### Title

A Phase 2b randomized trial of lorecivivint, a novel intra-articular CLK2/DYRK1A inhibitor and Wnt pathway modulator for knee osteoarthritis




### Journal

Osteoarthritis and Cartilage, 29(5)

### ISSN

1063-4584



### Authors

Yazici, Y
McAlindon, TE
Gibofsky, A
et al.



### Publication Date

2021-05-01

### DOI

10.1016/j.joca.2021.02.004

Peer reviewed

Osteoarthritis and Cartilage xxx (xxxx) xxx

Osteoarthritis and Cartilage

# A Phase 2b randomized trial of lorecivivint, a novel intra-articular CLK2/DYRK1A inhibitor and Wnt pathway modulator for knee osteoarthritis

Y. Yazici † ‡ *, T.E. McAlindon §, A. Gibofsky ‖, N.E. Lane ¶, C. Lattermann #, N. Skrepnik ††, C.J. Swearingen †, I. Simsek †, H. Ghandehari †, A. DiFrancesco †, J. Gibbs †, J.R.S. Tambiah †, M.C. Hochberg ‡‡

† *Samumed, LLC, San Diego, CA, USA*
‡ *New York University School of Medicine, New York, NY, USA*
§ *Tufts Medical Center, Boston, MA, USA*
‖ *Weill Cornell Medical College, New York, NY, USA*
¶ *University of California Davis Medical School, Burlingame, CA, USA*
# *University of Kentucky, Lexington, KY, USA*
†† *Tucson Orthopaedic Institute, Tucson, AZ, USA*
‡‡ *University of Maryland, College Park, MD, USA*

ARTICLE INFO

*Article history:*
Received 20 July 2020
Accepted 7 February 2021

*Keywords:*
Clinical trial
Wnt pathway
Patient-reported outcomes
CLK2
DYRK1A
Knee pain

SUMMARY

*Objective:* Lorecivivint (LOR; SM04690), an investigational Wnt pathway modulator, previously demonstrated patient-reported and radiographic outcome improvements vs placebo in clinically relevant subjects with moderate to severe knee osteoarthritis (OA). This study's objective was to identify effective LOR doses.

*Design:* Subjects in this 24-week, Phase 2b, multicenter, randomized, double-blind, placebo (PBO)-controlled trial received an intra-articular injection of 2 mL LOR (0.03, 0.07, 0.15, or 0.23 mg), PBO, or dry-needle sham. The primary efficacy endpoints were changes in Pain NRS [0–10], WOMAC Pain [0–100], WOMAC Function [0–100], and radiographic mJSW outcomes, which were measured using baseline-adjusted analysis of covariance at Week 24. Multiple Comparison Procedure-Modeling (MCP-Mod) was performed for dose modeling.

*Results:* In total, 695/700 subjects were treated. Pain NRS showed significant improvements vs PBO after treatment with 0.07 mg and 0.23 mg LOR at Weeks 12 (−0.96, 95% CI [−1.54, −0.37], $P = 0.001$; −0.78 [−1.39, −0.17], $P = 0.012$) and 24 (−0.70 [-1.34, −0.06], $P = 0.031$; −0.82 [−1.51, −0.12], $P = 0.022$). Additionally, 0.07 mg LOR significantly improved WOMAC Pain and Function subscores vs PBO at Week 12 ($P = 0.04$, $P = 0.021$), and 0.23 mg LOR significantly improved both WOMAC subscores at Week 24 ($P = 0.031$, $P = 0.017$). No significant differences from PBO were observed for other doses. No radiographic progression was observed in any group at Week 24. MCP-Mod identified 0.07 mg LOR as the lowest effective dose.

*Conclusion:* This 24-week Phase 2b trial demonstrated the efficacy of LOR on PROs in knee OA subjects. The optimal dose for future studies was identified as 0.07 mg LOR.



## Introduction

Knee osteoarthritis (OA) is a chronic joint disease with an estimated worldwide prevalence of 3.8%[1]. The most prominent symptom is chronic pain, which is related, in part, to structural changes, including articular cartilage degradation and osteophyte

*Address correspondence and reprint requests to: Y. Yazici, Samumed, LLC, 9360 Towne Centre Drive, San Diego, CA, 92121, USA. Tel: 858-926-2926.
*E-mail address:* yusuf@samumed.com (Y. Yazici).

https://doi.org/10.1016/j.joca.2021.02.004

formation precipitated by biomechanical forces. These structural changes are also mediated by various cellular mechanisms (e.g., local inflammation, cellular senescence, and apoptosis) involving complex cell signaling pathways (e.g., TGF-β, hedgehog, and Wnt signaling)[2–4]. The symptomatic benefits of existing treatments are relatively modest with significant safety concerns in some cases[5–11]. Currently, there are no structure-modifying agents approved for OA by the U.S. Food and Drug Administration or European Medicines Agency. Thus, there is an unmet medical need for safer therapeutics that treat underlying pathology and have symptomatic benefits.

Developing treatments for knee OA is challenging for several reasons. First, the disease itself is heterogeneous, etiologically diverse, and typically presents with symptoms at a relatively advanced stage[12]. Second, there are no validated surrogate endpoints for end-stage knee OA[13]. Third, pain reporting can be confounded by pain from multiple joints, comorbidities (common in patients with knee OA), and central and peripheral pain-processing mechanisms[14,15]. Finally, strong placebo (PBO) effects exist in clinical trials of intra-articular (IA) and oral treatments for knee OA[16].

Many investigated therapies for knee OA target single-joint tissues such as cartilage[17] or bone[7] or a process such as inflammation[8]. However, if OA is regarded as a heterogenous "whole-joint" disease[18], successful treatment approaches may require targeting several tissues and pathways at the same time or a pathway that influences multiple disease components in parallel. The Wnt signaling pathway is known to be a key regulator of progenitor cell differentiation, cartilage/bone metabolism, and inflammatory responses in the knee joint[19–23]. It has been shown to be abnormally upregulated in osteoarthritic joints and in preclinical OA models[18,19,24,25]. Therefore, targeting the Wnt signaling pathway presents a potential mechanism for treating knee OA.

Lorecivivint (LOR; previously SM04690) is in development as an IA, small-molecule drug with structure-modifying potential for OA. LOR inhibits the intranuclear kinases CLK2 and DYRK1A, leading to downstream modulation of the Wnt pathway and inflammation[19], thus affecting structural and symptomatic mechanisms underlying OA. In a previous randomized, PBO-controlled, 52-week Phase 2a trial (NCT02536833), LOR demonstrated significant improvements compared with PBO in pain and function patient-reported outcomes (PROs) and medial joint space width (mJSW) in clinically relevant subjects with predominantly unilateral symptoms and without comorbid widespread pain[26]. This 24-week Phase 2b trial was conducted to extend these findings and identify effective doses for future studies, and, as such, demonstrate the symptomatic benefits observed following treatment with LOR.

## Subjects and methods

### *Study design*

This study was a 24-week, Phase 2b, multicenter, randomized, double-blind, PBO-controlled, parallel-group trial of 4 doses of LOR injected into the target knee joint of subjects with moderate to severe symptomatic knee OA. The study was conducted at 75 U.S. clinical sites between April 2017 and April 2018. The primary objective was to determine the effective dose(s) of LOR for the treatment of knee OA. Primary efficacy endpoints included changes from baseline to Week 24 for each treatment group in target knee pain according to Pain Numeric Rating Scale (Pain NRS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain scores, in WOMAC Function scores, and in radiographic mJSW. Secondary endpoints included treatment-emergent adverse events (TEAEs) and changes from baseline in Patient Global Assessment (PtGA) score for each treatment group at Week 24. Comparisons of efficacy were conducted between all LOR dose groups and vehicle PBO; comparisons of vehicle PBO vs sham injection are reported separately.

The study was conducted in accordance with the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice Guidelines, and applicable regulations. The study protocol was approved at each clinic site by an independent ethics committee or an institutional review board. All subjects provided written informed consent prior to participating in any study-related procedures. The study has been registered at ClinicalTrials.gov (NCT03122860).

