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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Poster #340

Background

- Intra-articular (IA) saline or vehicle, used as placebo (PBO) comparators in knee osteoarthritis (OA) trials, 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.[1] These effects have called into question the interpretation of study results from putative IA therapeutic agents
- 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 lorecivivint, an IA Wnt pathway inhibitor in development as a potential disease-modifying knee osteoarthritis drug (DMOAD)
- 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 to ≤8 in target knee and <4 in contralateral knee
- Subjects were randomized to receive a blinded, single, IA, 2 mL vehicle injection (PBO, 0.5% carboxymethylcellulose sodium and 0.05% polysorbate 80 in pH 7.4 phosphate buffered saline), sham injection (dry needle only), or a dose of lorecivivint (0.03 mg, 0.07 mg, 0.15 mg, or 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 lorecivivint) they thought they received. Subjects' 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

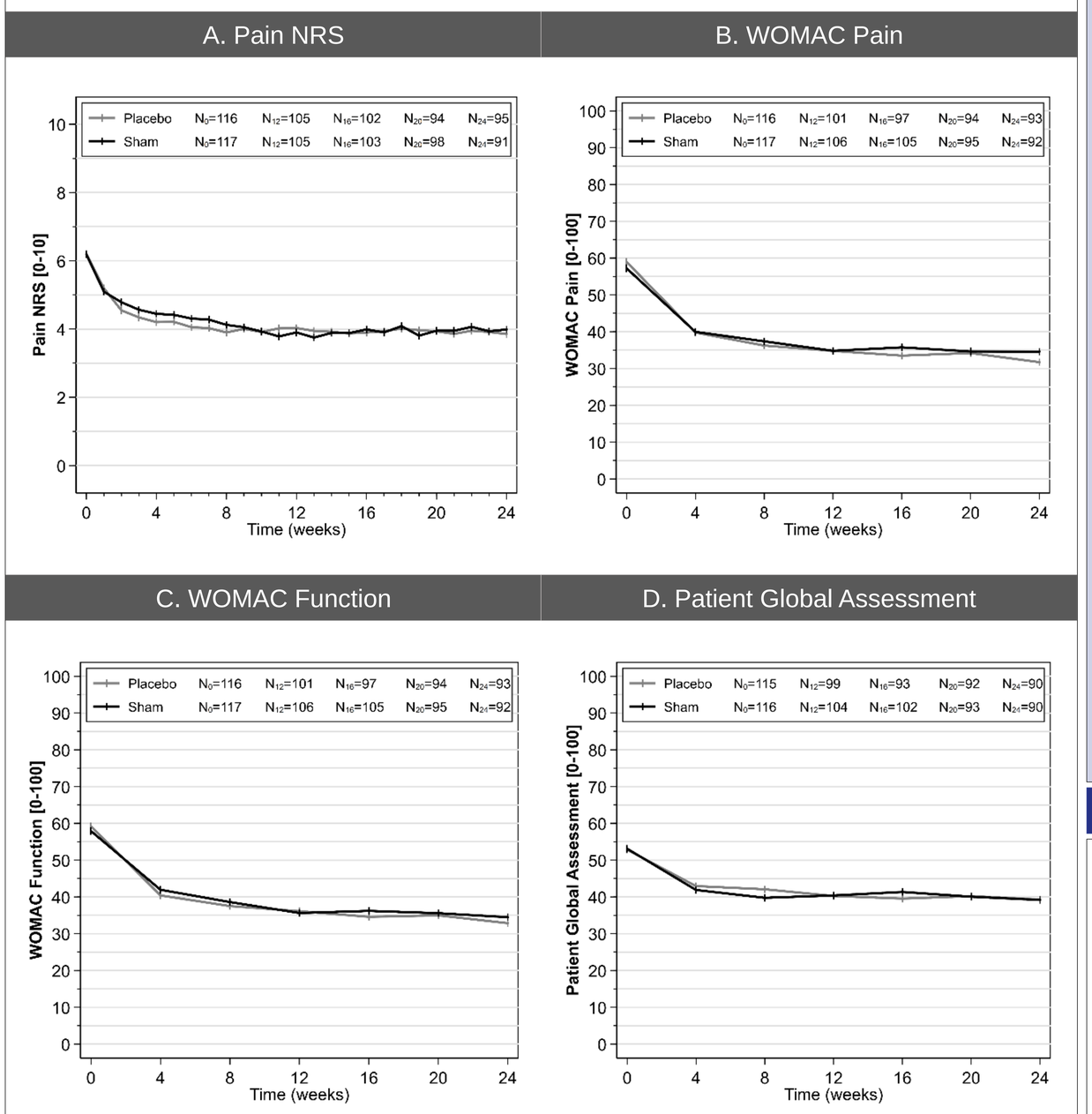

Figure 1. *Observations over time depicting baseline-adjusted mean improvements of PBO compared to sham injections*

Table 1. Subjects' treatment identification accuracy using BBI

		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

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

Conclusions

- **Subjects with knee OA receiving a single IA PBO injection reported no substantial differences in changes from baseline knee OA PROs compared to subjects who received a single IA sham injection**
- **Based on the BBI data, subjects appeared unable to discern which non-drug injection they received (either PBO or sham)**
- **While IA PBO injections often yield statistically 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**
- **To our knowledge, this is the first prospective comparison of the effect of PBO vs. sham on PROs**

Results

- 635/695 subjects (mean age 59.0 [±8.5] years, BMI 29.0 [±4.0] kg/m^2, female 58.4%, KL3 57.3%) completed the study
- No meaningful differences in incidences of adverse events were seen among any 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 lorecivivint 0.23 mg and 0.07 mg doses (Pain NRS only)
- 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[2] (>10%) at all time points compared to baseline
- However, no meaningful differences were evident between the two groups' changes in Pain NRS, WOMAC Pain, WOMAC Function, or PtGA **(Figure 1)** at any time point
- BBI did not indicate unblinding, however, increased negative values were observed for PBO and sham groups versus an increased positive value for the lorecivivint group at 24 weeks **(Table 1)**

References

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

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