. Cumulative frequency of baseline mJSW across LOR trials

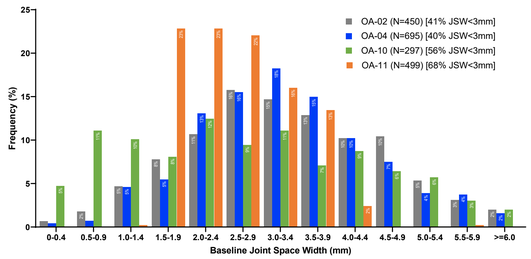
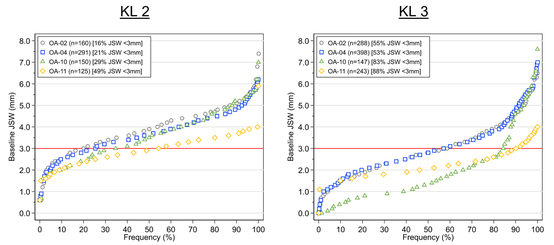


Figure 2. Cumulative frequency of baseline mJSW by KL grade across LOR trials

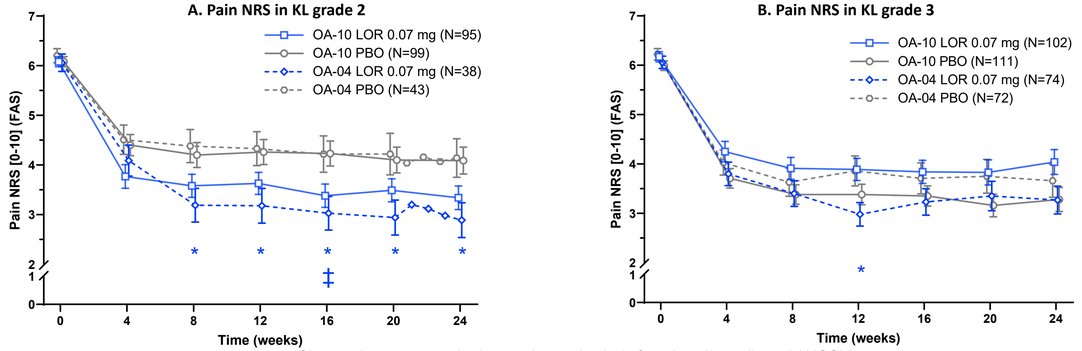


Cumulative frequency of baseline mJSW. Redline designates 3 mm as a surrogate for ~50% mJSW

Table. Medial JSN by KL Grade

			Grade 0	Grade 1	Grade 2	Grade 3
		N	n (%)	n (%)	n (%)	n (%)
KL Grade 2	OA-04	76	23 (30.2%)	48 (63.2%)	5 (6.6%)	0
	OA-10	201	54 (26.9%)	118 (58.7%)	29 (14.4%)	0
	OA-11	260	1 (0.4%)	229 (88.1%)	30 (11.5%)	0
KL Grade 3	OA-04	133	14 (10.5%)	87 (65.4%)	32 (24.1%)	0
	OA-10	212	2 (0.9%)	59 (27.8%)	128 (60.4%)	23 (10.9%)
	OA-11	245	0	116 (47.4%)	129 (52.6%)	0

Figure 3. Treatment effect of LOR vs. PBO by KL grade in OA-04 and OA-10 LOR trials



Observed mean ± standard error shown. Analysis from baseline-adjusted ANCOVA
*OA-04 P< 0.05 0.07 mg LOR vs PBO ‡OA-10 P < 0.05 0.07 mg LOR vs PBO

Results

- Baseline mJSW < 3mm for KL 2 participants were 16% (OA-02); 21% (OA-04), 30% (OA-10), and 49% (OA-11) (Fig. 1 and 2)
- Baseline mJSW < 3mm for KL 3 participants were 55% (OA-02), 53% (OA-04), 81% (OA-10), and 88% (OA-11)
- OARSI JSN 0 was more prevalent in OA-04 (40.7%) vs. OA-10 (27.8%) or OA-11 (0.4%)(Table)
- Beneficial treatment effects of LOR vs. PBO was seen in KL 2 for OA-04 and OA-10, but not OA-11, with similar magnitude of response seen for 0.07 mg (figure 3A).
- Beneficial treatment effects of LOR were seen only in OA-04 for KL 3, with similar magnitude of change for 0.07 mg and 0.23 mg LOR through week 12 (figure 3B).

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.**

References: 1. Deep et al. *JBJS* 2003
2. Culvenor et al. *KSSTA* 2015

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