### *Subjects*

Eligible subjects were adults aged 40–80 years with a diagnosis of primary idiopathic femorotibial OA in the target knee according to standard American College of Rheumatology clinical and radiographic criteria[27] at Screening Visit 1. Subjects underwent fixed-flexion (beam angle, 10°; knee flexion, 20°), posterior-anterior radiography of the tibiofemoral compartments using a QuAP™ positioning device (Medical Metrics, Inc, Houston, TX). A central imaging lab (Medical Metrics, Inc) that was blinded to treatment assignments quality controlled all radiographs, evaluated Kellgren-Lawrence (KL) grade, and measured mJSW using a landmark-based, fixed-location methodology. Quantitative joint space measurements were produced by trained analysts using Quantitative Motion Analysis software (QMA®) for radiographic image analysis. Subjects were expected to be in general good health and ambulatory with KL grade 2 or 3 in their target knee. Subjects had pain compatible with knee OA for at least 26 weeks prior to Screening Visit 1. For the target knee, subjects must have had a Pain NRS intensity score $\geq$4 and $\leq$8 on an 11-point [0–10] scale for 4 of 7 days immediately preceding Treatment Day 1. For the non-target knee, subjects must have had a daily average NRS intensity score <4 for 4 of 7 days immediately preceding Treatment Day 1. In addition, subjects were required to have a WOMAC (version 3.1) Total score of 96–192 (out of 240) for the target knee at baseline regardless of whether or not the subject was on symptomatic oral treatment (e.g., NSAIDs/acetaminophen). Subjects were allowed to start NSAIDs/acetaminophen during the study (if not already using them), and, if already on NSAIDs, subjects were not washed out from their stable NSAID regimens. There were no other restrictions on NSAID/acetaminophen usage during the study. Analgesic usage was captured via electronic diary as daily NSAID usage and at site visits as part of the concomitant medication review. Finally, to assess pain and symptoms related to comorbidities, subjects underwent an assessment with the Widespread Pain Index (WPI) and Symptom Severity (SS) Scale tools at screening[28].

Subjects were excluded if they were receiving opioid analgesics or glucocorticoids during the trial; only NSAIDs or acetaminophen could be used. Any new formalized (i.e., prescribed by a medical professional) physical therapy exercise programs for knee OA were prohibited while the subject participated in the trial, although continuation of formalized physical therapy exercise programs that were already in progress at the time of screening was allowed. Electrotherapy, acupuncture treatments, chiropractic treatments, and planned or elective surgery for knee OA were also prohibited while the subject participated in the study. IA injections of corticosteroids, hyaluronic acid, or other therapeutic agents into either knee were prohibited, although these injections were allowed for joints other than the knees. Subjects with comorbid conditions that could impact study assessments, including rheumatoid arthritis,

Please cite this article as: Yazici Y et al., A Phase 2b randomized trial of lorecivivint, a novel intra-articular CLK2/DYRK1A inhibitor and Wnt pathway modulator for knee osteoarthritis, Osteoarthritis and Cartilage, https://doi.org/10.1016/j.joca.2021.02.004

psoriatic arthritis, systemic lupus erythematosus, depressive disorders, or fibromyalgia, were also excluded.

*Treatment protocol*

Eligible subjects were randomized to 1 of 6 treatment groups (0.03 mg LOR, 0.07 mg LOR, 0.15 mg LOR, 0.23 mg LOR, Vehicle [PBO], or Sham [dry needle]) and received a single IA injection, per usual practice, into the target knee on Treatment Day 1. The volume of all injections was 2.0 mL (except for the sham injection). The vehicle contained 0.5% carboxymethylcellulose sodium and 0.05% polysorbate 80 in pH 7.4 phosphate-buffered saline. Subjects were randomized at a ratio of 1:1:1:1:1:1 to each treatment group using a permuted block design (block size of 6) that was stratified by presence of symptomatic knee OA (subjects with bilateral OA symptoms [50%], subjects with unilateral OA symptoms [50%]) and WPI and SS Scale Question 2 (SSQ2) scores (80% of subjects with WPI $\leq$4 and SSQ2 $\leq$2, 20% of subjects with WPI >4 and/or SSQ2 >2). Randomization of subjects was generated by Medidata Balance (Medidata Solutions, New York, NY). Study investigators and subjects were blinded to treatment assignments. Unblinded personnel prepared the medication and performed the injection; they were instructed to minimize contact with subjects and were not allowed to perform study assessments.

Subject characteristics, medical history, height, weight, and body mass index (BMI) were collected at screening. Subjects were required to complete an electronic diary (Rave, Medidata Solutions, New York, NY) for reporting daily Pain NRS and monthly WOMAC and PtGA scores. Subjects underwent fixed-flexion, posterior-anterior radiography of the tibiofemoral compartments for assessment of mJSW at baseline and Week 24 using the same parameters described at screening (see **Subjects**).

*Efficacy assessments*

Efficacy was assessed by determining 1) weekly averages of daily Pain NRS scores for the target knee, 2) monthly WOMAC Pain and WOMAC Function subscores for the target knee, 3) monthly PtGA scores, and 4) measured mJSW in the target knee at Week 24, and then analyzing changes between baseline and Weeks 4, 8, 12, 16, 20, and 24. Of these assessments, the primary endpoints comprised the Pain NRS, WOMAC Pain and Function, and mJSW results at Week 24, whereas PtGA score was considered a secondary endpoint. Based on published studies[29,30], the minimum clinically important difference (MCID) was considered to be $\geq$ 10% improvement from baseline for all outcome measurements.

*Safety assessments*

Safety analyses were performed on all subjects who received a study injection. The overall safety and tolerability of LOR were determined by TEAEs and clinically significant changes in clinical laboratory measures and vital signs. Specifically, safety was assessed by evaluating the incidence, severity (Vaccine Toxicity Scale), and seriousness of TEAEs and clinically significant changes in clinical laboratory measures and vital signs.

*Statistical analysis*

A sample size of approximately 630 subjects was selected for this study based upon accepted dose-finding statistical practice[26,31]. Briefly, the cited work by Ting utilized statistical simulations to evaluate the performance of MCP-Mod in detecting treatment differences in clinical outcomes (e.g., WOMAC Pain) in OA trials. It was found that a sample size of 91 per group would be sufficient to detect a linear dose–response relationship using WOMAC Pain, and the minimum sufficient sample size identified was then inflated to allow for dropout. All efficacy analyses were completed on the full analysis set (FAS), which was defined by ICH E9 as all subjects who were randomized and received an injection; the FAS differs from the "intention-to-treat ideal" only by the additional specification of the subject having received an injection[32].

For safety assessments, the number and percent of subjects experiencing TEAEs were summarized by seriousness, severity, and relationship for each treatment group.

Multiple Comparison Procedure-Modeling (MCP-Mod)[33] is a "fit-for-purpose" drug development tool[34,35] that was used to estimate the dose responses of LOR compared with PBO using efficacy outcomes. Instead of applying separate statistical tests to determine if a test drug has a dose–response relationship with an outcome, what that dose–response relationship looks like, and what the target dose for Phase 3 trials would be based on that relationship, MCP-Mod is an efficient way to accomplish all 3 tests at once without overly increasing the likelihood of false positive errors. MCP-Mod is a two-step process: First, it tests several candidate dose–response models for goodness of fit to the collected data using multiple comparison adjustment to protect against Type 1 (false positive) error inflation. If this (MCP) step successfully identifies a good-fitting dose–response model, that model is then used to estimate the candidate dose(s) for further study in pivotal, confirmatory trials.

The responses used for the MCP step were estimated from the Week 24, baseline-adjusted analysis of covariance (ANCOVA) tests of the primary outcome measures (weekly average of daily Pain NRS, WOMAC Pain, WOMAC Function, and mJSW), as these measures will be assessed in confirmatory trials to ultimately support regulatory decision-making. The secondary efficacy outcome (PtGA) was also examined using MCP-Mod for completeness. Because MCP-Mod makes no assumptions about which model (if any) will fit well with the data, both monotonic (e.g., linear) and non-monotonic (e.g., beta-mod, quadratic, E-max) models were used to explore the dose–response relationship based upon prior dose–response modeling of the Phase 2a trial[26]. Model selection from among only those models demonstrating statistically significant goodness of fit was based upon the Akaike Information Criteria (AIC)[36].

As this Phase 2b trial was purposed to estimate and characterize the dose responses of LOR and no formal hypotheses were tested, no formal Type 1 error control mechanism was used for the ANCOVA analysis; the efficacy dose response was modeled under the error control utilized by MCP-Mod. Estimated least-squares mean differences, unadjusted 95% confidence intervals, and *P* values are reported for the ANCOVA analyses to allow for further characterization of the dose response. Additionally, no imputation strategy was used for the primary ANCOVA analyses, although sensitivity analyses using both last-observation-carried-forward as well as mixed-method-repeated-measures (MMRM) modeling were conducted.

