USING PAIN TOLERABILITY THRESHOLDS TO CHARACTERIZE CLINICALLY MEANINGFUL TREATMENT OUTCOMES IN KNEE OSTEOARTHRITIS: POST HOC ANALYSIS OF A PHASE 2B TRIAL OF INTRA-ARTICULAR LORECIVIVINT

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Background

- The construct of pain tolerability reveals the complex burden of chronic knee osteoarthritis (OA) pain informing decisions regarding clinically meaningful treatment effects in clinical trials.
- A recent survey of 537 patients with chronic pain demonstrated respondents who reported pain numeric rating scale (NRS) scores ≤4 (0-10) almost exclusively report their pain as tolerable[1]. The percentage of respondents whose pain was reported to be intolerable increased with every increase in NRS point, with >50% of respondents reporting their pain as intolerable at an NRS score of ≥7.
- Retrospective analyses of clinical trial data may use cut-offs in NRS scores to define non-responders. Comparison of these results to other response definitions may help characterize the clinical meaningful response to particular interventions and could also inform how tolerability-based cut-offs would perform in regard to assay sensitivity of clinical trials.
- This post hoc analysis of a Phase 2b placebo (PBO)-controlled trial of lorecivivint (LOR) assessed the proportion of participants remaining with not tolerable pain using pain tolerability-based cut-offs (i.e., NRS ≥4, ≥5, ≥6, ≥7) and treatment responder by improvement over baseline of 30%, 50%, and 70% or OMERACT-OARSI response.

Purpose

To evaluate the performance of responder definitions using cut-offs in the pain NRS that correspond with patient-reported pain tolerability for randomized clinical trials.

Methods

- Data from a 24-week, Phase 2b (NCT03122860) trial[2] of participants with ACR-defined knee OA, Kellgren-Lawrence (KL) grades 2–3, and Pain NRS scores ≥4 and ≤8 in the target knee and ≤4 contralateral knee were analyzed.
- A single 2 mL IA injection of LOR or vehicle PBO was given in the target knee at baseline. This analysis included a pre-specified subgroup without widespread pain (defined as Widespread Pain Index (WPI) ≤ 4 and Symptom Severity Score Question 2 ≤ 2, stratified as 80% of enrollment) in the LOR 0.07 mg group and PBO.
- The proportions of participants who were classified as “responders” using the pain tolerability-based cut-offs (i.e., reporting pain levels of ≥4, ≥5, ≥6, or ≥7, ≥8 in their weekly average scores of daily Pain NRS Week 12) and those whose pain improved by 30%, 50%, or 70% or achieved OARSI “strict” response (≥50% improvement in pain or function and absolute change ≥20-point [0-100]) or response (OARSI “strict” or ≥20% improvement and absolute change ≥10-point [0-100] > 2 of pain, function, and/or patient global assessment) criteria at Week 12 were compared between LOR and PBO groups.
- The odds ratios (OR; 95% CI) of participants achieving each response level with LOR compared with PBO were estimated using logistic regression.

Results

Participants with Not Tolerable Pain at Week 12

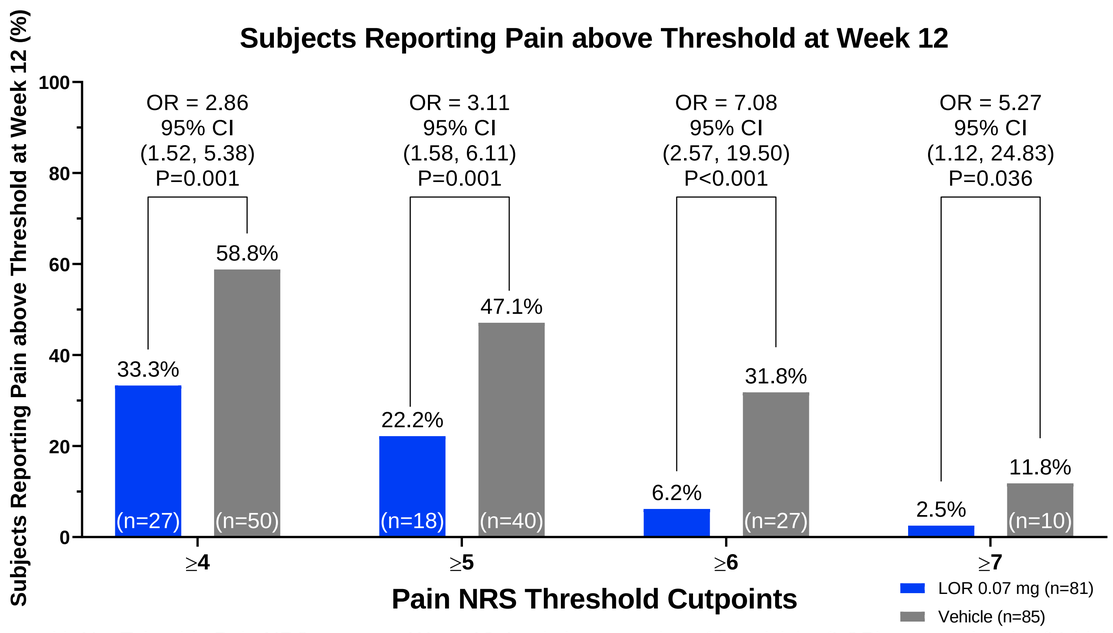

Figure 1. Participants with Not Tolerable Pain NRS scores at Week 12. Logistic regression of lorecivivint (LOR) versus placebo (Vehicle) using the Full Analysis Set (widespread-pain negative participants).

