Optimizing subject selection in knee osteoarthritis clinical trials by radiographic joint space width: post hoc clinical response analysis from a phase 2b trial of Wnt pathway inhibitor lorecivivint (SM04690)

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Disclosures

- Sarah Kennedy: Samumed LLC employee and shareholder
- Christopher Swearingen: Samumed LLC employee and shareholder
- Jeyanesh Tambiah: Samumed LLC employee and shareholder
- Philip Conaghan: AbbVie, AstraZeneca, Flexion Therapeutics, GlaxoSmithKline, Medivir, Merck Serono, Novartis, Pfizer, Samumed LLC, BMS, Lilly

Introduction

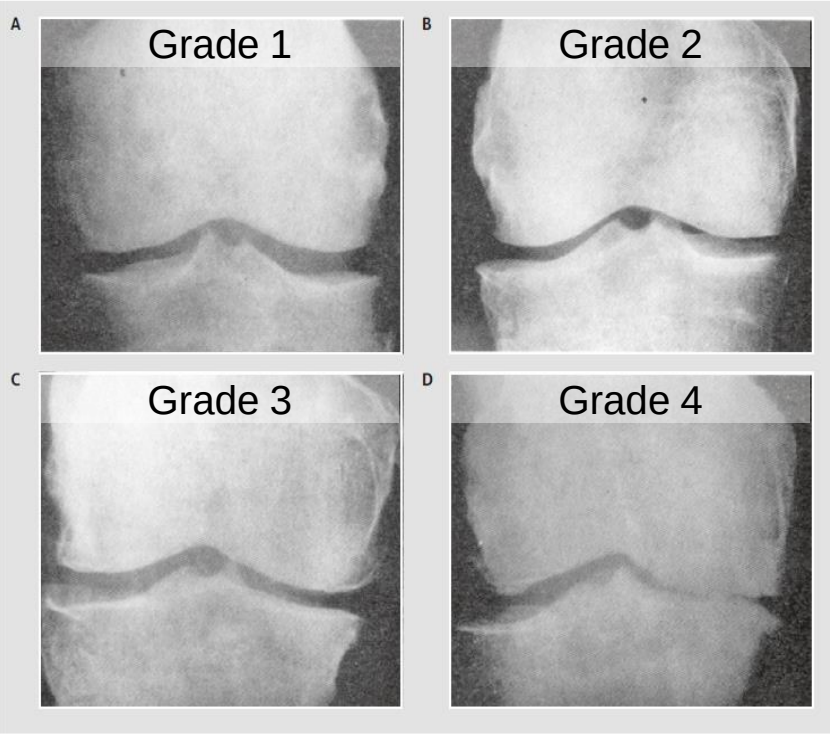
- Kellgren-Lawrence (KL) grades 2-3 are usual inclusion criteria for OA structure modification trials
- KL grading may be unreliable with positioning and rotational changes affecting assessment of joint space width and osteophytes