## Results

*Subject disposition and baseline characteristics*

In total, 2,672 subjects were screened, and 700 (26.0%) subjects were randomized. Within the randomized subject population, 695 subjects were treated; 5 subjects discontinued prior to dosing (Fig. 1). Groups of 116, 115, 115, and 116 subjects were randomized to receive either 0.03, 0.07, 0.15, or 0.23 mg of LOR, respectively. Additionally, 116 subjects were randomized into the

Please cite this article as: Yazici Y et al., A Phase 2b randomized trial of lorecivivint, a novel intra-articular CLK2/DYRK1A inhibitor and Wnt pathway modulator for knee osteoarthritis, Osteoarthritis and Cartilage, https://doi.org/10.1016/j.joca.2021.02.004

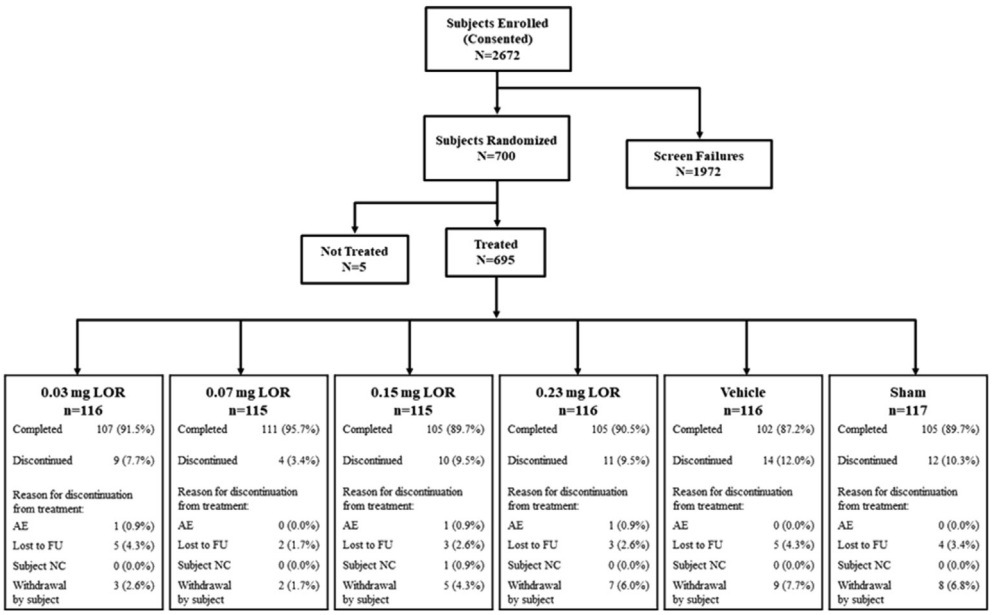


**Fig. 1** Subject disposition and reasons for discontinuation. The number and percent of subjects are provided for all treatment groups. The numbers are based on the planned treatment. Abbreviations – AE: Adverse event, FU: Follow-up, LOR: Lorecivivint, NC: Noncompliance.

PBO group, and 117 subjects were randomized into the Sham group (Table I).

Mean (±SD) age and BMI at enrollment were 59.0 (±8.5) years and 28.97 (±4.01) kg/m$^2$, respectively. Overall, 406 (58.4%) of enrolled subjects were women, 517 (75.5%) were White, 394 (57.3%) had KL grade 3 radiographic changes in the target knee, and 370 (53.2%) were classified as having unilateral symptomatic disease. Subjects' baseline characteristics were similar across the 6 treatment groups.

*Efficacy: primary and exploratory outcomes*

For all tested doses including PBO, baseline scores with standard deviations for each PRO, baseline mJSWs, and estimated changes from baseline with 95% CIs for each 4-week timepoint from Weeks 4 to 24 are presented in Table II. Statistically significant differences are described below.

*Pain NRS*: At Week 24, treatment with 0.07 mg and 0.23 mg LOR demonstrated significant (−0.70 [−1.34, −0.06], $P = 0.031$ and −0.82 [−1.51, −0.12], $P = 0.022$, respectively) improvements in

| | Lorecivivint | | | | | |
|---|---|---|---|---|---|---|
| | 0.03 mg | 0.07 mg | 0.15 mg | 0.23 mg | PBO | Sham |
| 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) |
| Race | | | | | | |
| *White* | 85 (73.3) | 83 (72.2) | 84 (73.0) | 89 (76.7) | 90 (77.6) | 86 (73.5) |
| *Black* | 24 (20.7) | 22 (19.1) | 25 (21.7) | 21 (18.1) | 17 (14.7) | 24 (20.5) |
| *Asian* | 5 (4.3) | 5 (4.3) | 6 (5.2) | 5 (4.3) | 6 (5.2) | 3 (2.6) |
| 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 (WPI <4) | 92 (79.3) | 93 (80.9) | 90 (78.3) | 93 (80.2) | 93 (80.2) | 94 (80.3) |

Abbreviations – PBO: Vehicle placebo injection group, BMI: Body Mass Index, KL: Kellgren–Lawrence, WPI: Widespread Pain Index.
* Mean (SD) reported. Otherwise, n (%) reported.

**Table I** Subject characteristics

Please cite this article as: Yazici Y et al., A Phase 2b randomized trial of lorecivivint, a novel intra-articular CLK2/DYRK1A inhibitor and Wnt pathway modulator for knee osteoarthritis, Osteoarthritis and Cartilage, https://doi.org/10.1016/j.joca.2021.02.004

| | Dose | Baseline* | Week-4 Change† | Week-8 Change† | Week-12 Change† | Week-16 Change† | Week-20 Change† | Week-24 Change† |
|---|---|---|---|---|---|---|---|---|
| Pain NRS | PBO | 6.2 (1.0) | | | | | | |
| | 0.03 mg | 6.2 (1.1) | −0.15 (−0.67, 0.36) | −0.21 (−0.78, 0.36) | −0.58 (−1.18, 0.03) | −0.45 (−1.09, 0.18) | −0.45 (−1.13, 0.23) | −0.46 (−1.13, 0.21) |
| | 0.07 mg | 6.1 (1.1) | −0.28 (−0.80, 0.24) | −0.54 (−1.12, 0.03) | −0.96 (−1.54, −0.37)§ | −0.69 (−1.30, −0.09)‡ | −0.66 (−1.32, 0.01) | −0.70 (−1.34, −0.06)‡ |
| | 0.15 mg | 6.1 (1.0) | −0.14 (−0.66, 0.38) | 0.11 (−0.48, 0.70) | −0.12 (−0.75, 0.50) | −0.15 (−0.78, 0.48) | −0.10 (−0.78, 0.58) | −0.14 (−0.81, 0.52) |
| | 0.23 mg | 6.1 (1.0) | −0.16 (−0.70, 0.39) | −0.51 (−1.10, 0.08) | −0.78 (−1.39, −0.17)‡ | −0.90 (−1.52, −0.28)§ | −0.92 (−1.60, −0.23)§ | −0.82 (−1.51, −0.12)‡ |
| WOMAC Pain | PBO | 59.0 (10.8) | | | | | | |
| | 0.03 mg | 58.1 (12.6) | −0.65 (−6.19, 4.89) | −3.28 (−9.03, 2.46) | −2.14 (−7.99, 3.72) | −2.09 (−8.49, 4.31) | −1.88 (−8.64, 4.87) | −1.70 (−8.32, 4.91) |
| | 0.07 mg | 57.8 (11.8) | −3.62 (−9.40, 2.15) | −6.29 (−12.26, −0.32)‡ | −6.31 (−12.33, −0.29)‡ | −5.90 (−11.92, 0.12) | −6.20 (−12.82, 0.42) | −4.01 (−10.47, 2.46) |
| | 0.15 mg | 59.3 (11.4) | −3.38 (−8.91, 2.15) | −0.90 (−6.78, 4.98) | 1.72 (−4.35, 7.79) | 0.87 (−5.71, 7.45) | −0.35 (−6.89, 6.19) | 1.84 (−4.89, 8.57) |
| | 0.23 mg | 58.1 (12.1) | −6.28 (−12.02, −0.54)‡ | −5.94 (−11.89, 0.01) | −8.95 (−14.90, −3.01)§ | −7.54 (−13.88, −1.20)‡ | −8.05 (−14.66, −1.43)‡ | −7.36 (−14.03, −0.69)‡ |
| WOMAC Function | PBO | 59.2 (9.8) | | | | | | |
| | 0.03 mg | 59.0 (10.9) | 0.56 (−4.72, 5.83) | −4.00 (−9.78, 1.79) | −3.05 (−8.83, 2.73) | −3.26 (−9.52, 3.00) | −1.87 (−8.60, 4.86) | −2.58 (−9.04, 3.88) |
| | 0.07 mg | 58.1 (11.2) | −3.29 (−9.01, 2.44) | −6.68 (−12.67, −0.69)‡ | −7.18 (−13.24, −1.12)‡ | −6.63 (−12.67, −0.59)‡ | −6.44 (−13.13, 0.25) | −4.34 (−10.69, 2.02) |
| | 0.15 mg | 57.7 (11.1) | −2.65 (−8.20, 2.89) | −1.19 (−7.13, 4.75) | 1.29 (−4.75, 7.33) | 1.24 (−5.23, 7.72) | −0.40 (−7.06, 6.25) | 1.19 (−5.33, 7.72) |
| | 0.23 mg | 57.3 (11.4) | −6.41 (−12.27, −0.54)‡ | −6.54 (−12.63, −0.46)‡ | −8.63 (−14.70, −2.55)§ | −7.95 (−14.29, −1.62)‡ | −7.50 (−14.15, −0.84)‡ | −7.99 (−14.54, −1.45)‡ |
| mJSW | PBO | 3.44 (1.31) | | | | | | |
| | 0.03 mg | 3.30 (1.26) | N/A | N/A | N/A | N/A | N/A | 0.02 (−0.16, 0.21) |
| | 0.07 mg | 3.16 (1.10) | N/A | N/A | N/A | N/A | N/A | −0.11 (−0.27, 0.04) |
| | 0.15 mg | 3.26 (1.24) | N/A | N/A | N/A | N/A | N/A | −0.12 (−0.34, 0.09) |
| | 0.23 mg | 3.27 (1.08) | N/A | N/A | N/A | N/A | N/A | −0.03 (−0.18, 0.12) |
| PtGA | PBO | 52.8 (18.2) | | | | | | |
| | 0.03 mg | 53.2 (18.2) | −4.74 (−10.17, 0.69) | −5.03 (−10.78, 0.72) | −3.32 (−9.04, 2.40) | −1.80 (−7.92, 4.32) | −2.62 (−9.24, 3.99) | −2.13 (−8.36, 4.10) |
| | 0.07 mg | 53.8 (15.6) | −6.89 (−12.37, −1.41)‡ | −10.60 (−16.28, −4.92)‖ | −6.86 (−13.10, −0.63)‡ | −10.29 (−15.88, −4.70)‖ | −6.37 (−13.03, 0.29) | −5.54 (−11.80, 0.72) |
| | 0.15 mg | 48.0 (20.6) | −4.43 (−9.60, 0.74) | −1.02 (−6.28, 4.25) | −1.46 (−7.20, 4.28) | 0.59 (−5.36, 6.53) | −2.12 (−8.32, 4.07) | −1.94 (−8.36, 4.48) |
| | 0.23 mg | 49.5 (16.7) | −9.31 (−15.14, −3.49)§ | −10.00 (−15.62, −4.38)‖ | −7.62 (−13.41, −1.82)‡ | −9.09 (−14.95, −3.22)§ | −7.85 (−13.99, −1.71)‡ | −6.86 (−13.16, −0.56)‡ |

