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Comparison of Intra-articular Sham and Vehicle Injection from a Phase 2b Trial of Lorecivivint (SM04690), a Small-Molecule Wnt Inhibitor, for Knee Osteoarthritis

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Background: Intra-articular (IA) saline or vehicle, commonly used as placebo (PBO) comparators in knee osteoarthritis (OA) randomized controlled trials (RCTs), have consistently demonstrated statistically significant and clinically meaningful improvements in patient-reported outcomes (PROs) from baseline. IA "PBO" effects have been attributed to contextual and/or possible physiological benefits of IA saline. These effects have called into question the interpretation of study results from IA therapeutic agents. Therefore, in a prospective, randomized controlled, 24-week Phase 2b study, the relative effects of a vehicle PBO injection were compared to those of a sham injection and SM04690, an IA Wnt pathway inhibitor in development as a potential disease-modifying knee osteoarthritis drug (DMOAD). Additionally, the potential unblinding impact of PBO or sham was tested. Full primary study results are presented separately.

Methods: Subjects had 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. Subjects were randomized to receive a blinded, single IA injection of 2 mL vehicle (PBO, 0.5% carboxymethylcellulose sodium and 0.05% polysorbate 80 in pH 7.4 phosphate buffered saline), sham (dry needle only), or one of four doses of SM04690 (0.03 mg, 0.07 mg, 0.15 mg, 0.23 mg) in the target knee at baseline. PROs included change from baseline in weekly average of daily target knee pain 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]). Immediately following the injection and again at Week 24, subjects were asked to identify which treatment (PBO, sham, or SM04690) they thought they received. The accuracy of subjects' responses was compared using Bang's Blinding Index (BBI) **(Table)**, a method to evaluate blinding across clinical trial treatment arms. The index scale is -1< 0 <+1, with values toward -1 indicating more subjects incorrectly guessing treatment allocations, toward 0 indicating perfect blinding, and toward +1 indicating more subjects correctly identifying treatment allocations.

Results: 695 subjects (mean age 59.0 [±8.5] years, BMI 29.0 [±4.0] kg/m^2, female 58.4%, KL3 57.3%) were injected; 635 (91.4%) subjects completed the study. No meaningful differences in incidence of adverse events were seen among treatment groups or between vehicle or sham groups.

The primary endpoint of change from baseline compared to PBO in Pain NRS, WOMAC Pain, WOMAC Function, and PtGA at 24 weeks was met for SM04690 0.23 mg and 0.07 mg (Pain NRS only) doses. In the Full Analysis Set population of PBO and sham subjects (N=233; 207 (89%) completed), both the PBO and sham subjects had statistically significant and clinically meaningful changes in comparison to baseline. However, no clinically meaningful or significant differences were evident between the two groups' changes in Pain NRS, WOMAC Pain, WOMAC Function, or PtGA **(Figure)** at any time point. BBI did not indicate unblinding, however, increased negative values were noted for PBO and sham groups versus an increased positive value for the SM04690 group over 24 weeks **(Table)**.

Conclusion: Subjects with knee OA receiving a single IA injection of PBO reported no substantial or significant differences in changes from baseline in knee OA PROs compared to subjects who received sham injections. Furthermore, from BBI data, subjects appeared unable to discern which non-drug injection they received (either PBO or sham). While IA PBO injections often yield statistical and clinically meaningful improvements from baseline in knee OA study PROs, these data suggested the effects were "contextual," meaning they resulted from the injection procedure rather than from a direct therapeutic effect of saline in the joint.

Figure: Observations over time depicting mean improvements (± 95% CI) of PBO compared to sham injection adjusted for baseline. A. Pain NRS, B. WOMAC Pain, C. WOMAC Function, and D. Patient Global in all subjects.