Grade 1: Doubtful joint space narrowing (JSN) and possible osteophyte lipping

Grade 2: Definite osteophytes and possible JSN

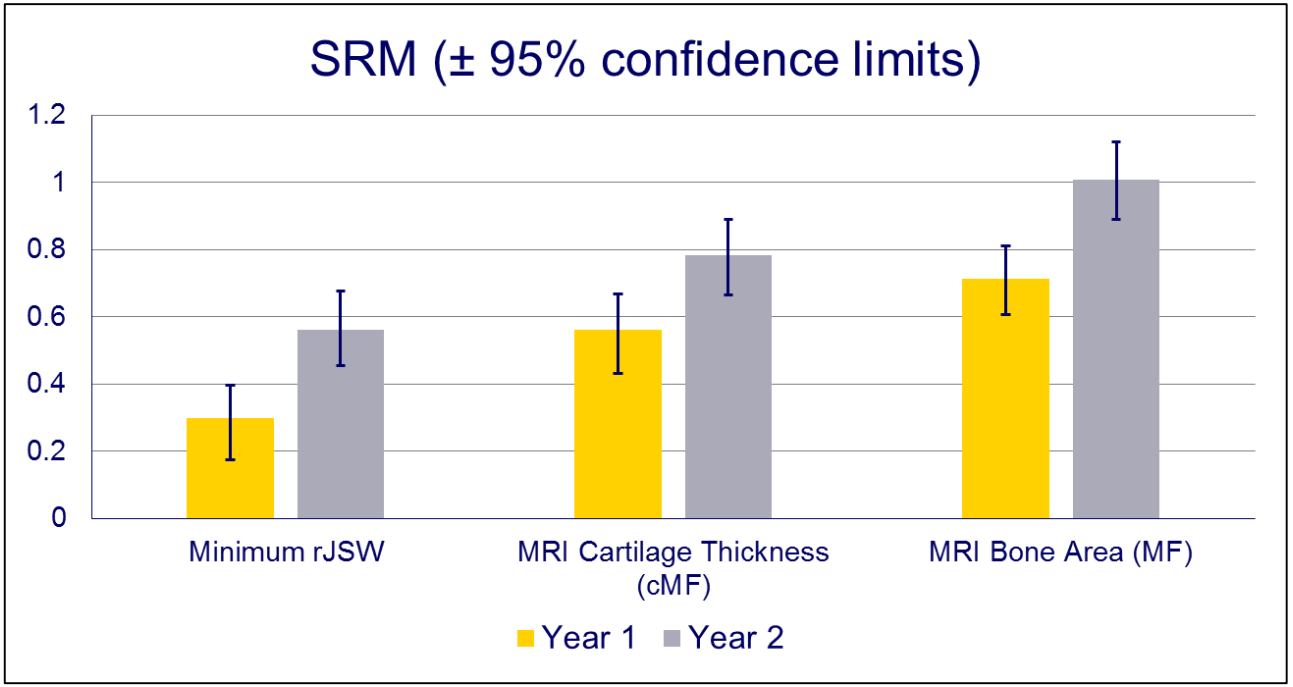
Grade 3: Moderate multiple osteophytes, definite JSN, some sclerosis, possible bone end deformity

Grade 4: Large osteophytes, marked JSN, severe sclerosis, definite deformity of bone ends



Kellgren J, et al. *Ann Rheum Dis*. 1957;16:49

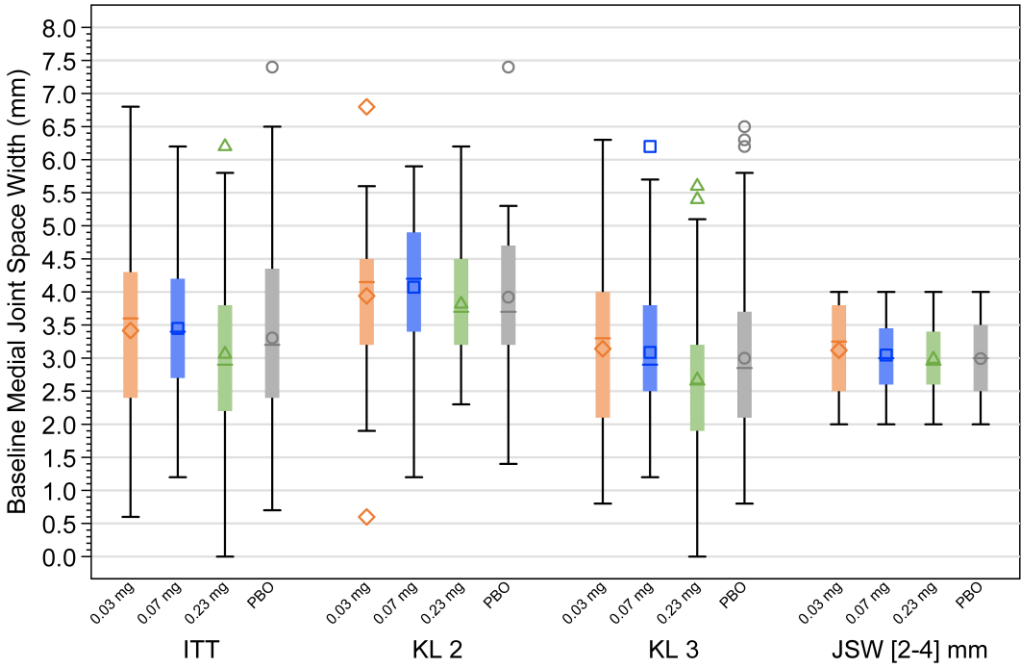
Improving responsiveness of imaging biomarkers by JSW criteria



