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

Yazici Y, Tambiah J, Swearingen C, Kennedy S, Strand V, Cole B, Hochberg M, Bannuru R, McAlindon T

All authors are employees or shareholders of Samumed, LLC

Potential pain effect of IA saline on IA therapies

Figure 1. IA saline effect compared with the MCID threshold range

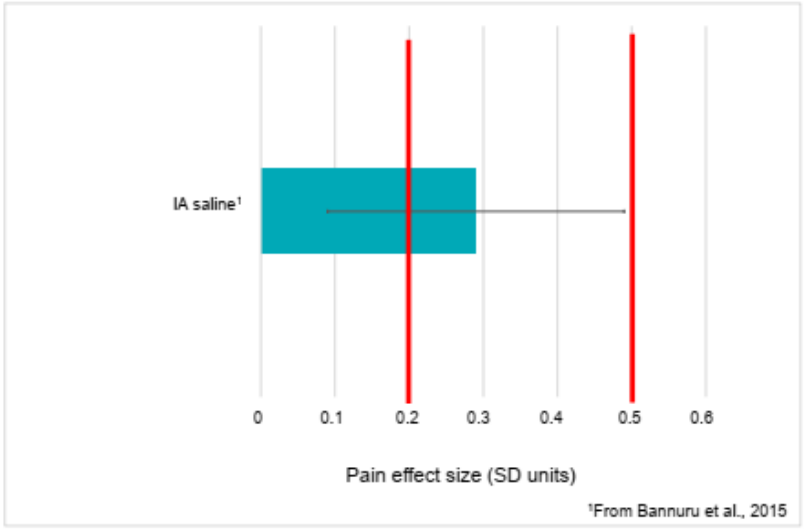


Figure 2. Unadjusted pain effect estimates for pharmacologic knee OA therapies

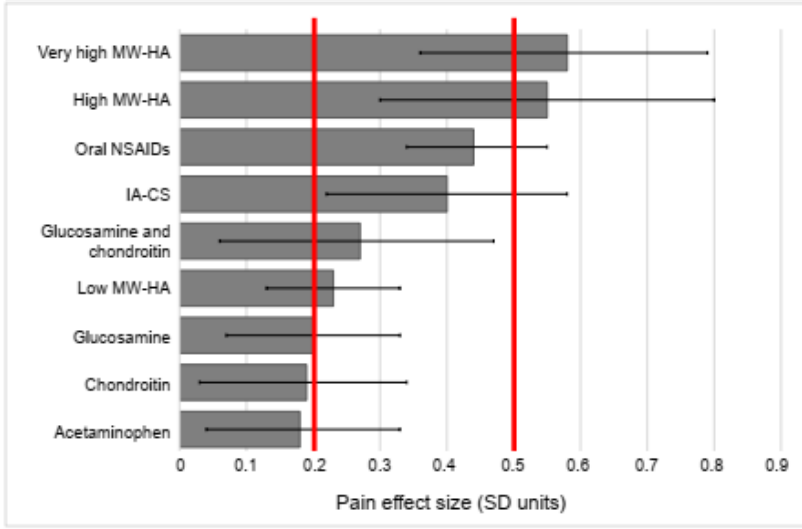
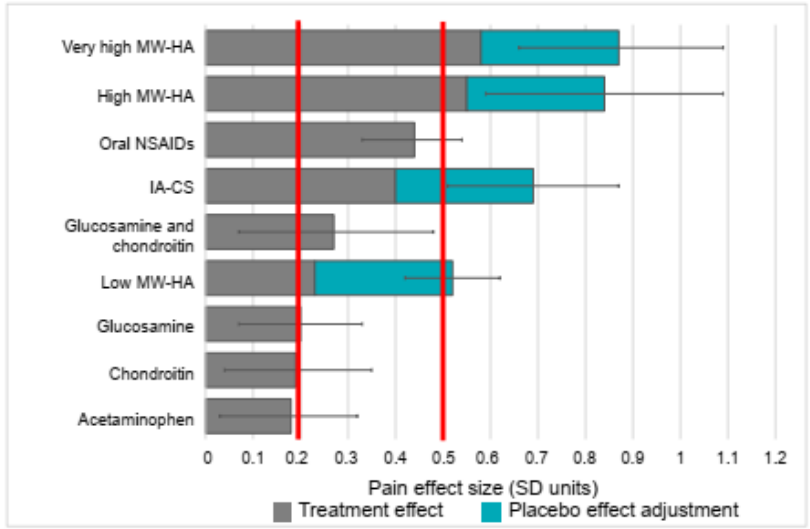


Figure 3. Pain effect estimates adjusted for IA saline effect



Red lines depict the range of plausible MCID cutoff values for clinical significance.