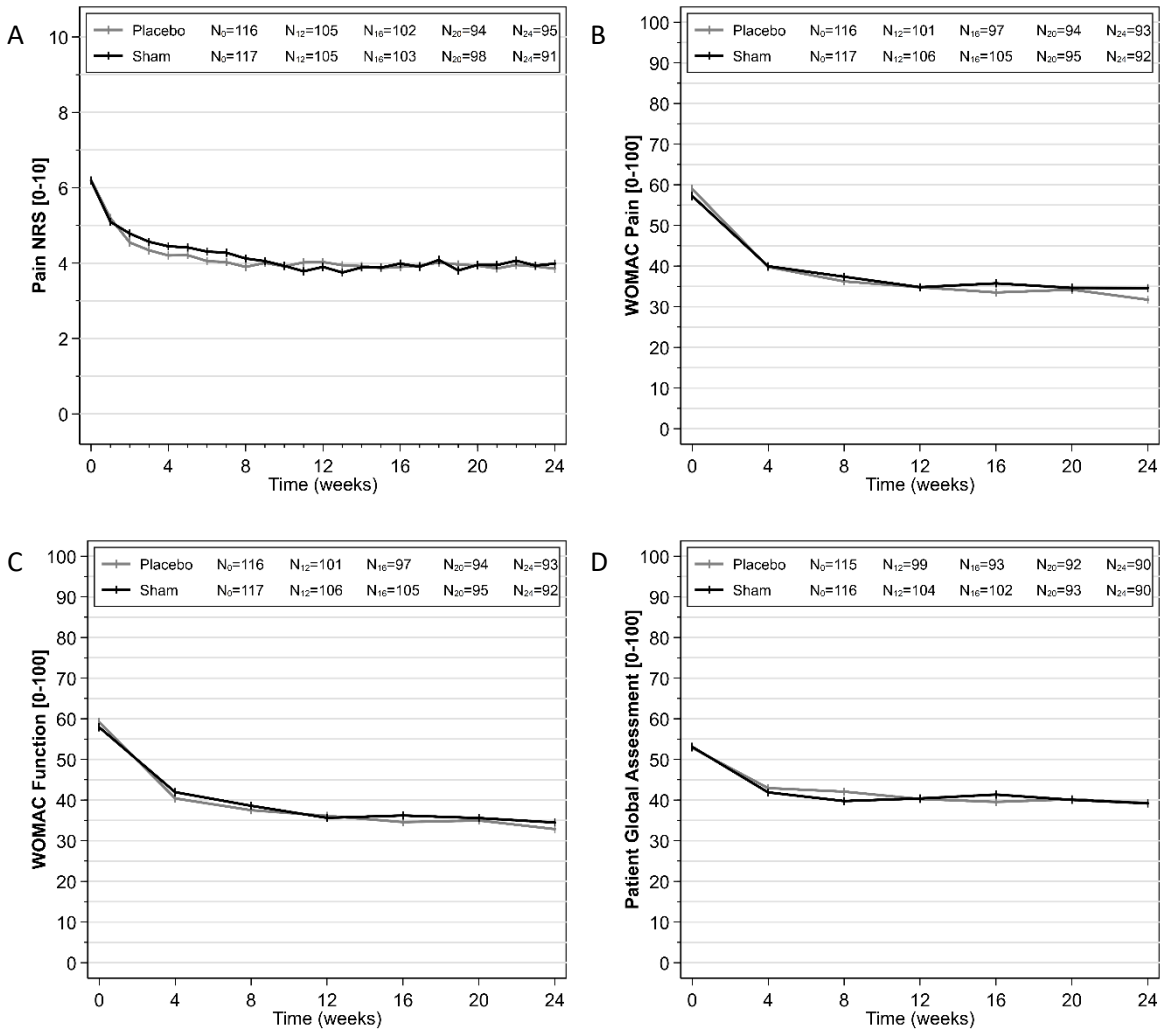

Table:

		Subject Response					
Visit	**Planned Treatment**	**SM04690**	**Vehicle**	**Sham**	**Don't Know**	**Total**	**Bang's BI[a]**
Day 1	SM04690	111	17	13	321	462	0.175
	Vehicle	23	2	4	87	116	-0.216
	Sham	29	7	3	78	117	-0.282
	Total	163	26	20	486	695	NA
Week 24	SM04690	193	50	37	147	427	0.248
	Vehicle	47	16	7	32	102	-0.373
	Sham	43	13	11	38	105	-0.429
	Total	283	79	55	217	634	NA

[a] Bang's Blinding Index (BI) determines the percentage of unblinding that is beyond chance
- BI = 1 represents complete unblinding
- BI = 0 represents random guessing
- BI = –1 represents opposite guessing