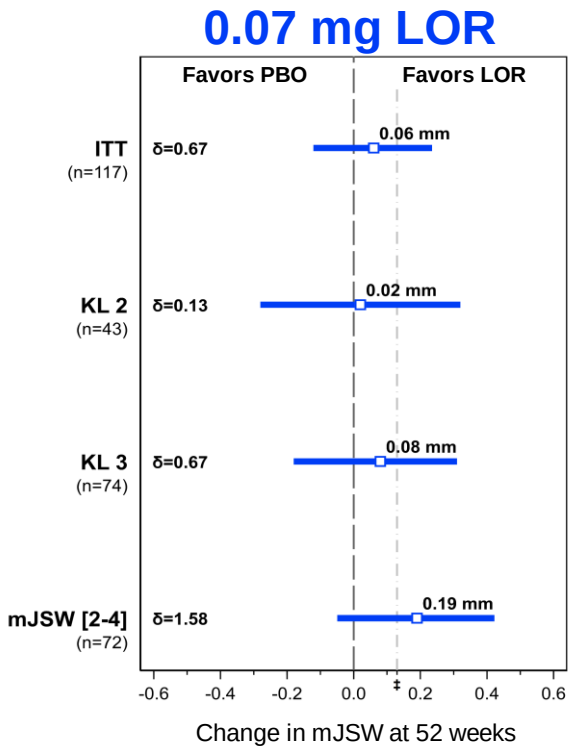
Responsiveness of knees selected for rJSW 2-4 mm and WOMAC Pain ≥3 (n=331, from OAI)

Bowes M, et al. *Ann Rheum Dis*. 2017

Selecting baseline mJSW [2-4] mm reduced heterogeneity and improved effect size compared to other groups



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



Reduced heterogeneity demonstrated in a Phase 2a trial of lorecivivint (LOR)

Yazici Y, et al. *Arthritis Rheumatol.* 2017

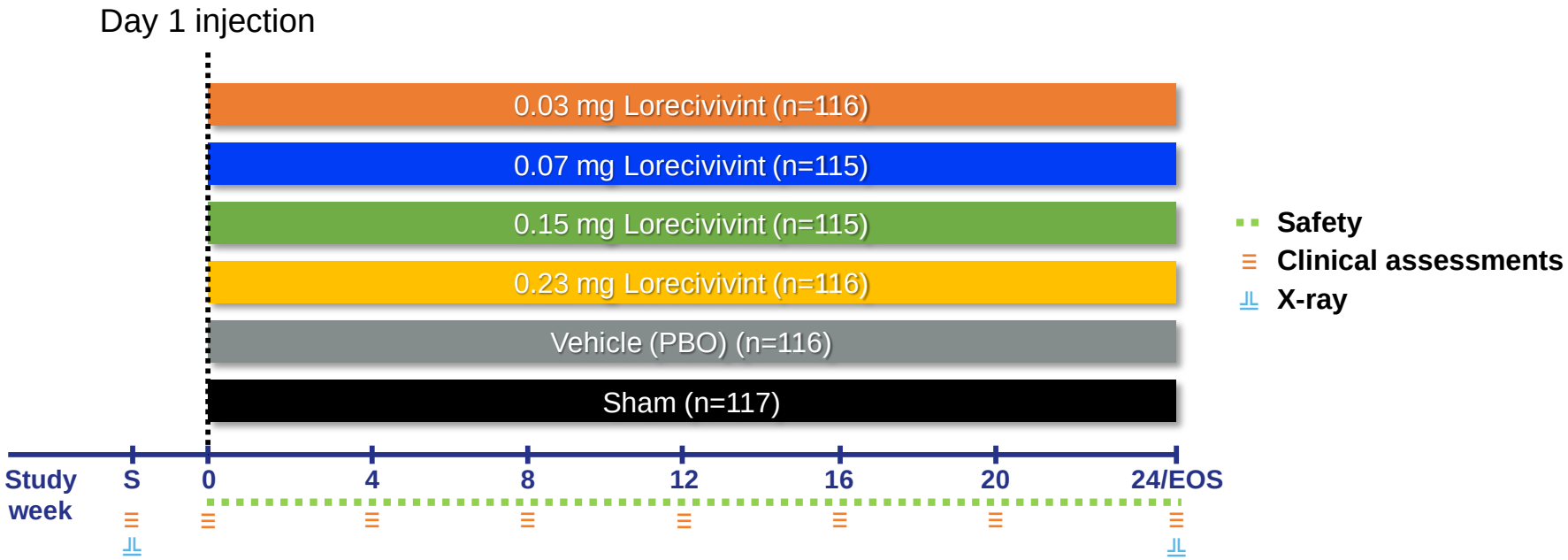
Objective

- The effects of baseline fixed-location mJSW on symptom responsiveness are unknown[1]