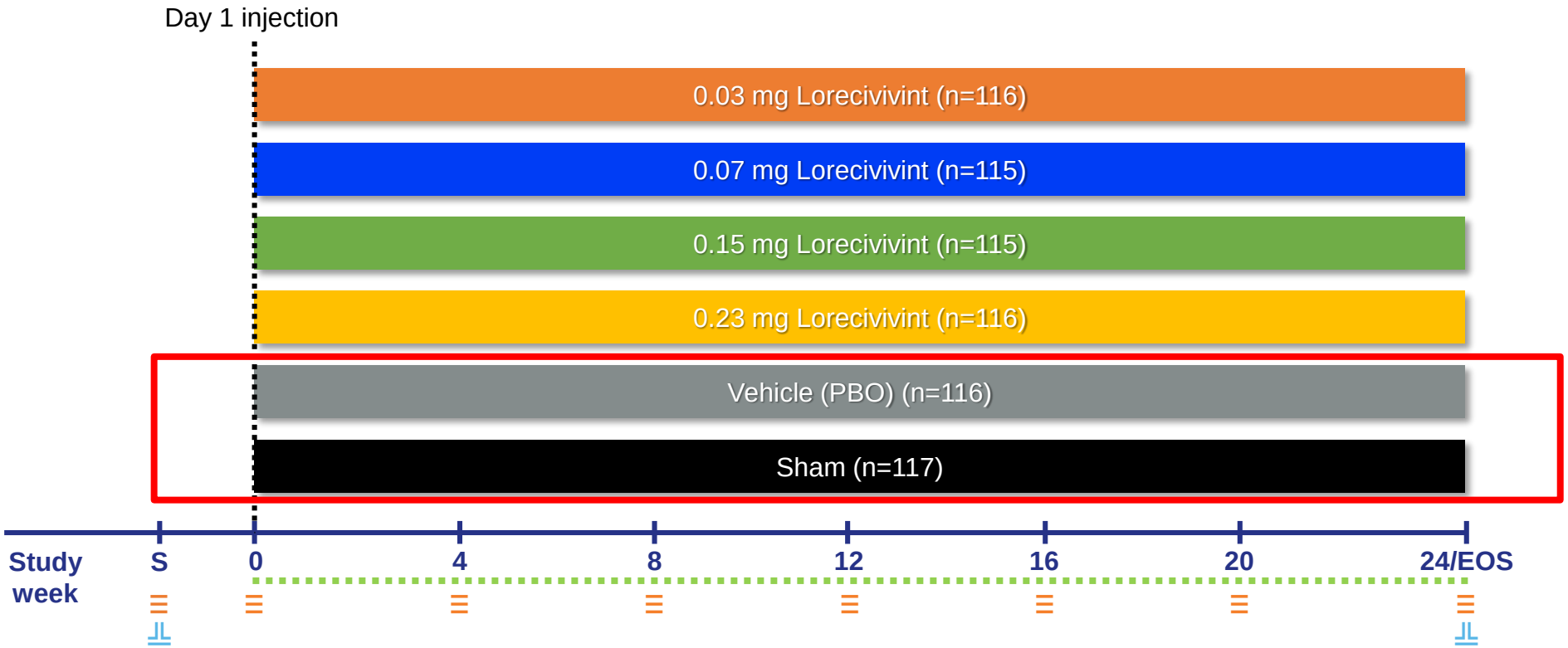
1. Simsek I, et al. *Ann Rheum Dis*. 2018;77(Suppl 2):1135

Does IA vehicle show symptomatic benefit over dry needle?

