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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 and has demonstrated beneficial effects on patient-reported outcomes (PROs) compared with placebo (PBO) in two Phase 2 trials for knee osteoarthritis (OA). Representing PROs as discrete threshold responses instead of as changes in mean point estimates may better evaluate clinically meaningful benefits experienced by trial subjects. This post hoc analysis was conducted to measure the proportion of subjects treated with LOR in a 24-week Phase 2b trial who achieved 30%, 50%, or 70% improvements over baseline in Pain Numeric Rating Scale (NRS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain, WOMAC Function, and Patient Global Assessment (PtGA). 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 proportion of subjects meeting thresholds of 30%, 50%, or 70% improvements 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 was determined. The odds ratios (ORs) of achieving each threshold improvement level were calculated.

Results: 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%).

Treatment with 0.07 mg LOR versus PBO at Week 12 led to

1. Significantly (P<0.05) increased odds of achieving a 30% threshold response in Pain NRS (OR 2.47 [1.45, 4.19]) and WOMAC Function (OR 1.86 [1.10, 3.12])

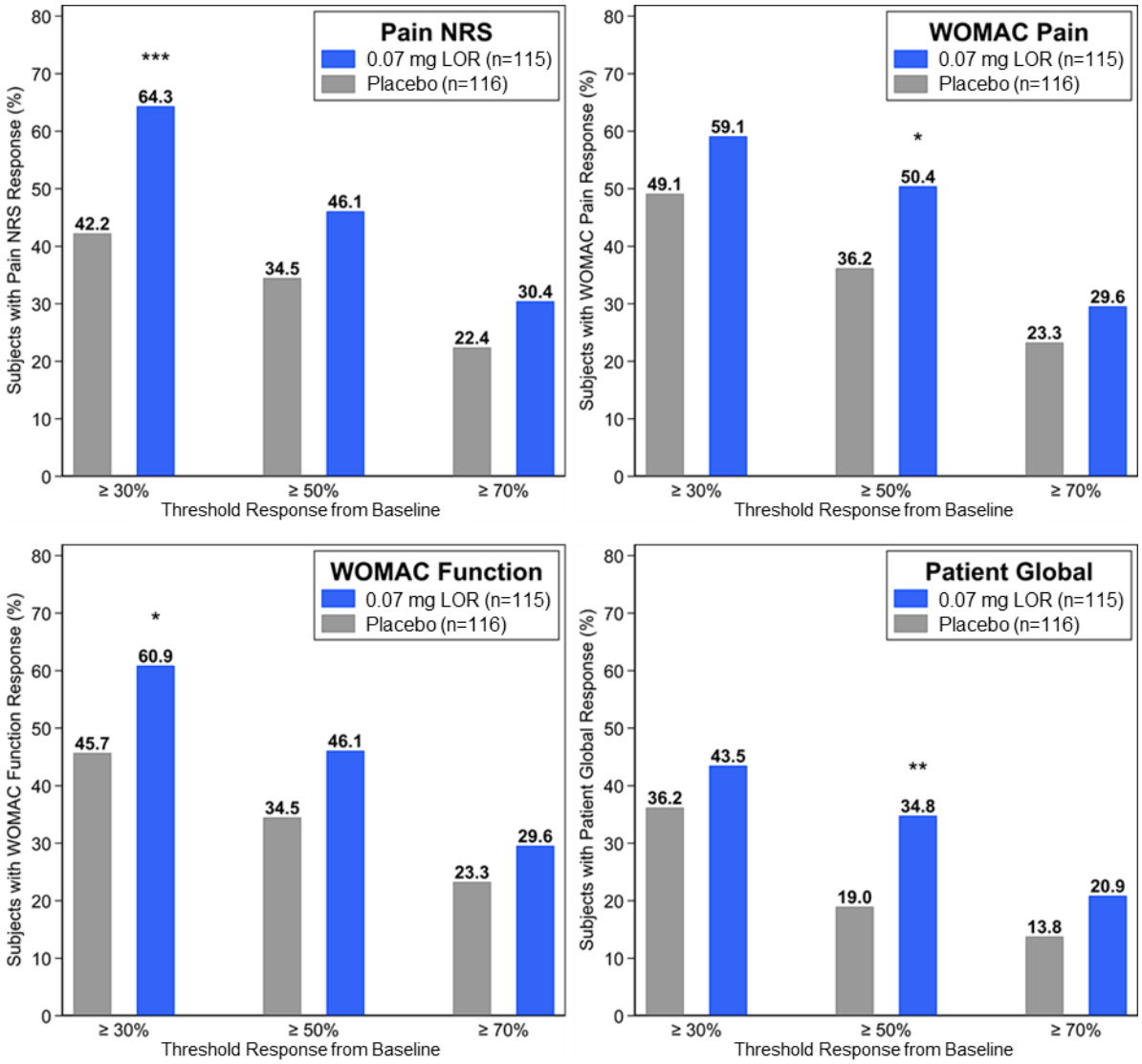
2. Significantly increased odds of achieving a 50% threshold response in WOMAC Pain (OR 1.79 [1.06, 3.03]) and PtGA (OR 2.28 [1.25, 4.16])

3. Numerically, but not significantly, more subjects achieving a 70% threshold response in all PROs

Improvements were maintained through Week 24.

Conclusion: LOR, in development as a potential disease-modifying knee OA drug, demonstrated significantly higher ORs of achieving and maintaining clinically relevant improvements in PROs compared with placebo from Week 12 through Week 24. Phase 3 trials are ongoing.

Figure: Responder outcomes from a Phase 2b trial of LOR: Pain NRS, WOMAC Pain, WOMAC Function, and Patient Global Assessment at Week 12.



Logistic regression of LOR versus placebo using the Full Analysis Set (FAS, all dosed subjects) and non-responder imputation. *P<0.05, **P<0.01, ***P<0.001