Efficacy and Safety from a Phase 2b Trial of Lorecivivint (LOR; SM04690), a Novel Intra-articular Wnt Pathway Inhibitor for the Treatment of Osteoarthritis of the Knee

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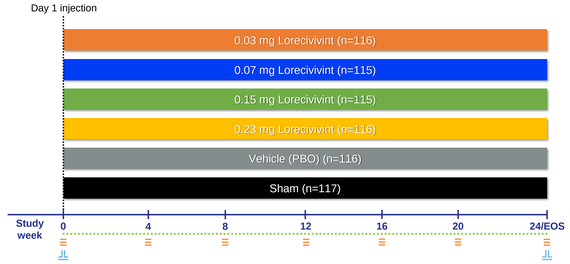
Background

- **Lorecivivint (LOR, SM04690) is an intra-articular (IA), small-molecule CLK/DYRK1A inhibitor that modulates the Wnt pathway; LOR is in development as a potential disease-modifying knee OA drug**
- Preclinical studies demonstrated that LOR inhibited inflammation and cartilage degradation compared to vehicle[1]
- A Phase 2a study demonstrated that LOR was well tolerated and had 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 of LOR compared to placebo (PBO)[2]
- **A 24-week Phase 2b study was performed to refine target population and dose as well as to evaluate patient-reported outcomes (PROs) and safety**

Methods

- Subjects with 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 <4 were given a single, 2 mL, IA LOR injection (0.03, 0.07, 0.15, 0.23 mg) or vehicle (PBO) injection in the target knee
- Subjects were stratified 50% unilateral symptomatic; 50% bilateral symptomatic; 80% Widespread Pain Index (WPI) ≤4, Symptom Severity Score (SSC) ≤2; 20% WPI >4 or 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]
- Structural endpoint mJSW change from baseline was measured at Week 24
- Sample size was based upon accepted dose-finding statistical practice[3]

LOR Phase 2b study design



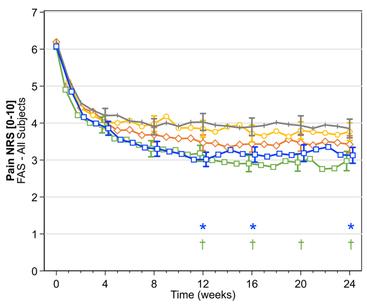
Clinical assessments: Daily Pain NRS, WOMAC Function, WOMAC Pain, Patient Global Assessment, Physician Global Assessment, KOOS, KOOS-PS, daily NSAID

Imaging: Knee x-ray

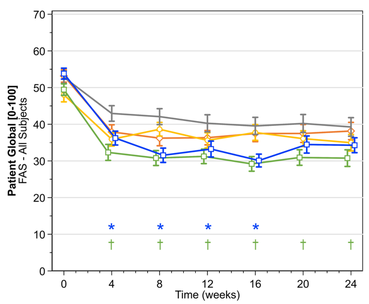
Safety assessments: AEs, vital signs, physical exam, laboratory panels

Results

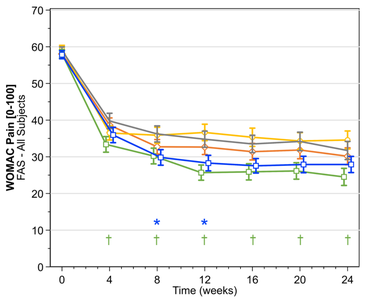
Pain NRS



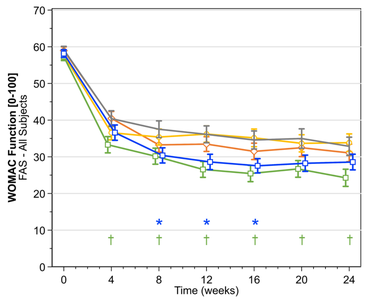
Patient Global



WOMAC Pain



WOMAC Function



*Lorecivivint 0.07 mg $p<0.05$ †Lorecivivint 0.23 mg $p<0.05$

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

mJSW (FAS)

	Lorecivivint				Placebo
	0.03 mg	0.07 mg	0.15 mg	0.23 mg	
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)

Conclusions

- **LOR showed statistically significant improvements in two dose groups for pain and function compared to PBO**
  - **0.07 mg and 0.23 mg doses met Pain NRS primary endpoint**
- **LOR appeared well tolerated**
- **Improvements in pain and function suggested that LOR has a potential role in the treatment of knee OA signs and symptoms**
- **Phase 3 studies of LOR as a potential disease-modifying OA drug are ongoing**

Results

Subject Characteristics

	Lorecivivint				Placebo	Sham
	0.03 mg	0.07 mg	0.15 mg	0.23 mg		
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.

- 635 out of 695 subjects completed the study
- All subjects achieved improvement over baseline >MCID (10%)[4] at all post-injection time points
- In the Full Analysis Set (FAS) population, positive responses were seen in 0.03 mg, 0.07 mg, and 0.23 mg dose groups compared to PBO, with statistical significance achieved in 0.07 mg at many and 0.23 mg groups at all time points **(Figure 1)**
- The structural endpoint of change from baseline in mJSW compared to PBO was not achieved. No mean changes in mJSW for any group beyond a minimal detectable difference[5] of 0.13 mm were observed
- LOR appeared safe and well tolerated. AE rates were similar between all groups

References

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Other disclosures are listed in the published abstract.

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