- The objective of this post hoc analysis was to evaluate the impact of baseline mJSW [2-4] mm on patient-reported outcomes (PROs) as measured by effect size in a 24-week Phase 2b trial of lorecivivint (LOR)[2]

1. Bowes M, et al. *Ann Rheum Dis.* 2017
2. Yazici Y, et al. *Arthritis Rheumatol.* 2017

LOR Phase 2b: Study design



- **Clinical assessments reported:** Daily Pain NRS, WOMAC Function, WOMAC Pain, Patient Global Assessment
- **Imaging:** Knee X-ray
- **Safety assessments:** AEs, vital signs, physical exam, laboratory panels

LOR Phase 2b: Study methods and analyses

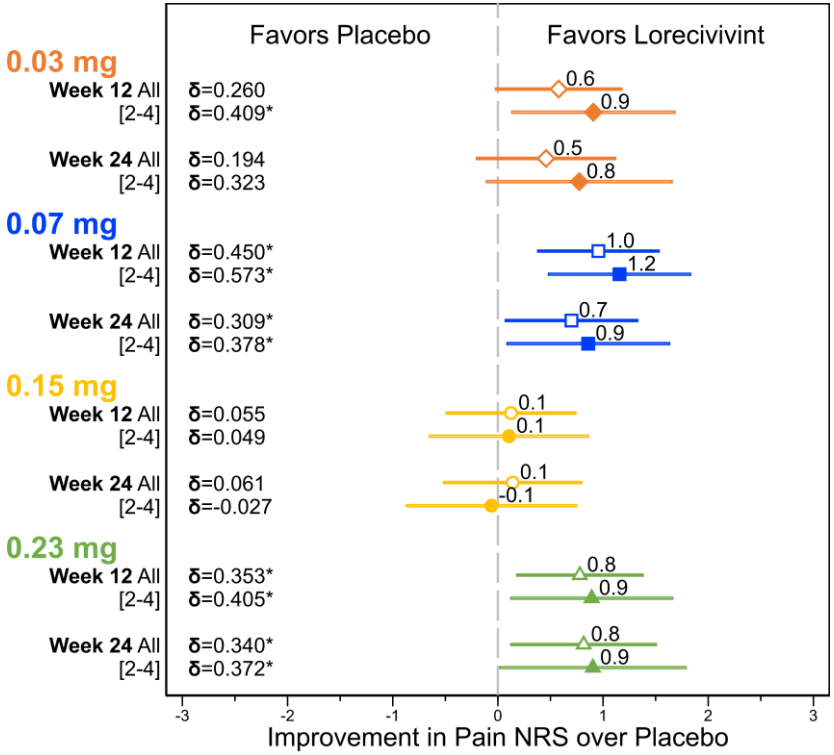
- Knee OA subjects: KL grade 2-3, target knee Pain Numeric Rating Scale (NRS [0-10]) ≥4 and ≤8, contralateral knee NRS <4, randomized
- Baseline radiographs (PA, positioned) taken. Blind-read, fixed-landmark mJSW measurement
- Post hoc analysis of subgroup with baseline mJSW [2-4] mm compared to Full Analysis Set (FAS)
- Effect sizes were calculated for treatment versus PBO using a baseline-adjusted ANCOVA

