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The Novel, Intra-articular CLK/DYRK1A Inhibitor Lorecivivint (LOR; SM04690), Which Modulates the Wnt Pathway, Improved Responder Outcomes in Subjects with Knee Osteoarthritis: A Post Hoc Analysis from a Phase 2b Trial

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Background: Lorecivivint (LOR; SM04690) is a small-molecule, intra-articular (IA) CLK/DYRK1A inhibitor that modulates the Wnt pathway[1] and has demonstrated some beneficial effects on patient-reported outcomes (PROs) versus placebo (PBO) in two Phase 2 knee osteoarthritis (OA) trials. With subjective measures such as PROs, meaningful benefits may be better characterized by representation as discrete threshold responses rather than by changes in mean point estimates.

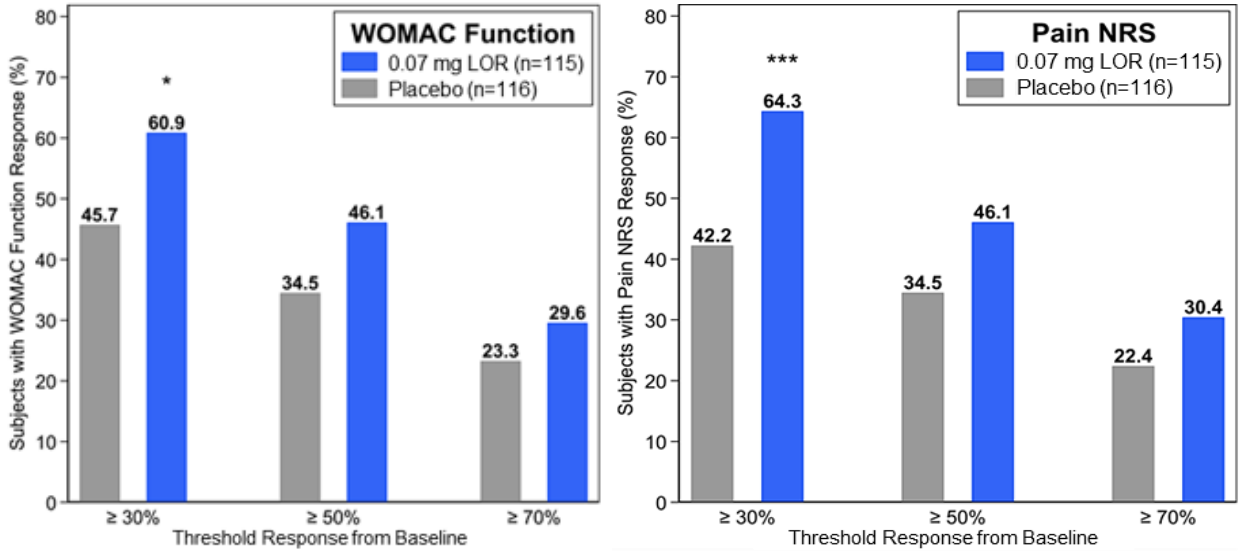
Objectives: To conduct a post hoc analysis of subjects in a 24-week Phase 2b trial by measuring the proportions of subjects treated with LOR and PBO who achieved 30%, 50%, or 70% threshold responses of improvement over baseline in Pain Numeric Rating Scale (NRS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain, WOMAC Function, and Patient Global Assessment (PtGA) at Week 12. Results from the Phase 3-selected dose of 0.07 mg LOR are presented here.

Methods: Subjects had ACR-defined knee OA, Kellgren-Lawrence (KL) grades 2–3, and Pain NRS scores ≥4 and ≤8 in the target knee and <4 in the contralateral knee. A single 2 mL IA injection of 0.03 mg, 0.07 mg, 0.15 mg, or 0.23 mg LOR or vehicle PBO was given in the target knee at baseline. The proportions of subjects meeting 30%, 50%, or 70% threshold responses over baseline in the weekly average of daily Pain NRS [0–10], WOMAC Pain [0–100], WOMAC Function [0–100], and PtGA [0–100] at Week 12 were determined. The odds ratios (OR [95% CI]) of achieving each threshold response level were calculated and compared between LOR and PBO.

Results: In total, 635 subjects (91.4%) completed the trial (mean age 59.0±8.5 years, BMI 29.0±4.0 kg/m^2, female 58.4%, KL grade 3 57.3%). At Week 12, treatment with 0.07 mg LOR significantly (P<0.05) increased the odds of a 30% threshold response in Pain NRS (OR 2.47 [1.45, 4.19]) and WOMAC Function (OR 1.86 [1.10, 3.12]) and a 50% threshold response in WOMAC Pain (OR 1.79 [1.06, 3.03]) and PtGA (OR 2.28 [1.25, 4.16]). Numerically, more (not statistically significant) subjects achieved a 70% threshold response in all PROs. All improvements were maintained through Week 24.

Conclusion: In this post hoc analysis, LOR-treated subjects reported greater improvements in PRO threshold responses versus PBO from Week 12 through Week 24. LOR demonstrated significantly higher odds of achieving and maintaining improvements in PROs at 30% and 50% thresholds. Phase 3 trials of 0.07 mg LOR are ongoing.

Figure: Percent of Phase 2b trial subjects in the LOR and placebo groups responding to treatment with 30%, 50%, or 70% threshold responses over baseline at Week 12. The Pain NRS and WOMAC Function outcomes are shown. **P*<0.05, ***P*<0.01, ****P*<0.001 versus placebo by logistic regression using the Full Analysis Set and non-responder imputation.



References: 1. Deshmukh V, et al. *Osteoarthr Cartil*. 2019.