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Efficacy and Safety from a Phase 2b Trial of Lorecivivint (SM04690), a Novel Intra-articular Wnt Pathway Inhibitor for the Treatment of Osteoarthritis of the Knee

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Background: A phase 2a study of SM04690, a small-molecule, intra-articular (IA) Wnt pathway inhibitor, demonstrated positive beneficial effects on knee pain, improved physical function, and increased medial joint space width (mJSW) at 52 weeks in key subgroups of subjects with knee osteoarthritis (OA) compared to placebo (PBO). A 24-week phase 2b study was conducted to refine patient-reported outcome (PRO) measures, target population, medication dose, and to evaluate safety. PRO results for Weeks 12 and 24 are presented here.

Methods: Subjects had ACR-defined knee OA, Kellgren-Lawrence (KL) grades 2-3, and Pain Numeric Rating Scale (NRS) scores ≥ 4 and ≤ 8 in the target knee and < 4 in the contralateral knee. A single IA injection of 2 mL SM04690 (0.03, 0.07, 0.15 or 0.23 mg), vehicle PBO, or sham (dry needle only) was given in the target knee at baseline. PRO endpoints included change from baseline in weekly average of daily pain in the target knee by NRS diary (NRS [0-10]), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain [0-100], WOMAC Function [0-100], and Patient Global Assessment (PtGA) (VAS [0-100]). This study was not formally powered, and sample size was based upon accepted dose-finding convention.

Results: 695 subjects (mean age 59.0 [± 8.5] years, BMI 29.0 [± 4.0] kg/m², female 58.4%, KL3 57.3%) were enrolled and dosed; 635 (91.4%) subjects completed the study. No meaningful differences in incidence of adverse events were seen between treatment and control groups.

In the "Full Analysis Set" (all randomized, dosed subjects), significant improvements from baseline to with PBO were observed in Pain NRS for 0.07 mg (Week 12 [$P=0.001$], Week 24 [$P=0.031$]) and 0.23 mg (Week 12 [$P=0.012$], Week 24 [$P=0.022$]) SM04690 dose groups (**Figure**). Similar improvements were observed in WOMAC Pain for 0.07 mg (Week 12 [$P=0.04$]) and 0.23 mg (Week 12 [$P=0.003$], Week 24 [$P=0.031$]) dose groups. For WOMAC Function, improvements were observed for 0.07 mg (Week 12 [$p=0.021$]) and 0.23 mg (Week 12 [$p=0.006$], Week 24 [$P=0.017$]) dose groups. PtGA improvements were observed for 0.07 mg (Week 12 [$P=0.031$]) and 0.23 mg (Week 12 [$P=0.010$], Week 24 [$P=0.033$]) dose groups.

Conclusion: SM04690, in development as a potential disease-modifying OA drug, showed in this phase 2b study statistically significant improvements from baseline in both the 0.07 mg and 0.23 mg dose groups compared to PBO for Pain NRS, WOMAC Pain, WOMAC Function, and PtGA. These data support the continued development of SM04690 as a potential treatment for knee OA. Phase 3 studies are being planned.

Figure. Actual observations over time and ladder plots depicting mean improvement (\pm 95% CI) of SM04690 compared to placebo adjusted for baseline for Pain NRS.