Hypothesis: There is no difference in treatment response between PBO and sham

- In a prospective, randomized, 24-week Phase 2b study of lorecivivint (LOR; SM04690)
  - Effects of IA vehicle PBO were compared to sham (dry needle) injection
  - Potential unblinding impact was also tested
  - Full study results from LOR, a potential disease-modifying knee OA drug, are presented separately

Lorecivivint Phase 2b study design



≡	**Clinical assessments:**	Daily Pain NRS, WOMAC Function, WOMAC Pain, Patient Global Assessment, Physician Global Assessment, KOOS, KOOS-PS, daily NSAID
⫫	**Imaging:**	Knee X-ray
···	**Safety assessments:**	AEs, vital signs, physical exam, laboratory panels

Main study results

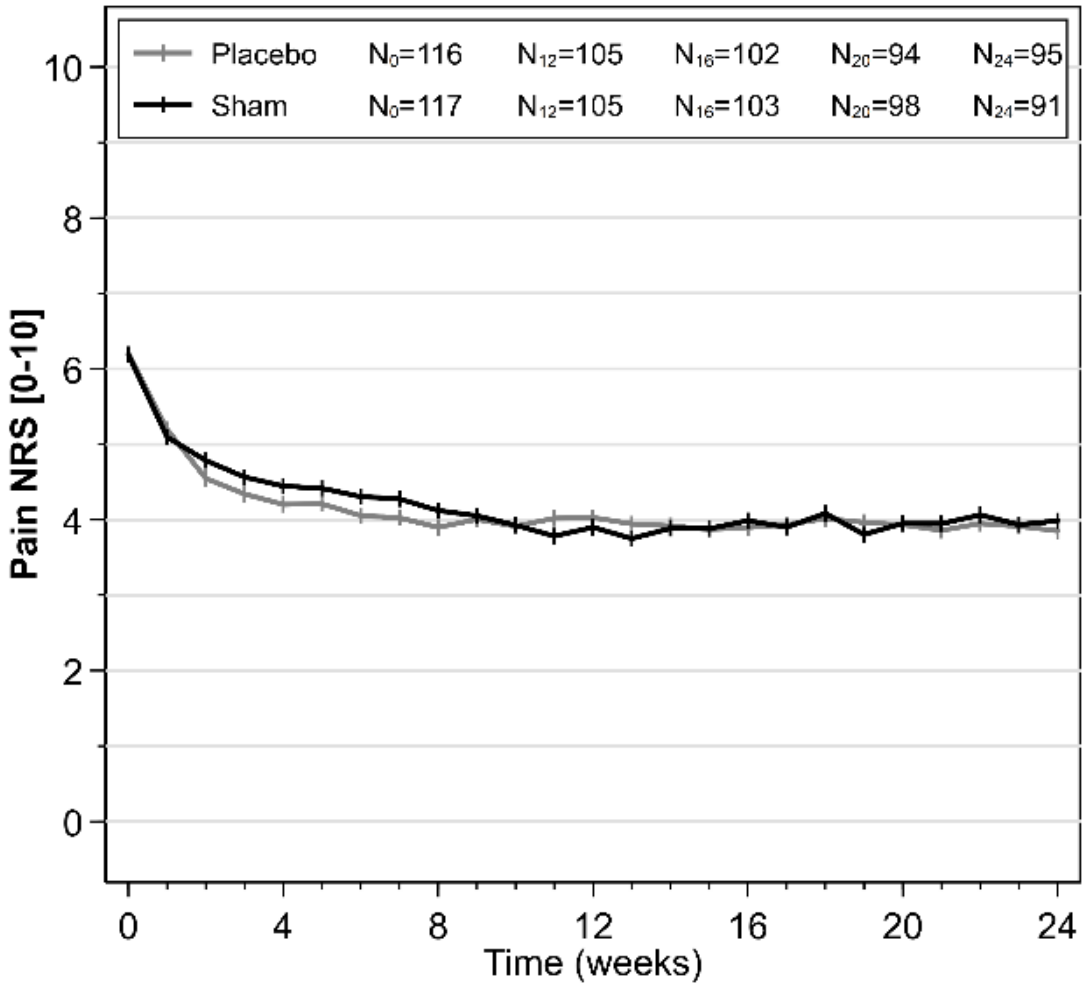
- Primary endpoints of Pain NRS, WOMAC Pain/Function, and PtGA at 24 weeks were met for LOR 0.23 mg and 0.07 mg doses (Pain NRS only) compared to PBO
- Incidence of adverse events was similar between groups
- PBO vs. sham: N=233; 207 subjects [89%] completed the study

