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

- **Lorecivivint (LOR, SM04690) is an intra-articular (IA), small-molecule Wnt pathway inhibitor in development as a potential disease-modifying knee OA drug (DMOAD)**
- Preclinical studies demonstrated that LOR inhibited inflammation and cartilage degradation compared to vehicle[1]
- A phase 2a study demonstrated positive effects on Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain, WOMAC Function, and medial joint space width (mJSW) at 52 weeks in key subgroups for LOR compared to placebo (PBO)[1]
- **A 24-week phase 2b study was performed to refine target population and dose and to evaluate patient-reported outcomes (PROs) and safety**

Methods

- Subjects had ACR-defined knee OA, Kellgren-Lawrence (KL) grades 2-3, and target knee Pain Numeric Rating Scale (NRS) ≥4 and ≤8, contralateral knee <4
- A single, 2 mL, IA LOR injection (0.03, 0.07, 0.15, 0.23 mg) or vehicle (PBO) was given in the target knee
- Subjects were stratified 50% unilateral symptomatic, 50% bilateral symptomatic, 80% Widespread Pain Index (WPI) ≤4, Symptom Severity Score (SSC) ≤2, and 20% WPI >4, SSC >2
- PRO endpoints included change from baseline in weekly average daily target knee Pain NRS [0-10], WOMAC Pain [0-100], WOMAC Function [0-100], and Patient Global Assessment (PtGA) [0-100]
- Radiographic endpoint of mJSW change from baseline was measured at Week 24
- Sample size was based upon accepted dose-finding statistical practice[2]

Conclusions

- **LOR showed statistically significant improvements in pain and function compared to PBO**
  - **0.07 mg and 0.23 mg are potentially efficacious doses**
- **LOR appeared well tolerated**
- **Improvements in pain and function suggest that LOR has a potential role in the treatment of knee OA signs and symptoms**
- **Further studies of LOR as a potential DMOAD are underway. These studies will evaluate the effects of LOR on knee OA structure and morphology**

Results

Subject Characteristics

	lorecivivint					
	0.03 mg	0.07 mg	0.15 mg	0.23 mg	Placebo	Sham
N	116	115	115	116	116	117
Age at Consent (years)*	57.9 (7.9)	59.9 (8.6)	58.4 (8.3)	58.5 (9.0)	60.1 (9.0)	59.0 (8.0)
BMI (kg/m^2)*	29.2 (3.8)	29.1 (3.6)	29.4 (4.1)	28.5 (4.4)	28.6 (4.3)	29.0 (3.8)
Female	76 (65.5%)	66 (57.4%)	69 (60.0%)	61 (52.6%)	64 (55.2%)	70 (59.8%)
KL Grade 3	63 (54.3%)	74 (64.3%)	68 (59.1%)	63 (54.3%)	72 (62.1%)	58 (49.6%)
Unilateral Symptomatic	59 (50.9%)	62 (53.9%)	63 (54.8%)	63 (54.3%)	61 (52.6%)	62 (53.0%)
Widespread Pain Negative	92 (79.3%)	93 (80.9%)	90 (78.3%)	93 (80.2%)	93 (80.2%)	94 (80.3%)

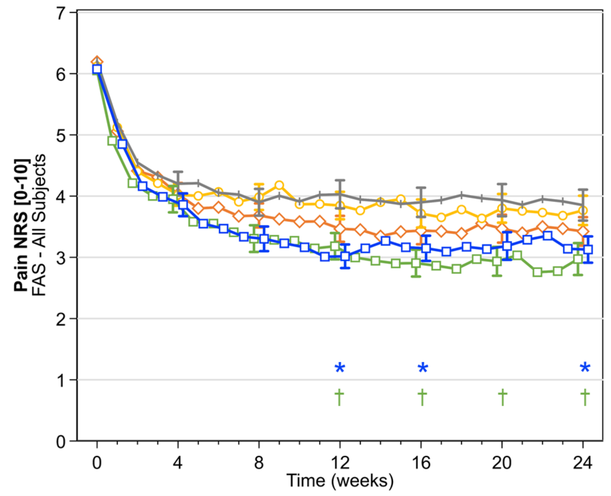
*Mean (SD) reported. Otherwise N (%) reported.

mJSW (FAS)

