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Items Driving WOMAC Pain Subscore Changes Due to Lorecivivint, a Potential Disease-Modifying Treatment for Knee Osteoarthritis: A Post Hoc Analysis of Phase 2b Trial Data

Sarah Kennedy, PhD, Christopher J. Swearingen, PhD, Ismail Simsek, MD, Jeyanesh Tambiah, MD

Samumed, LLC, San Diego, CA

Background: Knee osteoarthritis (OA) is a disease characterized by pain, loss of function, and structural deformities, causing a heterogeneous disease state that confounds patient-reported outcomes (PROs). The WOMAC Pain subscore addresses this reporting variability by capturing multiple pain items related to "active" and "static" subject states. We hypothesize that measurement of these items may demonstrate differential effect sizes when assessing treatment benefit. Lorecivivint (LOR; SM04690), a small-molecule, intra-articular CLK/DYRK1A inhibitor that modulates the Wnt pathway, is in development as a potential disease-modifying treatment for knee OA. To test this, a post hoc analysis of Pain NRS, WOMAC Pain, and individual WOMAC PROs from a Phase 2b LOR trial was performed to examine effect size (ES) changes.

Methods: Pain was assessed using the weekly average of daily Pain NRS and WOMAC Pain subscore. Subjects treated with 0.07 mg LOR were analyzed for "active" (walking on flat surface [A1], going up/down stairs [A2]) and "static" (in bed [A3], sitting/lying [A4], standing [A5]) pain PROs and compared with the primary 24-week trial outcomes of mean Pain NRS and summed mean WOMAC Pain subscore at Week 12. Baseline-adjusted analysis of covariance for WOMAC A1–A5 scores was conducted on LOR-treated subjects versus placebo (PBO) in the Full Analysis Set (FAS) and a target population (TP) with fixed baseline joint space width (JSW) [2–4] mm without widespread pain (WPI ≤4, Symptom Severity Score Question 2 ≤2).

Results: The primary trial analysis (N=231, KL grade 3 63.2%) demonstrated efficacy of LOR versus PBO for Pain NRS and WOMAC Pain (ES: 0.450 and 0.293, respectively). In the TP, Pain NRS and WOMAC A ES increased (0.637 and 0.410, respectively). Each WOMAC A item had lower ES than Pain NRS at Week 12. LOR treatment versus PBO showed significant improvements in ES of A1 (FAS: ES=0.315, *P*=0.028; TP: ES=0.421, *P*=0.035) and A2 (FAS: ES=0.392, *P*=0.006; TP: ES=0.510, *P*=0.011). A3–A5 did not show statistical improvement for LOR compared with PBO.

Conclusion: In this post hoc analysis, Pain NRS exhibited the greatest ES after treatment with 0.07 mg LOR versus compared with PBO, which were enhanced in the TP. "Active" items demonstrated greater ES than "static" items and the full WOMAC Pain domain, providing support for the hypothesized dimensional constructs in knee OA pain assessment.

Figure: Effect sizes for 0.07 mg LOR compared with PBO for the FAS and TP at Week 12.