Subject Characteristics			
		Vehicle	**Sham**
N		116	117
Age at Consent (years)*		60.1 (9.0)	59.0 (8.0)
BMI (kg/m^2)*		28.62 (4.29)	28.97 (3.84)
Female		63 (55.3)	72 (60.0)
Race	*White*	89 (78.1)	86 (71.7)
	Black / AA	16 (14.0)	27 (22.5)
	Asian	6 (5.3)	3 (2.5)
Hispanic / Latino		16 (14.0)	24 (20.0)
KL3		71 (62.3)	59 (49.2)

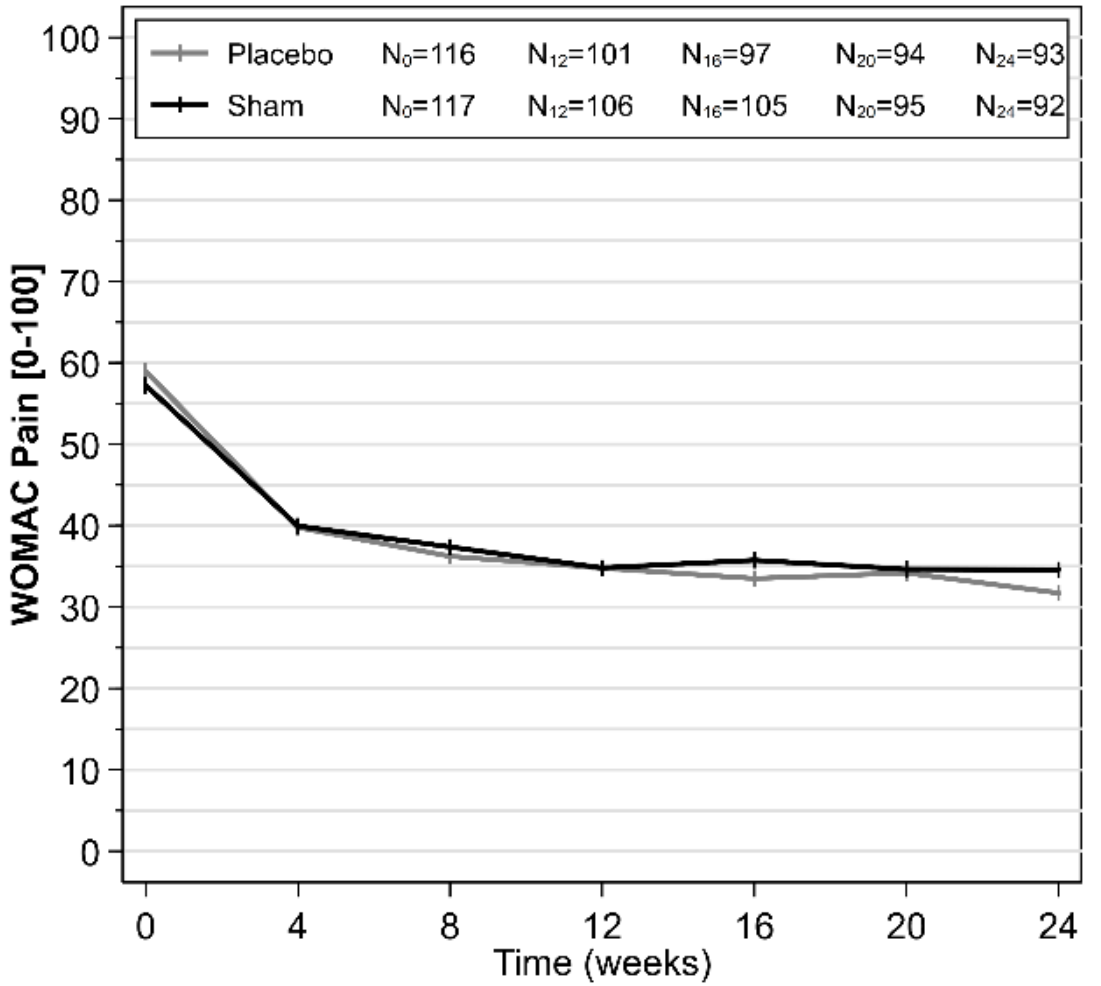
*Mean (SD) reported. Otherwise n (%) reported.

