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

Sarah Kennedy1, Christopher J. Swearingen1, Jeyanesh R.S. Tambiah1, Daniel Clauw2, Philip G. Conaghan3
1Samumed, LLC, San Diego, CA; 2University of Michigan Chronic Pain and Fatigue Research Center, Ann Arbor, MI; 3University of Leeds and NIHR Leeds Biomedical Research Centre, Leeds, UK

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 pathway2
• 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 [0-10], and Patient Global Assessment (PGA) [0-100]
• Pre-specified stratification: 80% widespread Pain Index 4x and Symptom Severity Score (SSS) Question 2 ≥2 randomized at screening (Widespread Pain negative: [WP ≤4 mm]
• The Full Analysis Set (FAS, all dosed subjects) and baseline mJSW [2-4] mm with and without widespread pain were compared with point estimates (95% CI) and effect sizes

Results

• All outcomes scaled (0-100)
• 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

Background

Figure 1. Box and whisker plot of baseline mJSW for all subjects, KL 2, KL 3, and 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 [0-10], and Patient Global Assessment (PGA) [0-100]
• Pre-specified stratification: 80% widespread Pain Index 4x and Symptom Severity Score (SSS) Question 2 ≥2 randomized at screening (Widespread Pain negative: [WP ≤4 mm]
• The Full Analysis Set (FAS, all dosed subjects) and baseline mJSW [2-4] mm with and without widespread pain were compared with point estimates (95% CI) and effect sizes

Results

• All outcomes scaled (0-100)
• 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

Background

Figure 1. Box and whisker plot of baseline mJSW for all subjects, KL 2, KL 3, and 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-lanmark methodology)
• PRO endpoints: Change from baseline in weekly average of daily target knee Pain NRS [0-10], WOMAC Pain [0-100], WOMAC Function [0-10], and Patient Global Assessment (PGA) [0-100]
• Pre-specified stratification: 80% widespread Pain Index 4x and Symptom Severity Score (SSS) Question 2 ≥2 randomized at screening (Widespread Pain negative: [WP ≤4 mm]
• The Full Analysis Set (FAS, all dosed subjects) and baseline mJSW [2-4] mm with and without widespread pain were compared with point estimates (95% CI) and effect sizes

Results

• All outcomes scaled (0-100)
• 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

Reference

3. All authors are employees, shareholders, or consultants of Samumed, LLC. Other disclosures are listed in the published abstract.

Conclusion

In this post hoc analysis of a LOR Phase 2b knee OA trial:

- PRO effects were improved in all subjects and mJSW [2-4] mm without widespread pain 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

Poster #1308

References

3. All authors are employees, shareholders, or consultants of Samumed, LLC. Other disclosures are listed in the published abstract.