mJSW: Medial joint space width, Pain NRS: Pain Numeric Rating Scale, PBO: Vehicle placebo injection group, PtGA: Patient Global Assessment.
N/A: Not applicable (per the trial protocol, measurements were not taken).

* Mean (SD) baseline score/medial joint space width.

† Estimated least-squares mean difference between LOR and PBO in the change in outcome from baseline using baseline-adjusted ANCOVA (95% confidence interval) applied to the full analysis set (all subjects who received an injection).

‡ $P < 0.05$.

§ $P < 0.01$.

‖ $P < 0.001$.

**Table II** Baseline scores and changes from baseline at each timepoint for all lorecivivint dose groups

Osteoarthritis and Cartilage

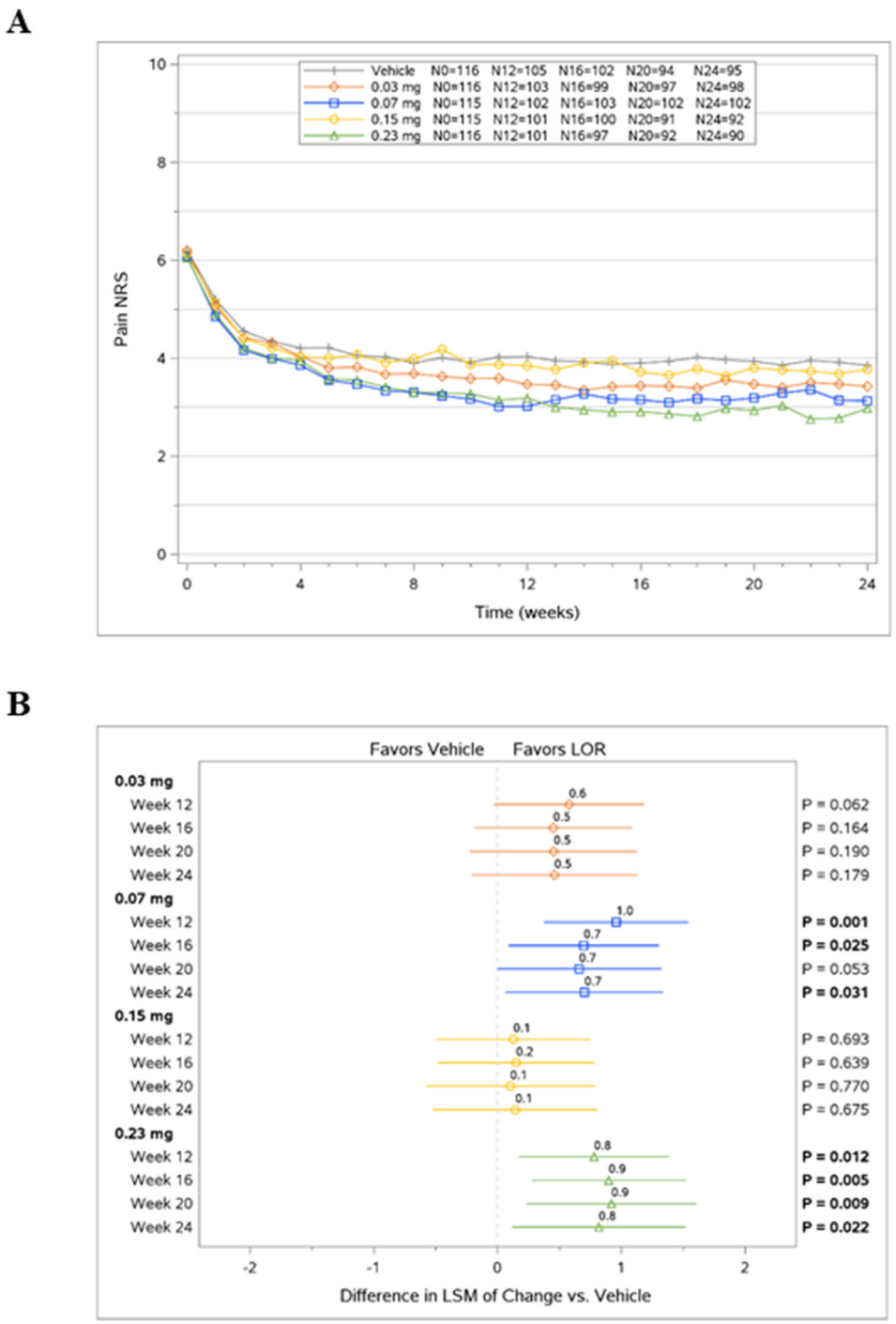


**Fig. 2**

Group means and statistical analysis of Pain NRS scores for the FAS (A) Group means of Pain NRS scores for the vehicle (PBO) group and all LOR dose (0.03, 0.07, 0.15, and 0.23 mg) groups at each timepoint. Lower scores indicate symptomatic improvements (B) Groupwise analysis of estimated least-squares mean differences in changes in the weekly average Pain NRS scores by ANCOVA after adjusting for baseline values. Statistical significance was set at $P < 0.05$. Abbreviations – ANCOVA: Analysis of covariance, FAS: Full analysis set, LOR: Lorecivivint, Pain NRS: Pain Numeric Rating Scale.