No differences in PROs between PBO and sham

Pain NRS



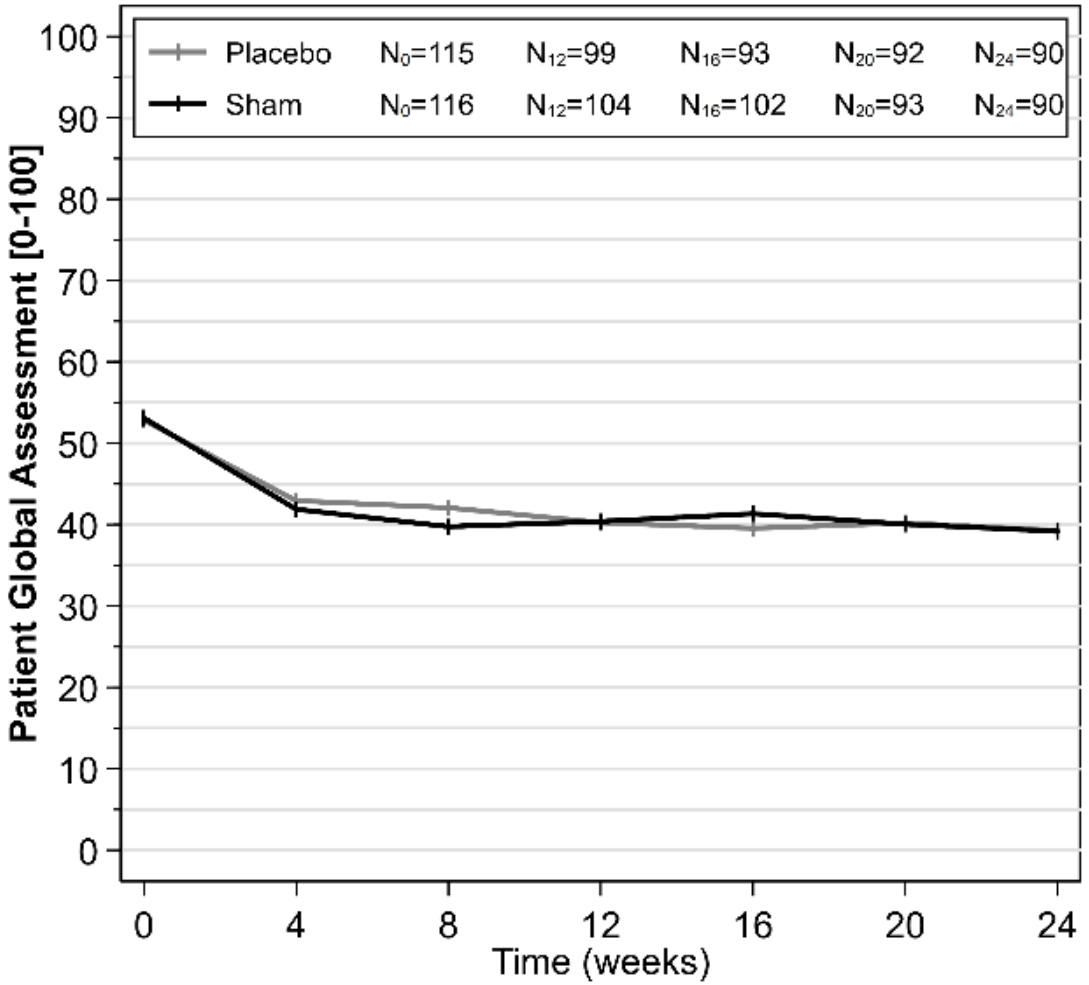
WOMAC Pain



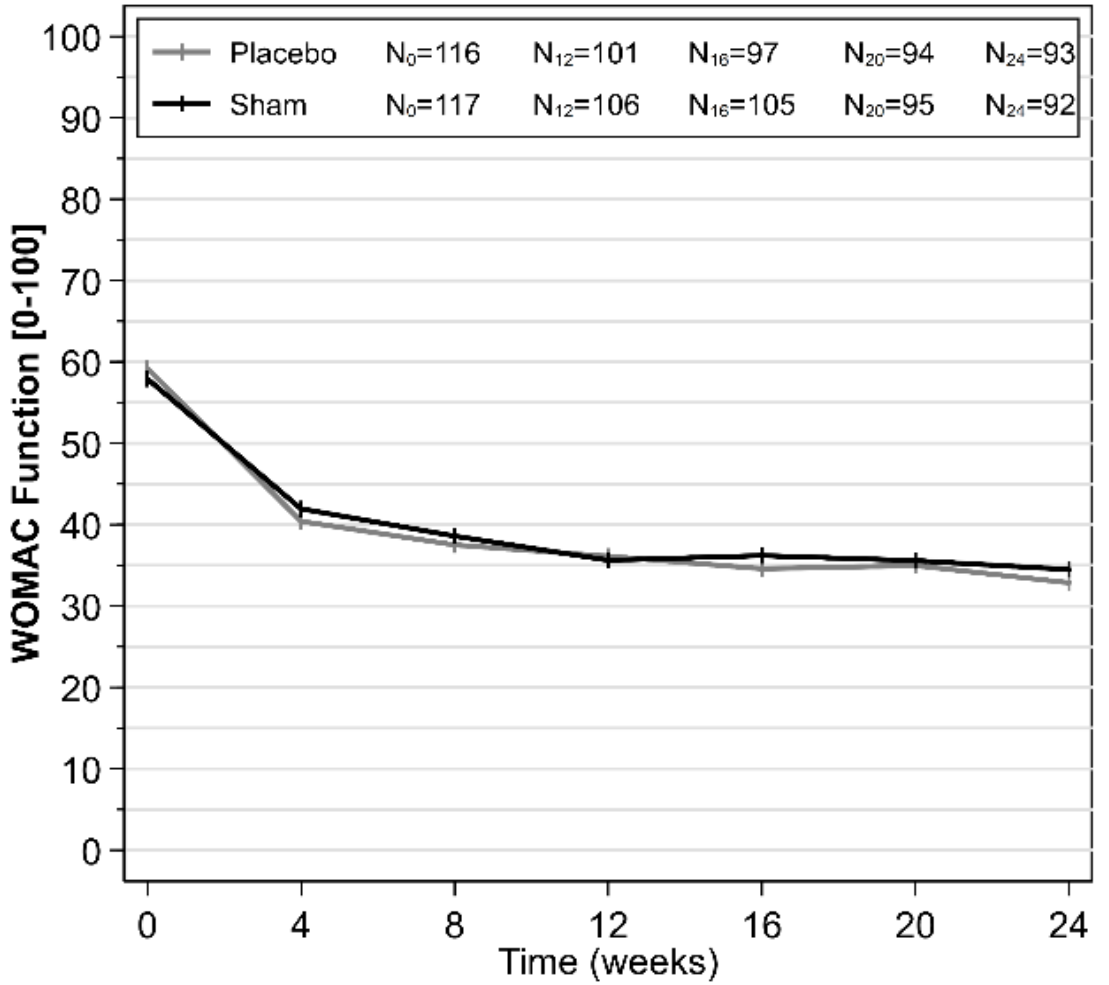
Observations over time depicting baseline-adjusted mean improvements in PROs of PBO compared to sham injections (FAS)

No differences in PROs between PBO and sham

Patient Global



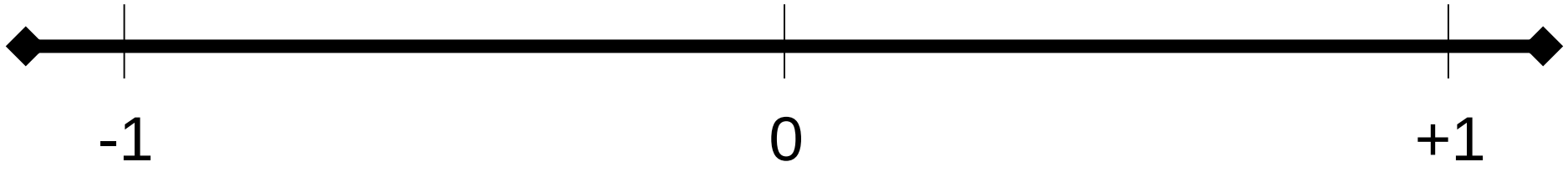
WOMAC Function



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

Bang's Blinding Index

- 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)
  - BBI scale is –1 ≤ 0 ≤ +1



Subjects ***incorrectly*** guessing treatment allocations

Perfect blinding

Subjects ***correctly*** identifying treatment allocations

No differences were detected between PBO and sham

Compared 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

Subjects were unable to discern which treatment they received

In PBO and sham subjects

- No meaningful differences were evident between groups' changes in Pain NRS, WOMAC Pain and Function, or PtGA