Results

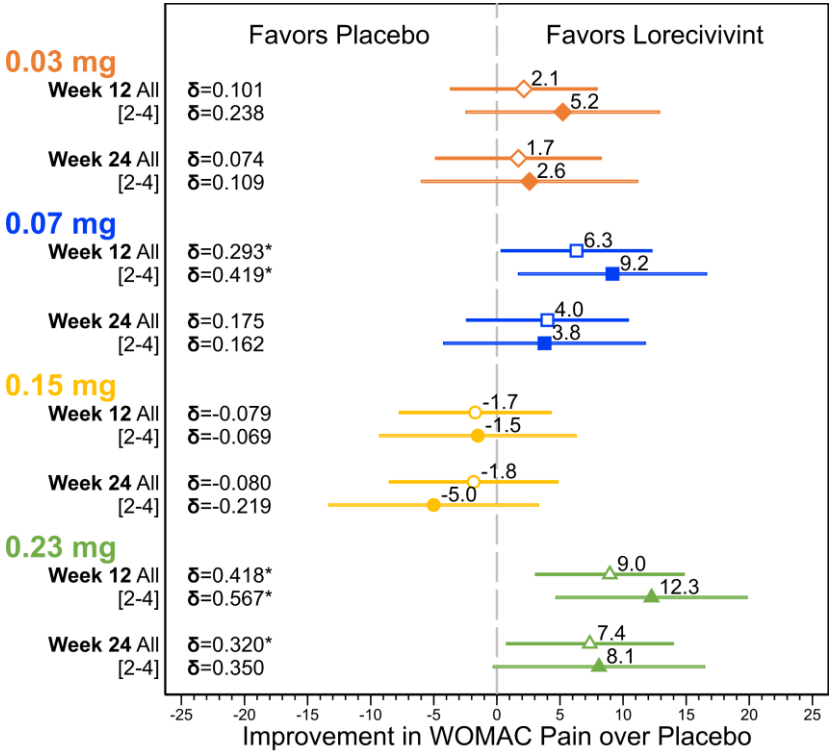
- 635 subjects (91%) completed the study
  - Mean age 59 (±8.5) years, BMI 29 (±4.0) kg/m^2, female 58%, KL3 57%
- Incidence of AEs across treatment arms were similar
- In FAS and mJSW [2-4] mm subjects, significant improvements compared to PBO ($P<0.05$) observed in Pain NRS, WOMAC Pain, WOMAC Function, PtGA for 0.07 mg and 0.23 mg LOR dose groups at Week 12

Effect sizes increased in subjects with baseline mJSW [2-4] mm

Pain NRS [0-10]



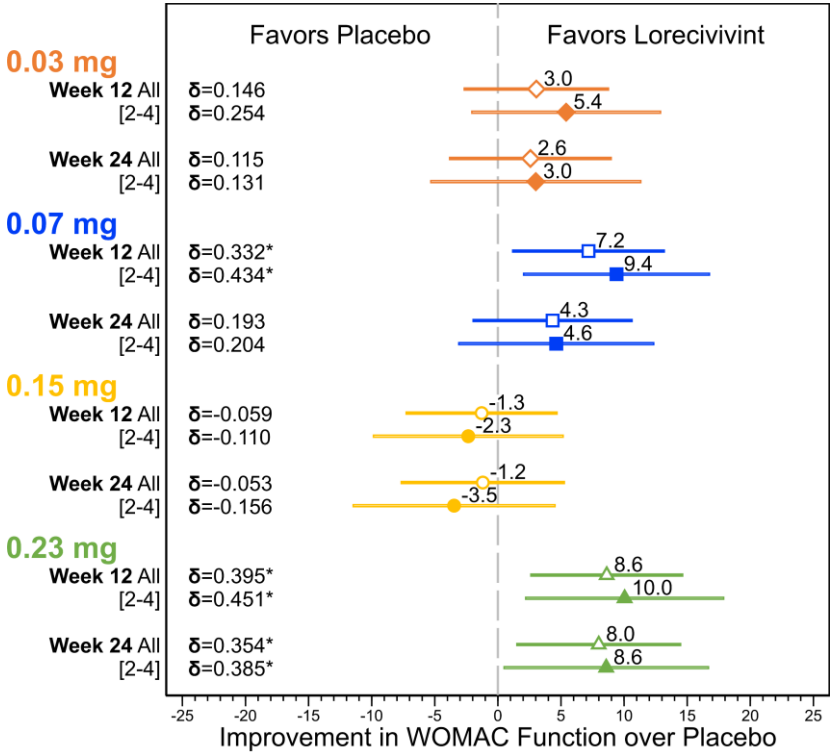
WOMAC Pain [0-100]



