The Novel, Intra-articular CLK/DYRK1A Inhibitor Lorecivivint (LOR; SM04690), Which Modulates the Wnt Pathway, Improved Responder Outcomes in Subjects with Knee Osteoarthritis: A Post Hoc Analysis from a Phase 2b Trial

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Background

- Patient-reported outcomes (PROs) assess drug responses but are subject to high individual variability
- Evaluating discrete threshold responses can help identify how many subjects achieve clinically meaningful PRO changes
- Lorecivivint (LOR), an intra-articular (IA) CLK/DYRK1A inhibitor that modulates the Wnt pathway[1], showed improved PRO scores compared to PBO in a 24-week Phase 2b knee osteoarthritis (OA) trial[3]
- This post hoc analysis of these data presents the PRO results as ≥30/50/70% response improvements over baseline
- Week 12 results for the Phase 3-selected 0.07 mg dose are shown

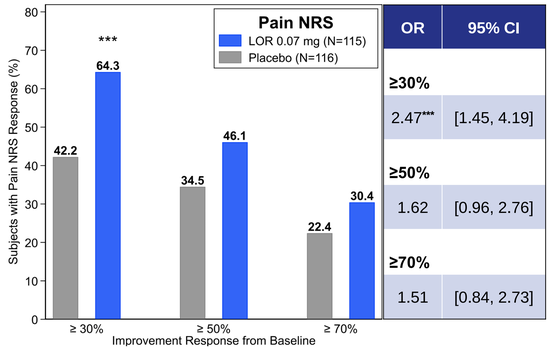
Methods

- Knee OA subjects: KL grade 2-3, target knee Pain Numeric Rating Scale (NRS [0-10]) ≥4 and ≤8, contralateral knee NRS <4, randomized
- Dosing: Single, 2mL, IA injection of 0.03 mg, 0.07 mg, 0.15 mg, or 0.23 mg LOR or placebo (PBO; vehicle) at baseline
- PRO endpoints: Change from baseline in weekly average of daily target knee Pain NRS [0-10], WOMAC Pain [0-100], WOMAC Function [0-100], and Patient Global Assessment (PtGA) [0-100]
- Percent of subjects achieving 30/50/70% thresholds of improvement over baseline and odds ratios (95% CI) of achieving each were calculated using non-responder imputation

Results

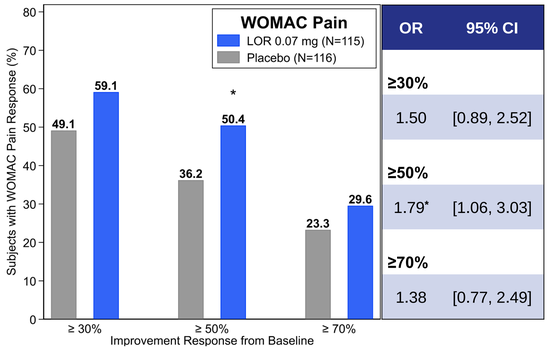
Figure 1. PRO responder analyses at Week 12

Pain NRS



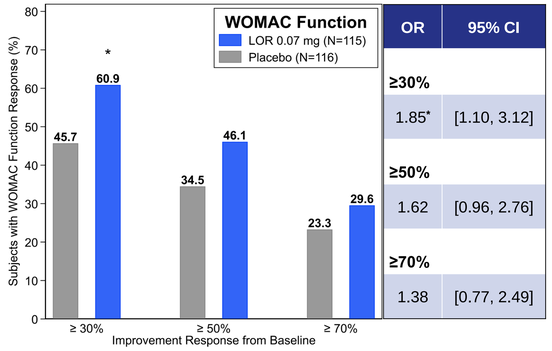
	OR	95% CI
≥30%	2.47***	[1.45, 4.19]
≥50%	1.62	[0.96, 2.76]
≥70%	1.51	[0.84, 2.73]

WOMAC Pain



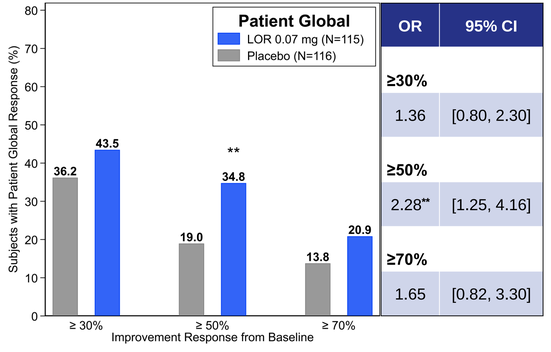
	OR	95% CI
≥30%	1.50	[0.89, 2.52]
≥50%	1.79*	[1.06, 3.03]
≥70%	1.38	[0.77, 2.49]

WOMAC Function



	OR	95% CI
≥30%	1.85*	[1.10, 3.12]
≥50%	1.62	[0.96, 2.76]
≥70%	1.38	[0.77, 2.49]

Patient Global



	OR	95% CI
≥30%	1.36	[0.80, 2.30]
≥50%	2.28**	[1.25, 4.16]
≥70%	1.65	[0.82, 3.30]

Logistic regression of LOR vs. placebo using the Full Analysis Set (all subjects) and non-responder imputation; *P<0.05, **P<0.01,***P<0.001; OR: Odds Ratio, CI: Confidence Interval

Conclusions

- **IA 0.07 mg LOR increased the proportion of subjects achieving 30%, 50%, and 70% thresholds of improvement in PROs relative to PBO**
- **LOR significantly increased the odds of subjects achieving 30% and 50% thresholds of improvement in specific PROs relative to PBO**
- **These effects were observed in all analyzed PROs at Week 12**

Results

635 subjects (91.4%) completed the study: Mean age 59.0±8.5 years, BMI 29.0±4.0 kg/m^2, female 58.4%, KL grade 3 57.3%

Treatment with 0.07 mg LOR vs. PBO at Week 12 (**Fig. 1**) led to

1. Significantly increased odds of achieving ≥30% response in Pain NRS and WOMAC Function
2. Significantly increased odds of achieving ≥50% response in WOMAC Pain and PtGA
3. Improved numerical (but not statistically significant) odds of achieving ≥70% response

References

1. Deshmukh V, et al. *Osteoarthritis Cartilage.* 2019.
2. Yazici Y, et al. *Arthritis Rheumatol.* 2017; 69 (suppl 10).
3. Yazici Y, et al. *Arthritis Rheumatol.* 2018; 70 (suppl 10).

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