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Optimizing Subject Selection in Knee Osteoarthritis Trials by Joint Space Width: Analysis from a Phase 2b Trial of Lorecivivint (SM04690)

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Background: Radiographic Kellgren-Lawrence (KL) grading is used as an inclusion criterion in knee osteoarthritis (OA) trials, yet it is associated with excessive subject heterogeneity. Selecting subjects with baseline medial joint space width (mJSW) 2-4 mm reduces heterogeneity and improves radiographic change responsiveness. This study evaluated the impact of baseline mJSW 2-4 mm on patient-reported outcomes (PROs) in a 24-week phase 2b trial of lorecivivint, a Wnt pathway inhibitor in development as a potential disease-modifying OA drug (DMOAD).

Methods: Knee OA subjects with KL grades 2-3 and Pain Numeric Rating Scale (NRS) ≥4 and ≤8 in the target knee and <4 in the contralateral knee received a single, intra-articular, lorecivivint (0.03, 0.07, 0.15, 0.23 mg) or vehicle placebo (PBO) injection at baseline. PRO endpoints (24 weeks) included change from baseline in weekly average of daily OA target knee pain by NRS, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain [0-100], WOMAC Function [0-100], and Patient Global Assessment (PtGA) [0-100]. A post hoc analysis of subject results with baseline mJSW 2-4 mm is reported.

Results: 635 subjects (91.4%) completed the study (mean age 59.0 [±8.5] years, BMI 29.0 [±4.0] kg/m^2, female 58.4%, KL3 57.3%). In both Full Analysis Set (FAS) and mJSW 2-4 mm subjects, significant improvements compared to PBO ($P<0.05$) were seen in Pain NRS, WOMAC Pain, WOMAC Function, and PtGA for the 0.07 and 0.23 mg lorecivivint dose groups at Week 12. Larger effect sizes were observed in the mJSW 2-4 mm group for most doses at Weeks 12 and 24.

Conclusion: In this analysis, subjects with baseline mJSW 2-4 mm showed increased PRO effect sizes than those observed in the FAS. Baseline mJSW 2-4 mm should be considered as an inclusion criterion for trials of potential knee DMOADs.

Figure: Ladder plot of effect size and treatment estimates (95% CI) for improvement in Pain NRS over PBO