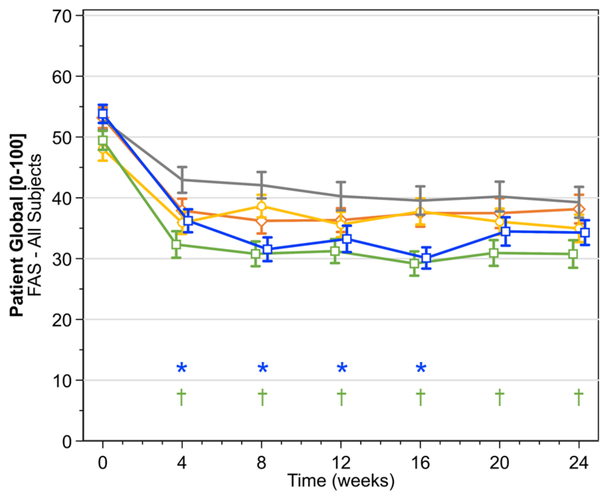
	0.03 mg lorecivivint	0.07 mg lorecivivint	0.15 mg lorecivivint	0.23 mg lorecivivint	PBO
N Baseline Mean mm (SD)	116 3.30 (1.26)	115 3.16 (1.10)	115 3.26 (1.24)	116 3.27 (1.08)	116 3.44 (1.31)
N Week 24 Change Mean mm (SD)	104 0.02 (0.72)	109 -0.11 (0.53)	103 0.11 (0.92)	101 -0.03 (0.45)	96 -0.01 (0.60)

- 635 / 695 subjects completed the study
- Positive PRO responses were seen in 0.03, 0.07, and 0.23 mg dose groups compared to PBO with statistical significance achieved in the 0.07 mg dose at most time points and 0.23 mg dose at all time points (**Figure 1**)
- No mean changes in mJSW from baseline to Week 24 in PBO or treatment groups achieved the minimal detectable difference of 0.13 mm
- LOR appeared safe and well tolerated. Six serious AEs in 6 subjects were observed and deemed unrelated by study physicians

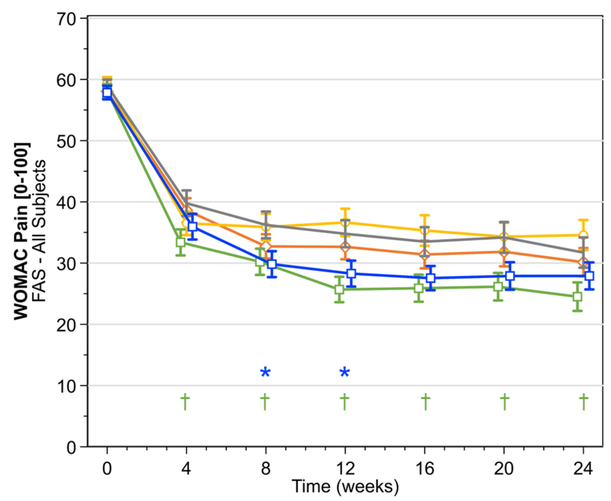
Pain NRS (FAS)



Patient Global (FAS)



WOMAC Pain (FAS)



WOMAC Function (FAS)

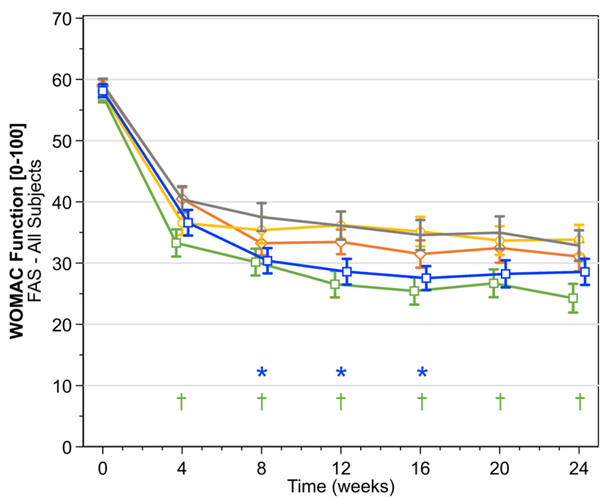


Figure 1. PROs: Change from baseline compared to PBO over time

Figure 1. *Comparisons of LOR vs. PBO using a baseline-adjusted ANCOVA, presented at 4-week intervals. Data on X-axis offset for visual clarity.*

References

1. Yazici Y, et al. *Arthritis Rheumatol.* 2017; 69 (suppl 10).
2. Ting N, et al. Phase II Clinical Development of New Drugs. Singapore: Springer; 2017.

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