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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 reduced knee pain and improved physical function and medial joint space width (mJSW) at 52 weeks in subgroups of subjects with unilateral symptomatic knee osteoarthritis (OA) compared to placebo (PBO).¹

Objective: 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: Study subject inclusion criteria required ACR-defined knee OA, Kellgren-Lawrence (KL) grades 2-3, and Pain Numeric Rating Scale (NRS) ≥ 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 Physical Function [0-100], and Patient Global Assessment (PtGA) [0-100]. Differences between active treatment groups and vehicle PBO were analyzed with baseline-adjusted analysis of covariance (ANCOVA).

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 subjects (91.4%) completed the study. No meaningful differences in the incidence of adverse events were observed between treatment and control groups.

In the Full Analysis Set, significant improvements from baseline compared to vehicle 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 Physical 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 vehicle PBO for Pain NRS, WOMAC Pain, WOMAC Physical Function, and PtGA. These data support the continued development of SM04690 as a treatment for knee OA. Phase 3 studies are being planned.

References:

1. Yazici Y, et al. *Arthritis Rheumatol.* 2017; 69 (suppl 10).

Figure. Actual observations over time and ladder plots depicting least squares mean (LSM) improvement of Pain NRS (\pm 95% CI) in SM04690 compared to vehicle PBO, adjusted for baseline.