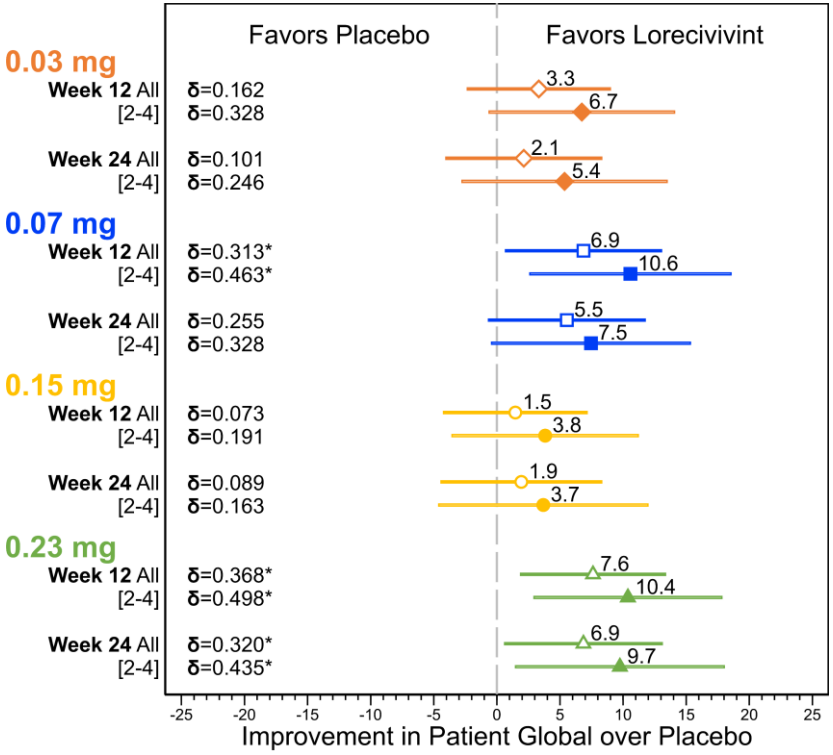
*P<0.05

Effect sizes increased in subjects with baseline mJSW [2-4] mm

WOMAC Function [0-100]



Patient Global Assessment [0-100]



*P<0.05

Conclusions

- Effect sizes were improved in the mJSW [2-4] mm group relative to FAS for most doses ranging from 14%-162% at Week 12 and 9%-144% at Week 24

- While previous analyses suggest that increased structural measurement responsiveness is related to a minimum JSW, this post hoc analysis also suggests a possible link between a specific range of mJSW and symptom responses

- Data from LOR studies suggest that mJSW [2-4] mm should be considered as an inclusion criterion for trials of potential knee DMOADs

Thank you

LOR Phase 2b: Key inclusion/exclusion criteria

Key Inclusion Criteria	Key Exclusion Criteria
40-80 years, good health	**BMI >35**
Ambulatory (aids allowed if needed <50%)	Major surgery in target knee within 12 months
Clinical and radiological ACR diagnosis of primary femorotibial OA in target knee >6 months	IA steroids within 2 months Hyaluronic acid, PRP, stem cell therapies within 6 months
Kellgren-Lawrence grade 2-3 in target knee	Target knee effusion requiring aspiration within 3 months
Daily pain diary average ≥4 and ≤8 on 0-10 NRS in target knee at least 4 of 7 days	Opioids >1x/week within 12 weeks screening Subjects not on stable NSAID regimen
Daily pain diary average <4 on 0-10 NRS in contralateral knee at least 4 of 7 days	Any chronic condition not well controlled >3 months

LOR Phase 2b: Subject characteristics

Full analysis set

	Lorecivivint				
	0.03 mg	**0.07 mg**	**0.15 mg**	**0.23 mg**	**Placebo**
N	116	115	115	116	116
Age at Consent (years)*	57.9 (7.9)	59.9 (8.6)	58.4 (8.3)	58.5 (9.0)	60.1 (9.0)
BMI (kg/m^2)*	29.2 (3.8)	29.1 (3.6)	29.4 (4.1)	28.5 (4.4)	28.6 (4.3)
Female	76 (65.5%)	66 (57.4%)	69 (60.0%)	61 (52.6%)	64 (55.2%)
Race					
White	85 (73.3%)	83 (72.2%)	84 (73.0%)	89 (76.7%)	90 (77.6%)
African American	24 (20.7%)	22 (19.1%)	25 (21.7%)	21 (18.1%)	17 (14.7%)
Asian	5 (4.3%)	5 (4.3%)	6 (5.2%)	5 (4.3%)	6 (5.2%)
KL Grade 3	63 (54.3%)	74 (64.3%)	68 (59.1%)	63 (54.3%)	72 (62.1%)
Unilateral Symptomatic†	59 (50.9%)	62 (53.9%)	63 (54.8%)	63 (54.3%)	61 (52.6%)
Widespread Pain Negative††	92 (79.3%)	93 (80.9%)	90 (78.3%)	93 (80.2%)	93 (80.2%)

*Mean (SD) reported. Otherwise, N (%) reported.
† Unilateral Symptomatic vs. Bilateral Symptomatic stratified to 50% each.
†† Widespread Pain Negative (WPI ≤4 and Symptom Severity score ≤2) stratified to 80% of population.