Subject Enrichment Criteria for Phase 3 Studies of Lorecivivint (SM04690), a Potential Disease-Modifying Knee Osteoarthritis Drug: A Post Hoc Study on the Effects of Baseline Comorbid Pain and Joint Space Width on Patient-Reported Outcomes

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Poster #1308

Background

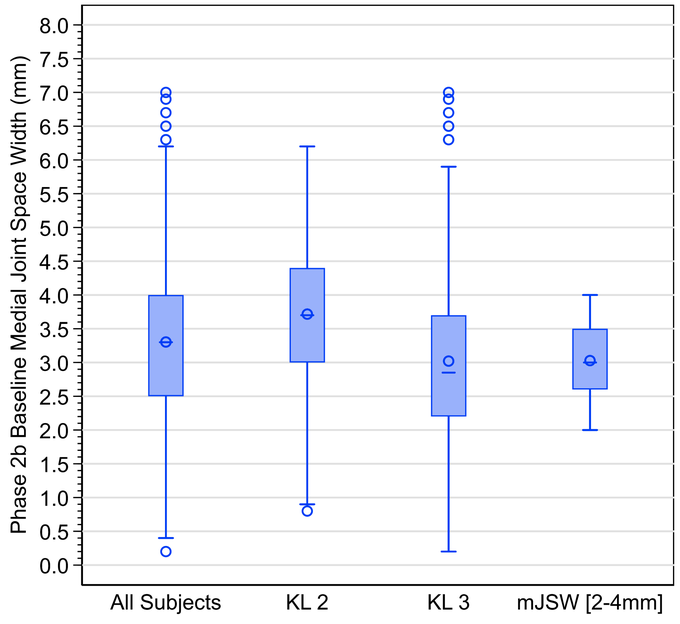
- Detecting change in pain using patient-reported outcomes (PROs) in knee osteoarthritis (OA) trials is complex due to multiple sources of pain in individual subjects
- Refining a subject population with trial inclusion criteria can result in improved patient-reported pain discrimination (e.g., excluding subjects with widespread pain)
- Previous work has demonstrated that assessment of structural progression can be enhanced by restricting medial joint space width (mJSW) inclusion criteria, though the relationship to symptom outcomes is unknown
- Lorecivivint (LOR) is an intra-articular (IA) CLK/DYRK1A inhibitor that modulates the Wnt pathway[1,2]
- The objective of this post hoc analysis from a 24-week Phase 2b trial of LOR was to assess the effects of the 0.07 mg Phase 3 dose on PROs in subjects without comorbid pain and with baseline mJSW [2-4] mm

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
- Baseline radiographic mJSW was measured (PA, positioned, fixed-landmark methodology)
- 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]
- Pre-specified stratification: 80% Widespread Pain Index ≤4 and Symptom Severity Score (SSC) Question 2 ≤2 randomized at screening (Widespread Pain negative: [WP-])
- The Full Analysis Set (**FAS**, all dosed subjects) and baseline mJSW [2-4] mm and WP- subjects (**mJSW [2-4] mm WP-**) for 0.07 mg LOR versus placebo (PBO) were compared with point estimates (95% CI) and effect sizes

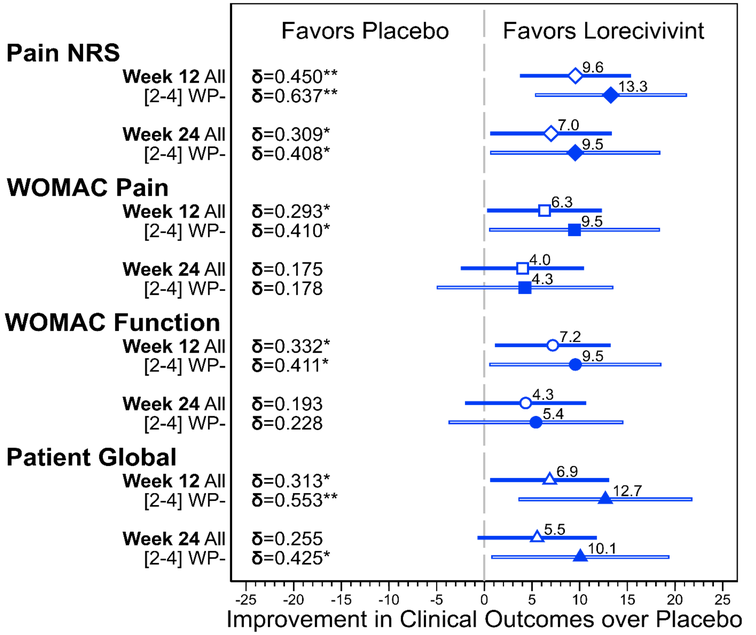
Results

Figure 1. Box and whisker plot of baseline mJSW for all subjects, KL 2, KL 3, and mJSW [2-4] mm



Box: Interquartile range [25 -75%] **Whisker**: 1.5x Interquartile range
Interior Bar: Median **Interior Circle**: Mean **Exterior Circle**: Outlier

Figure 2. LOR 0.07 mg PROs: Change from baseline and effect sizes compared to PBO for all subjects and mJSW [2-4] mm WP-



δ: Effect size, **P*<0.05, ***P*<0.01; LOR vs. PBO using a baseline-adjusted ANCOVA
FAS: LOR N=117, PBO N=116; [2-4] WP-: LOR N=67, PBO N=55; All outcomes scaled (0-100)

Conclusions

- **In this post hoc analysis of a LOR Phase 2b knee OA trial:**
  - **PRO effect sizes in subjects with mJSW [2-4] mm without widespread pain were improved at Weeks 12 and 24 relative to the Full Analysis Set**
  - **These data suggested a possible link between a fixed range of mJSW and symptom responses**
  - **Combining symptomatic and structural criteria appeared to enhance PRO responsiveness**

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%)
- Wide ranges of mJSW were observed at baseline within KL grades (**Fig. 1**). However, variability was reduced when using the [2-4] mm criterion
- Improvements in 0.07 mg LOR effects compared to PBO (***P*<0.05**) were seen in Pain NRS, WOMAC Pain, WOMAC Function, and PtGA between all subjects and mJSW [2-4] mm WP- subjects (**Fig. 2**)

References

1. Deshmukh V, et al. *Osteoarthritis Cartilage.* 2017.
2. Deshmukh V, et al. *Osteoarthritis Cartilage.* 2019.

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