Please cite this article as: Yazici Y et al., A Phase 2b randomized trial of lorecivivint, a novel intra-articular CLK2/DYRK1A inhibitor and Wnt pathway modulator for knee osteoarthritis, Osteoarthritis and Cartilage, https://doi.org/10.1016/j.joca.2021.02.004

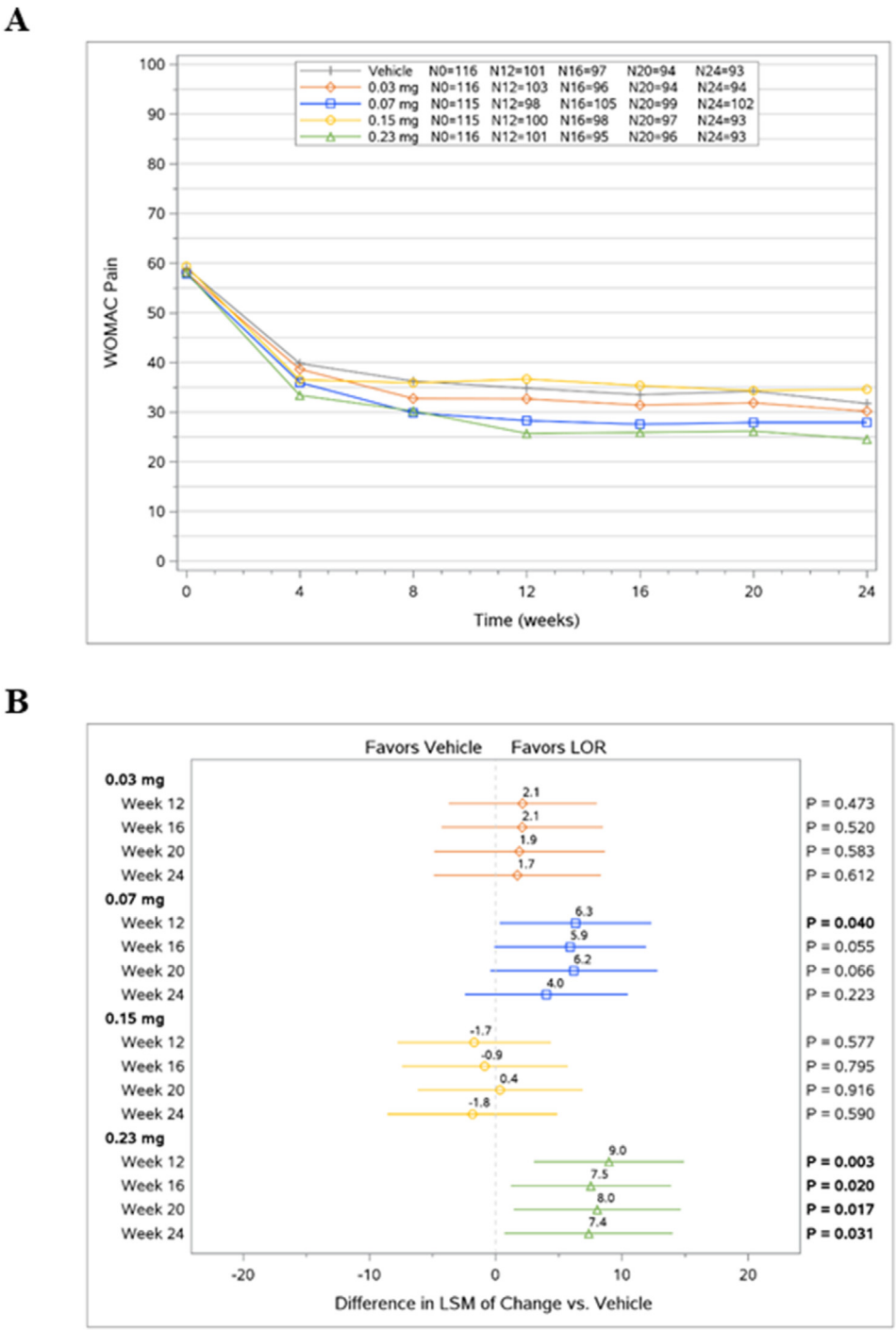


**Fig. 3**

Group means and statistical analysis of WOMAC Pain scores for the FAS (A) Group means of WOMAC Pain scores for the vehicle (PBO) group and all LOR dose (0.03, 0.07, 0.15, and 0.23 mg) groups at each timepoint. Lower scores indicate symptomatic improvements (B) Groupwise analysis of estimated least-squares mean differences in changes in the average WOMAC Pain scores by ANCOVA after adjusting for baseline values. Statistical significance was set at $P < 0.05$. Abbreviations – ANCOVA: Analysis of covariance, FAS: Full analysis set, LOR: Lorecivivint, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Osteoarthritis and Cartilage

Please cite this article as: Yazici Y et al., A Phase 2b randomized trial of lorecivivint, a novel intra-articular CLK2/DYRK1A inhibitor and Wnt pathway modulator for knee osteoarthritis, Osteoarthritis and Cartilage, https://doi.org/10.1016/j.joca.2021.02.004

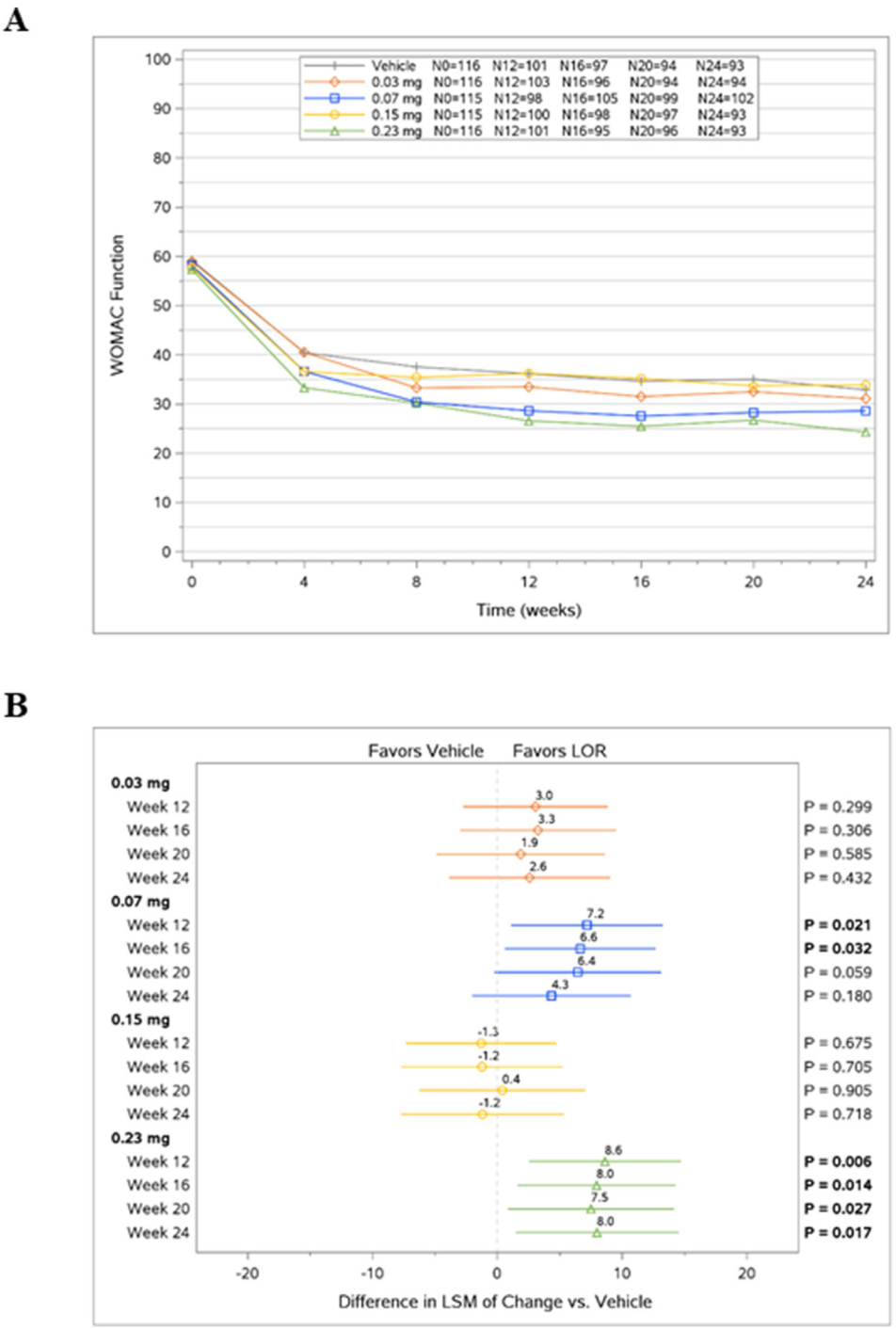


**Fig. 4**

Group means and statistical analysis of WOMAC Function scores for the FAS (A) Group means of WOMAC Function scores for the vehicle (PBO) group and all LOR dose (0.03, 0.07, 0.15, and 0.23 mg) groups at each timepoint. Lower scores indicate symptomatic improvements (B) Groupwise analysis of estimated least-squares mean differences in changes in the average WOMAC Function scores by ANCOVA after adjusting for baseline values. Statistical significance was set at $P < 0.05$. Abbreviations – ANCOVA: Analysis of covariance, FAS: Full analysis set, LOR: Lorecivivint, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

Please cite this article as: Yazici Y et al., A Phase 2b randomized trial of lorecivivint, a novel intra-articular CLK2/DYRK1A inhibitor and Wnt pathway modulator for knee osteoarthritis, Osteoarthritis and Cartilage, https://doi.org/10.1016/j.joca.2021.02.004

Pain NRS compared with PBO (Fig. 2). Significant improvements in Pain NRS compared with PBO were also observed at Week 12 (−0.96 [−1.54, −0.37], $P = 0.001$) and Week 16 (−0.69 [−1.30, −0.09], $P = 0.025$) in the 0.07 mg group and at Week 12 (−0.78 [−1.39, −0.17], $P = 0.012$), Week 16 (−0.90 [−1.52, −0.28], $P = 0.005$), and Week 20 (−0.92 [−1.60, −0.23], $P = 0.009$) in the 0.23 mg group. No significant differences compared with PBO were observed in either the 0.03 mg or 0.15 mg group at any tested timepoint.