Participants Achieving Clinical Response Thresholds

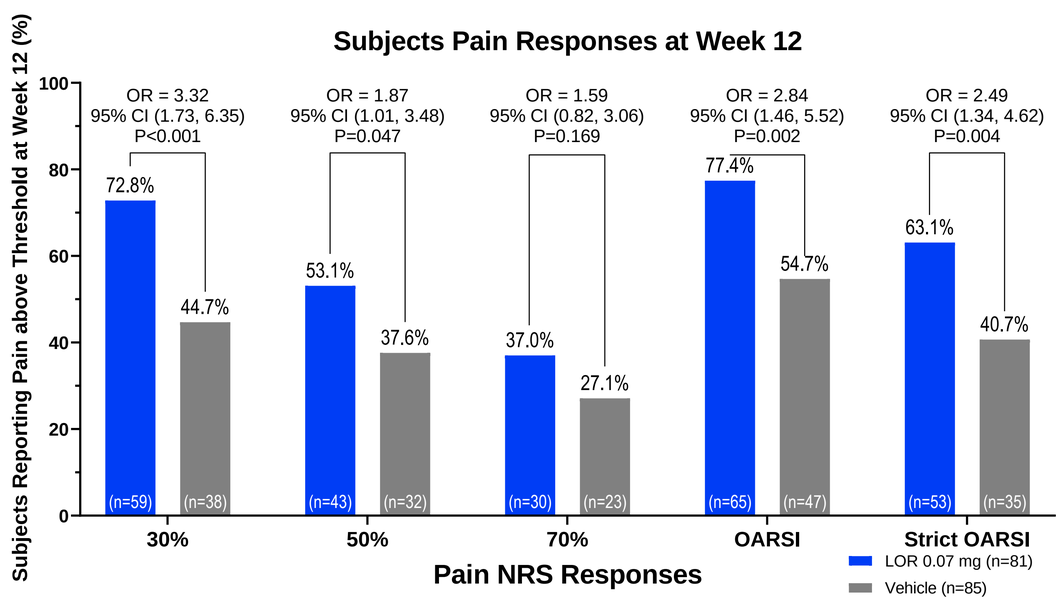

Figure 2. Participants achieving 30%, 50%, or 70% improvement over baseline, or meeting OARSI response criteria. OARSI “strict” response: ≥50% improvement in pain or function and absolute change ≥20-point [0-100]. OARSI response: OARSI “strict” or ≥20% improvement and absolute change ≥10-point [0-100] in two of pain, function, and/or patient global assessment. Logistic regression of lorecivivint (LOR) versus placebo (Vehicle).

- Ninety-three participants (mean age 60.4 [±8.4] years, BMI 29.2 [±3.6] kg/m^2, female 57.0%, Kellgren-Lawrence grade 3 67.7%) were randomized to the 0.07 mg LOR group and 93 (mean age 60.4 [±8.9] years, BMI 28.4 [±4.3] kg/m^2, female 52.7%, Kellgren-Lawrence grade 3 60.2%) were randomized to the vehicle PBO group.
- Treatment with 0.07 mg LOR versus PBO significantly (P<0.05) decreased the odds of reporting NRS pain level above cut-offs defined based on pain tolerability as well as increased the odds of achieving percent improvement in pain or OMERACT-OARSI response criteria (Figures 1 and 2).
- The ORs comparing the percentages of responders in the LOR versus PBO groups were higher for the NRS cut-offs of 6 and 7 than for cut-offs defined using the percent improvement in pain or the OARSI definition.
- Interestingly, using the NRS cut-off of 6, only 6% of LOR-treated participants were labeled as non-responders, whereas 32% of PBO-treated participants were non-responders (Figure 1).
- In contrast to OARSI response at Week 12, 23% of LOR participants and 45% of PBO participants did not achieve clinical response (Figure 2).

Conclusions

- In this Phase 2b post hoc analysis, significantly fewer participants treated with LOR remained at an NRS score indicative of intolerable levels of pain at week 12 in comparison to participants treated with PBO.
- Furthermore, these data suggest that asking participants whether their pain is tolerable could provide a highly clinically-meaningful outcome measure with good assay sensitivity. Future clinical trials should include this low-burden question in order to further characterize its utility as an outcome measure.
- The development of LOR as a potential treatment for painful knee OA is ongoing.

References

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2. Yazici et al. Osteoarthritis and Cartilage. 2021; 29 (5): doi.org/10.1016/j.joca.2021.02.004

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