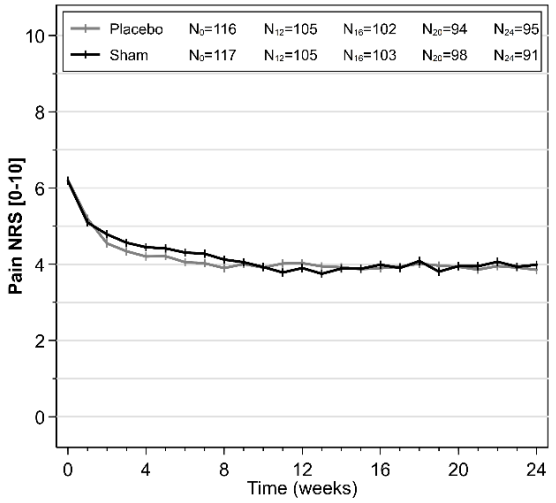
- Both demonstrated statistically significant changes (>MCID[1] at all time points) compared to baseline

- BBI did not indicate unblinding

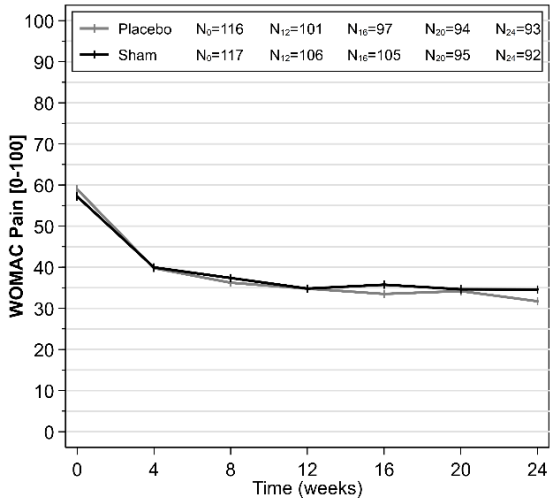
1. Devji T, et al. *BMJ Open*. 2017

IA PBO effects on PROs were “contextual”

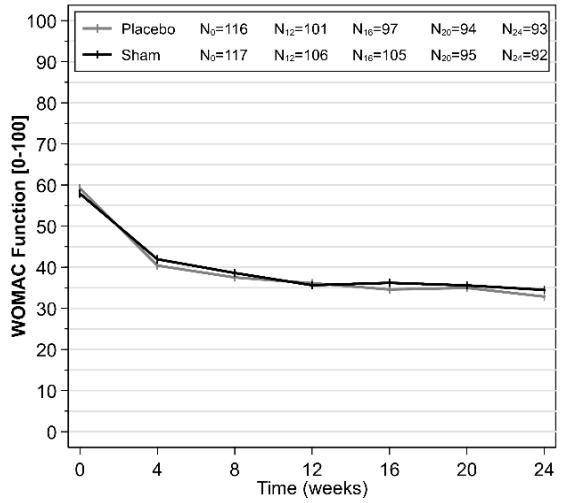
Pain NRS



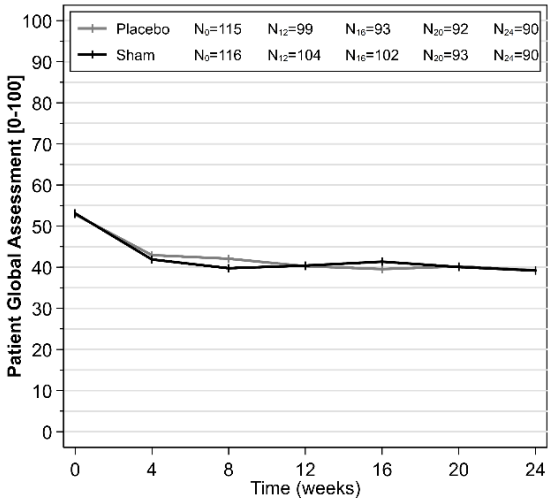
WOMAC Pain



WOMAC Function



Patient Global Assessment



- This is the first prospective comparison of PBO vs. sham IA injections
- Observed PRO effects appeared to be “contextual,” meaning they resulted from the injection procedure rather than from therapeutic effects of saline

Thank you