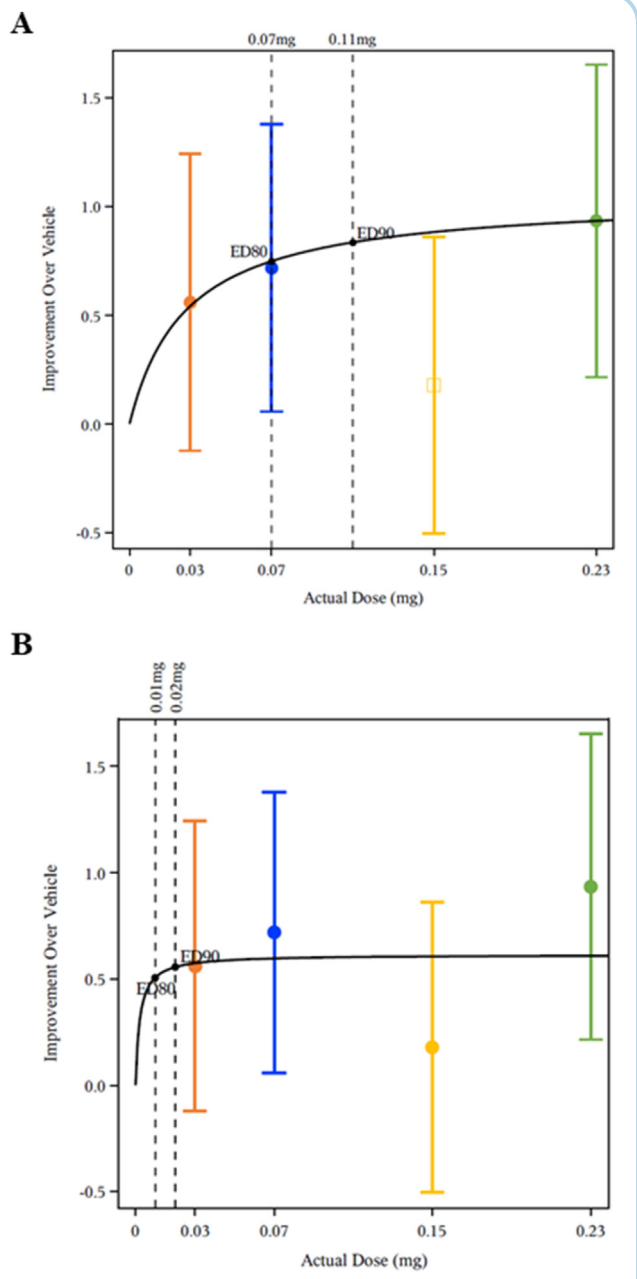


**Fig. 5** Pain NRS dose–response curves from the (A) primary (E-max ***P*** = 0.027) and (B) sensitivity (E-max ***P*** = 0.003) MCP-Mod analyses.

*WOMAC Pain and Function*: The 0.23 mg dose of LOR demonstrated significant improvements in WOMAC Pain (Fig. 3) at Week 24 (−7.36 [−14.03, −0.69], $P = 0.031$) compared with PBO. Significant improvements were also identified at Week 12 (−8.95 [−14.90, −3.01], $P = 0.003$), Week 16 (−7.54 [−13.88, −1.20], $P = 0.02$), and Week 20 (−8.05 [−14.66, −1.43], $P = 0.017$). The 0.23 mg dose demonstrated significant improvements compared with PBO in WOMAC Function (Fig. 4) at Week 24 (−7.99 [−14.54, −1.45], $P = 0.017$) as well as Week 12 (−8.63 [−14.70, −2.55], $P = 0.006$), Week 16 (−7.95 [−14.29, −1.62], $P = 0.014$), and Week 20 (−7.50 [−14.15, −1.45], $P = 0.027$).

While there was no significant improvement in either WOMAC Pain or Function at Week 24 in the 0.07 mg group, significant improvements were seen at Week 12 (−6.31 [−12.33, −0.29], $P = 0.04$) in the WOMAC Pain score (Fig. 3) and at Week 12 (−7.18 [−13.24, −1.12], $P = 0.021$) and Week 16 (−6.63 [−12.67, −0.59], $P = 0.032$) in the WOMAC Function score (Fig. 4). Neither the 0.03 mg nor the 0.15 mg group demonstrated a significant difference compared with PBO in either WOMAC score at any tested timepoint.

*mJSW*: No groups demonstrated statistically significant differences in mJSW at Week 24 compared with PBO (Supplemental Fig. 1). The mean change from baseline in mJSW at Week 24 was +0.02 mm in the 0.03 mg group, −0.11 mm in the 0.07 mg group, −0.11 mm in the 0.15 mg group, and −0.03 mm in the 0.23 mg group, whereas the mean change from baseline at Week 24 was −0.01 mm in the PBO group. No changes in any group exceeded the minimum detectable difference of 0.13 mm[29].

### *Efficacy: secondary outcomes*

*PtGA*: For all tested doses including PBO, baseline scores with standard deviations and estimated changes from baseline with 95% CIs for each 4-week timepoint from Weeks 4 to 24 are presented in Table II. Compared with PBO, treatment with 0.23 mg LOR demonstrated significant improvements in PtGA at Weeks 12, 16, 20, and 24 ($P = 0.01$, 0.003, 0.013, and 0.033, respectively); 0.07 mg LOR significantly improved PtGA scores at Weeks 12 and 16 ($P = 0.031$ and $P < 0.001$, respectively) compared with PBO (Supplemental Fig. 2). Neither 0.03 mg nor 0.15 mg LOR demonstrated a significant difference in PtGA compared with PBO at any tested timepoint.

### *Sensitivity analyses*

Neither of the sensitivity analyses provided a different overall inference from the primary analysis. Between-group comparisons of daily NSAID/acetaminophen usage showed no significant differences between any pairing. Of note, the MMRM analysis, which modeled all timepoints in the analysis while adjusting for the within-subject correlation, indicated that 0.07 mg established a statistically significant improvement compared with PBO starting at Week 5 (−0.57 [−1.09, −0.05], $P = 0.032$) that persisted through Week 24 (−0.66 [−1.20, −0.12], $P = 0.016$) in Pain NRS; no other dose demonstrated the same treatment pattern (Supplemental Table 1).

### *MCP-Mod analysis*

The initial MCP-Mod analysis of Pain NRS at Week 24 estimated that 0.01 mg and 0.03 mg could be considered the 80%- and 90%-effective doses, respectively, under the E-max model (AIC = 2,150.41, $P = 0.042$, Fig. 5(A)). The MCP-Mod analyses of additional endpoints (WOMAC Pain, WOMAC Function, and mJSW at Week 24) failed to provide a candidate dose-relationship model.

Please cite this article as: Yazici Y et al., A Phase 2b randomized trial of lorecivivint, a novel intra-articular CLK2/DYRK1A inhibitor and Wnt pathway modulator for knee osteoarthritis, Osteoarthritis and Cartilage, https://doi.org/10.1016/j.joca.2021.02.004

| TEAEs Reported [#TEAE/*n* (%)] | Lorecivivint (LOR) | | | | PBO* $n = 114$ | Sham $n = 120$ | All Subjects* $N = 695$ |
|---|---|---|---|---|---|---|---|
| | 0.03 mg $n = 106$ | 0.07 mg $n = 104$ | 0.15 mg $n = 106$ | 0.23 mg $n = 106$ | | | |
| **Total TEAEs/Unique Subjects (%)**** | **62/36 (34.0)** | **63/40 (38.5)** | **61/30 (28.3)** | **71/32 (30.2)** | **64/36 (31.6)** | **61/39 (32.5)** | **405/223 (32.1)** |
| *Arthralgia* | 6/6 (5.7) | 8/7 (6.7) | 2/2 (1.9) | 12/9 (8.5) | 3/3 (2.6) | 7/7 (5.8) | 42/37 (5.3) |
| *URT† Infection* | 2/2 (1.9) | 5/5 (4.8) | 0/0 (0.0) | 3/3 (2.8) | 4/4 (3.5) | 5/4 (3.3) | 20/19 (2.7) |
| *Sinusitis* | 1/1 (0.9) | 1/1 (1.0) | 1/1 (0.9) | 3/3 (2.8) | 1/1 (0.9) | 4/4 (3.3) | 11/11 (1.6) |
| *Urinary Tract Infection* | 1/1 (0.9) | 1/1 (1.0) | 1/1 (0.9) | 1/1 (0.9) | 1/1 (0.9) | 4/4 (3.3) | 10/10 (1.4) |
| *Viral URT† Infection* | 2/2 (1.9) | 2/2 (1.9) | 0/0 (0.0) | 1/1 (0.9) | 3/3 (2.6) | 1/1 (0.8) | 9/9 (1.3) |
| *Osteoarthritis* | 2/2 (1.9) | 2/2 (1.9) | 1/1 (0.9) | 1/1 (0.9) | 1/1 (0.9) | 1/1 (0.8) | 8/8 (1.2) |
| *Bronchitis* | 3/3 (2.8) | 1/1 (1.0) | 1/1 (0.9) | 1/1 (0.9) | 0/0 (0.0) | 0/0 (0.0) | 7/7 (1.0) |

Bold font represents the proportion of total treatment-emergent adverse events and total number of unique subjects per treatment group, also expressed as a percentage in parentheses.

