

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

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Poster #THU0414

Background

- Intra-articular (IA) saline or vehicle, used as placebo (PBO) comparators in knee osteoarthritis (OA) trials, have 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 saline¹, calling into question the interpretation of study results from putative IA therapeutic agents
- In a prospective, randomized controlled, 24-week Phase 2b study of lorecivivint (LOR), an IA CLK/DYRK1A inhibitor that modulates the Wnt pathway, the relative effects of vehicle PBO injection were prospectively compared to those of a sham injection
- The potential unblinding impact of PBO or sham was also tested
- Full study results from LOR, in development as a potential disease-modifying knee osteoarthritis drug, are presented separately (THU0458)

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, 2 mL, IA vehicle injection (PBO, 0.5% carboxymethylcellulose sodium, 0.05% polysorbate 80 in pH 7.4 PBS), sham injection (dry needle only), or LOR injection (0.03 mg, 0.07 mg, 0.15 mg, 0.23 mg) in the target knee at Day 0
- PROs included change from baseline in weekly average of daily OA target knee pain by NRS [0-10], WOMAC Pain [0-100], WOMAC Function [0-100], and Patient Global Assessment (PtGA) [0-100]
- Immediately following injection and at Week 24, subjects were asked to identify which treatment (PBO, sham, or LOR) they thought they had received
 - Subject responses were compared using Bang's Blinding Index (BBI) (Table 1). The BBI scale is $-1 < 0 < +1$
 - Values toward -1 indicate more subjects incorrectly guessing treatment allocations, toward 0 indicate perfect blinding, and toward +1 indicate more subjects correctly identifying treatment allocations

Results

Figure 1. PROs: Change from baseline, PBO compared to sham over time

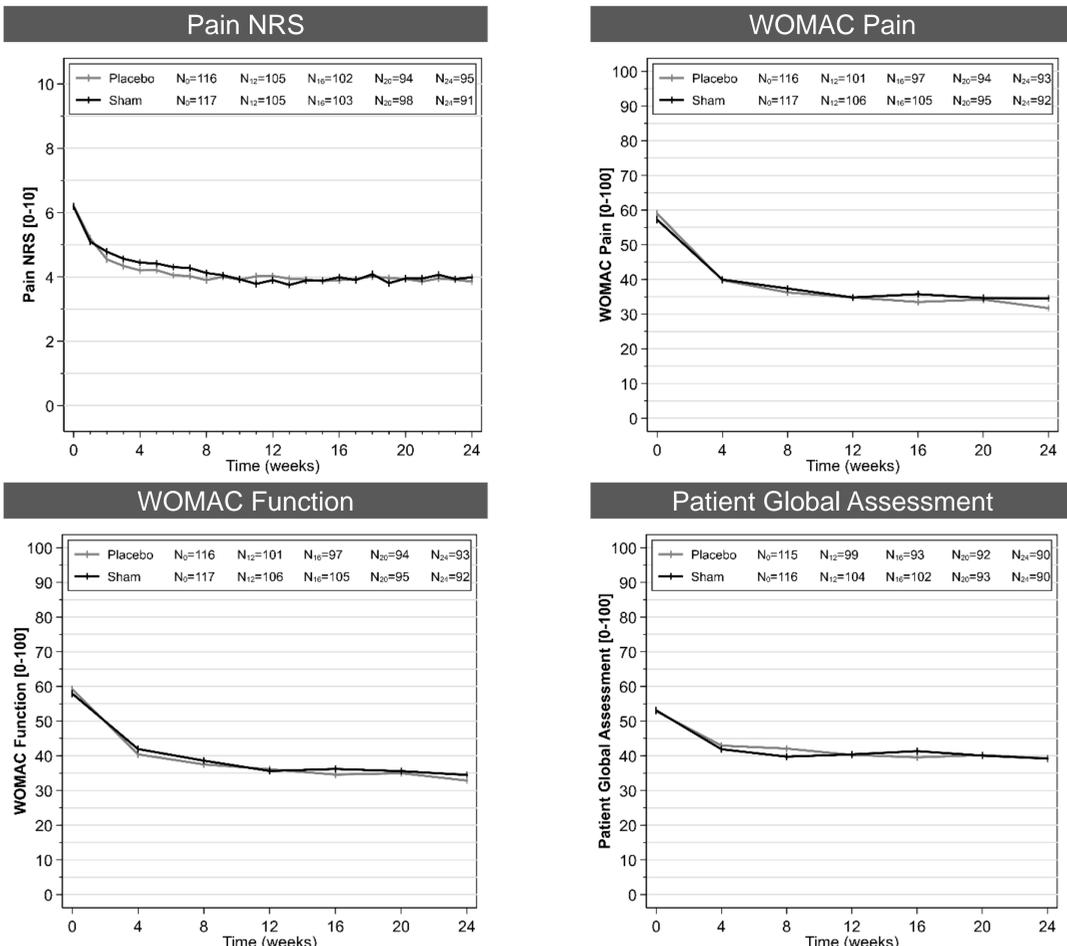


Figure 1. Observations over time depicting baseline-adjusted mean improvements in PROs of PBO compared to sham injections (FAS).

Table 1. Subjects' treatment identification accuracy using BBI

Visit	Planned Treatment	Subject Response				Total	Bang's BI*
		SM04690	Vehicle	Sham	Don't Know		
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

* 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

Table 1. Compared subjects' treatment identification (PBO, sham, or lorecivivint) accuracy using BBI.

Conclusions

- To our knowledge, this is the first prospective comparison of the effects of IA injections of PBO vs. sham on PROs
- Subjects who received IA PBO reported no differences in change from baseline in PROs compared to those who received IA sham
- From the BBI data, subjects appeared unable to discern which injection (PBO or sham) they received
- These data suggested that the observed PRO effects were "contextual," meaning that they resulted from the injection procedure rather than from a direct therapeutic effect of saline in the joint

Results

- 635 out of 695 subjects completed the study (mean age 59.0 ± 8.5 years, BMI 29.0 ± 4.0 kg/m², female 58.4%, KL3 57.3%)
- Adverse events rates were similar between groups
- The primary endpoints of change from baseline compared to PBO in Pain NRS, WOMAC Pain, WOMAC Function, and PtGA at 24 weeks were met for LOR 0.23 mg and 0.07 mg (Pain NRS only) doses
- In the Full Analysis Set (FAS) of PBO and sham subjects (N=233; 207 [89%] completed), both groups demonstrated statistically significant changes $> MCID (>10\%)^2$ at all time points compared to baseline
- No meaningful differences were evident between the two groups' changes in Pain NRS, WOMAC Pain, WOMAC Function, or PtGA at any time point (Figure 1)
- BBI did not indicate unblinding, however, increased negative values were observed for PBO and sham groups versus an increased positive value for the LOR group at 24 weeks (Table 1)

References

- Altman RD, et al. *Semin. Arthritis Rheum.* 2016.
- Devji T, et al. *BMJ Open.* 2017.

All authors are employees, shareholders, or consultants of Samumed, LLC. Other disclosures are listed in the published abstract.