* PBO: Vehicle placebo injection group. All subjects: Includes those who received an unspecified dose of LOR ($n = 39$).

** The totals include TEAEs reported at a rate of <1%.

† URT: Upper respiratory tract.

**Table III** Number of treatment-emergent adverse events (#TEAEs) ≥1% with number (n) and percent (%) of reporting subjects by group

Osteoarthritis and Cartilage

The complete MCP-Mod results table and analysis of the secondary outcome are provided in Supplemental Table 2.

*Safety*

No clinically significant differences between active treatment and PBO groups were noted for TEAEs (Table III), clinical laboratory results, or vital signs. All doses appeared to be well tolerated.

Six serious adverse events (SAEs) were reported: nephrolithiasis (1 event/1 subject, 0.9% of the group) and supraventricular tachycardia (1/1, 0.9%) in the 0.03 mg group; breast cancer (1/1, 0.9%) and nephrolithiasis (1/1, 0.9%) in the 0.23 mg group; coronary artery disease (1/1, 0.9%) in the PBO group; and perforated appendicitis (1/1, 0.1% of all subjects) in a subject who received an unspecified dose. All SAEs from this study were assessed as "not related" or "unlikely related" to study medication by the investigators. There were no deaths reported in this 24-week trial.

## Discussion

In this 24-week Phase 2b trial, 0.07 mg and 0.23 mg LOR demonstrated clinically meaningful and statistically significant improvements in pain and function compared with PBO in subjects with knee OA at Week 24. Both doses also met many of the additional clinical endpoints at other timepoints (Weeks 12, 16, and 20) on all 3 scales, indicative of clinically relevant (>MCID) subject-reported benefits compared with PBO. LOR demonstrated a good safety profile with no serious drug-related adverse events and no differences in TEAEs from the control groups.

While providing evidence that LOR is therapeutically beneficial was an important aspect of this Phase 2b trial, its key goal was to narrow the candidate doses to be studied in Phase 3 trials. Employing the MCP-Mod approach allows for accomplishment of this goal with statistical rigor[35]. When the results of this trial were explored using MCP-Mod, the dose modeling suggested that LOR could be efficacious at all tested doses; that is, the model identified 0.03 mg LOR as potentially being the 90%-effective dose. However, the primary analyses demonstrated that while the 0.03 mg and 0.15 mg doses of LOR could produce clinically meaningful (>MCID[29]) improvements, only the 0.07 mg and 0.23 mg doses were significantly more efficacious than PBO. A sensitivity analysis on the MCP-Mod results subsequently estimated the lowest candidate dose achieving clinically meaningful benefits to be 0.07 mg.

The ability of a study population to discriminate pain between target and non-target knees is critical within a knee OA clinical trial to accurately assess changes in target knee pain. In the current study, this was addressed by enrolling subjects who had more pain in the target knee compared with the non-target knee based on Pain NRS cutoff points. The PRO results from other knee OA studies have been potentially compromised due to subjects' inability to discriminate target knee pain from bilateral knee pain[37] or from comorbid widespread pain due to conditions such as fibromyalgia[15]. In a previous Phase 2a trial, LOR failed to achieve the primary endpoint of Week 13 improvement in WOMAC Pain compared with PBO for the FAS, which did not exclude subjects with bilateral symptoms and comorbid pain[26]. However, when those results were analyzed using a prespecified subject subgroup of "unilateral symptomatic knee OA" and a *post hoc* "unilateral symptomatic knee OA without widespread pain" subgroup, the 0.07 mg dose demonstrated significantly improved WOMAC Pain and Function scores compared with PBO from Week 26 to 52. The enrollment stratification used in this Phase 2b trial allowed for prospective evaluation of specific subject-selection criteria, specifically with regard to bodily pain outside the target knee. Briefly, the effects of unilateral vs bilateral symptomatic knee OA appeared to be ameliorated by using Pain NRS cutoffs between knees during screening. Similar to the effects seen in the Phase 2a trial, subjects with WPI ≤4 and SSQ2 ≤2 showed better treatment discrimination than those above these thresholds. Overall, when the stratifications were considered, they revealed previously obscured distinctions between groups, suggesting population enhancements that could benefit future studies of LOR. Prospectively testing these eligibility criteria by trial stratification validated them for such studies. Similar selection criteria have been employed to enhance subject selection and enrichment in other OA clinical trials[29,38].

Treatment with IA injection produced clinically meaningful improvements from baseline in pain for LOR (all doses, ~50% improvement in Pain NRS and 55–57% in WOMAC Pain) and PBO (~33% improvement in Pain NRS and 43% in WOMAC Pain)

Please cite this article as: Yazici Y et al., A Phase 2b randomized trial of lorecivivint, a novel intra-articular CLK2/DYRK1A inhibitor and Wnt pathway modulator for knee osteoarthritis, Osteoarthritis and Cartilage, https://doi.org/10.1016/j.joca.2021.02.004

injections. The placebo effects observed replicated typical placebo effects in other IA knee OA studies[30]. However, the 0.07 mg and 0.23 mg doses of LOR significantly improved pain and function PROs compared with PBO at several timepoints. Importantly, this trial was conducted on a background of NSAID analgesia, unlike most other trials in which background analgesia washout designs are employed. Thus, LOR was tested as an "add-on" analgesic treatment, reflecting likely use in clinical practice. Analysis of background analgesic usage found no significant differences between any treatment groups, which suggests that the observed efficacy responses of LOR compared with the PBO group were not related to subjects' analgesic usage. Furthermore, no imputation was conducted for missing data; the placebo effects seen at Week 24 may have been impacted by an increase in PBO subjects leaving the trial due to lack of efficacy at that timepoint.

There were no significant differences in mJSW compared with PBO in this 24-week study, which was too short of an interval to detect significant changes in radiographic mJSW. These subjects are being followed up in a long-term extension that will include further X-rays. Also, this study excluded subjects with BMI >35 kg/m$^2$, which may have decreased the rate of group mean structural progression[39]. Future studies of longer duration will further evaluate the structure-modifying potential of LOR with regard to mJSW changes.

Concerns exist regarding the long-term safety of many currently prescribed systemic pharmacologic treatments for OA[5] and other drug interactions due to the high rate of comorbidities[40] that accompany OA. LOR appeared well tolerated in this Phase 2b trial, and no major safety signals have been identified to date. As previous studies of LOR[41] have detected no systemic exposure after a single injection, its localized pharmacokinetics likely limit off-target effects and other drug- and comorbidity-related interactions[42]. However, longer-term exposure data are needed to establish the drug's safety profile.

In this 24-week Phase 2b trial, LOR met primary clinical endpoints and appeared safe and well tolerated. As a confirmatory trial of a previous proof-of-concept Phase 2a trial[26], the results identified a potential target population for future studies and provided further evidence that LOR improved symptoms of knee OA compared with either baseline or PBO. MCP-Mod analysis determined that the 0.07 mg LOR dose should be the lowest dose considered for future studies. Based on the totality of the data from preclinical studies[19] and Phase 1 and 2 trials of LOR, the 0.07 mg dose is being advanced into pivotal efficacy and safety studies, which are ongoing.

## Contributions

Yusuf Yazici: Study design, data acquisition, data analysis, and data interpretation; critical revision and final approval of the manuscript.

Timothy E. McAlindon: Data interpretation; critical revision and final approval of the manuscript.

Allan Gibofsky: Data interpretation; critical revision and final approval of the manuscript.

Nancy E. Lane: Data interpretation; critical revision and final approval of the manuscript.

Christian Lattermann: Data interpretation; critical revision and final approval of the manuscript.

Nebojsa Skrepnik: Data acquisition and data interpretation; critical revision and final approval of the manuscript.

Christopher J. Swearingen: Study design, data acquisition, data analysis, and data interpretation; drafting, critical revision, and final approval of the manuscript.

Ismail Simsek: Study design, data acquisition, data analysis, and data interpretation; drafting, critical revision, and final approval of the manuscript.

Heli Ghandehari: Data analysis and data interpretation; drafting, critical revision, and final approval of the manuscript.

Anita DiFrancesco: Study design, data acquisition, data analysis, and data interpretation; drafting, critical revision, and final approval of the manuscript.

Jamielle Gibbs: Study design, data acquisition, and data analysis; drafting, critical revision, and final approval of the manuscript.

Jeyanesh R.S. Tambiah: Study design, data acquisition, data analysis, and data interpretation; drafting, critical revision, and final approval of the manuscript.

Marc. C. Hochberg: Data interpretation; critical revision and final approval of the manuscript.

## Conflict of interest

Drs. Yazici, Swearingen, Simsek, and Tambiah and Ms. DiFrancesco own stock or stock options in Samumed. Dr. McAlindon has received consulting fees from Samumed, Astellas, Flexion, Pfizer, Regeneron, and Seikugaku (less than $10,000 each) and research support from Samumed. Dr. Gibofsky has received consulting fees, speaking fees, and/or honoraria from AbbVie, Pfizer, Relburn Pharma, Samumed, Flexion, Celgene, and Eli Lilly (less than $10,000 each), owns stock or stock options in Amgen, AbbVie, Pfizer, and Johnson & Johnson, and has served as a paid consultant with investment analysts on behalf of the Gerson Lehman Group. Dr. Lane has received consulting fees from Samumed, Amgen, Eli Lilly, and Pfizer (less than $10,000 each). Dr. Lattermann has received consulting fees from Samumed, Flexion, Vericel, and Joint Restoration Foundation (less than $10,000 combined). Dr. Hochberg has received consulting fees, speaking fees, and/or honoraria from Bone Therapeutics, Bristol Myers Squibb, EMD Serono, IBSA, Novartis Pharma AG, Regenosine, Samumed, Symic Bio, Theralogix, TissueGene, Vertex Pharmaceuticals, Vizuri Health Sciences, Zynerva, Covance, Galapagos, ICON, and IQVIA (less than $10,000 each) and Eli Lilly and Pfizer (more than $10,000), owns stock or stock options in BriOri Biotech and Theralogix, and receives royalties from Wolters Kluwer for *UpToDate* and from Elsevier for *Rheumatology 7th Edition*.

## Role of the study sponsor

Samumed, LLC designed, funded, and monitored the study and also conducted the data management and statistical analysis. The authors independently interpreted the results and had the final decision to submit the manuscript for publication.

## Acknowledgments

The authors gratefully acknowledge and thank the study subjects, investigators, and associated research professionals who contributed their time and efforts to these clinical studies. The authors would also like to thank Andrew Ray, Elizabeth Orient, and Sarah Kennedy for critical revision of this manuscript and the Samumed team for their contributions to these clinical studies. All studies described in this report and the preparation of this manuscript were funded by Samumed, LLC.

## Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joca.2021.02.004.

Please cite this article as: Yazici Y et al., A Phase 2b randomized trial of lorecivivint, a novel intra-articular CLK2/DYRK1A inhibitor and Wnt pathway modulator for knee osteoarthritis, Osteoarthritis and Cartilage, https://doi.org/10.1016/j.joca.2021.02.004

## References

1. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, *et al*. The global burden of hip and knee osteoarthritis: estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis 2014;73(7):1323–30, https://doi.org/10.1136/annrheumdis-2013-204763.
2. Zhang R-K, Li G-W, Zeng C, Lin C-X, Huang L-S, Huang G-X, *et al*. Mechanical stress contributes to osteoarthritis development through the activation of transforming growth factor beta 1 (TGF-β1). Bone Joint Res 2018, https://doi.org/10.1302/2046-3758.711.bjr-2018-0057.r1. Published online.
3. Lin NY, Distler A, Beyer C, Philipi-Schöbinger A, Breda S, Dees C, *et al*. Inhibition of Notch1 promotes hedgehog signalling in a HES1-dependent manner in chondrocytes and exacerbates experimental osteoarthritis. Ann Rheum Dis 2016, https://doi.org/10.1136/annrheumdis-2015-208420. Published online.
4. Zhou Y, Wang T, Hamilton JL, Chen D. Wnt/β-catenin signaling in osteoarthritis and in other forms of arthritis. Curr Rheumatol Rep 2017, https://doi.org/10.1007/s11926-017-0679-z.
5. Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA, *et al*. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthr Cartil 2019;27(11):1578–89, https://doi.org/10.1016/j.joca.2019.06.011.
6. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, *et al*. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Rheumatol 2020;72(2):220–33, https://doi.org/10.1002/art.41142.
7. Conaghan PG, Bowes MA, Kingsbury SR, Brett A, Guillard G, Rizoska B, *et al*. Disease-modifying effects of a novel cathepsin k inhibitor in osteoarthritis: a randomized controlled trial. Ann Intern Med 2020;172(2):86–95, https://doi.org/10.7326/M19-0675.
8. Fleischmann RM, Bliddal H, Blanco FJ, Schnitzer TJ, Peterfy C, Chen S, *et al*. A phase II trial of lutikizumab, an anti-–interleukin-1α/β dual variable domain immunoglobulin, in knee osteoarthritis patients with synovitis. Arthritis Rheumatol 2019;71(7):1056–69, https://doi.org/10.1002/art.40840.
9. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis. Ann Intern Med 2015, https://doi.org/10.7326/m14-1231.
10. Roberts E, Nunes VD, Buckner S, Latchem S, Constanti M, Miller P, *et al*. Paracetamol: not as safe as we thought? A systematic literature review of observational studies. Ann Rheum Dis 2016, https://doi.org/10.1136/annrheumdis-2014-206914. Published online.
11. da Costa BR, Reichenbach S, Keller N, Nartey L, Wandel S, Jüni P, *et al*. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. Lancet 2017, https://doi.org/10.1016/S0140-6736(17)31744-0. Published online.
12. Mobasheri A, Saarakkala S, Finnilä M, Karsdal MA, Bay-Jensen AC, van Spil WE. Recent advances in understanding the phenotypes of osteoarthritis. F1000Research 2019;8, https://doi.org/10.12688/f1000research.20575.1.
13. Kraus VB, Collins JE, Hargrove D, Losina E, Nevitt M, Katz JN, *et al*. Predictive validity of biochemical biomarkers in knee osteoarthritis: data from the FNIH OA Biomarkers Consortium. Ann Rheum Dis 2017;76(1):186–95, https://doi.org/10.1136/annrheumdis-2016-209252.
14. Neogi T, Felson D, Niu J, Nevitt M, Lewis CE, Aliabadi P, *et al*. Association between radiographic features of knee osteoarthritis and pain: results from two cohort studies. BMJ 2009;339. b2844-b2844. Available at, http://www.bmj.com/cgi/doi/10.1136/bmj.b2844.
15. Clauw DJ, Hassett AL. The role of centralised pain in osteoarthritis. Clin Exp Rheumatol. 35 Suppl 107(5):79-84.
16. Altman RD, Devji T, Bhandari M, Fierlinger A, Niazi F, Christensen R. Clinical benefit of intra-articular saline as a comparator in clinical trials of knee osteoarthritis treatments: a systematic review and meta-analysis of randomized trials. Semin Arthritis Rheum 2016;46(2):151–9, https://doi.org/10.1016/J.SEMARTHRIT.2016.04.003.
17. Hochberg MC, Guermazi A, Guehring H, Aydemir A, Wax S, Fleuranceau-Morel P, *et al*. Effect of intra-articular sprifermin vs placebo on femorotibial joint cartilage thickness in patients with osteoarthritis: the FORWARD randomized clinical trial. JAMA - J Am Med Assoc 2019;322(14):1360–70, https://doi.org/10.1001/jama.2019.14735.
18. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. Arthritis Rheum 2012, https://doi.org/10.1002/art.34453.
19. Deshmukh V, O'Green AL, Bossard C, Seo T, Lamangan L, Ibanez M, *et al*. Modulation of the Wnt pathway through inhibition of CLK2 and DYRK1A by lorecivivint as a novel, potentially disease-modifying approach for knee osteoarthritis treatment. Osteoarthr Cartil 2019;27:1347–60, https://doi.org/10.1016/j.joca.2019.05.006.
20. Lories RJ, Corr M, Lane NE. To Wnt or not to Wnt: the bone and joint health dilemma. Nat Rev Rheumatol 2013;9(6):328–39, https://doi.org/10.1038/nrrheum.2013.25.
21. de Boer J, Wang HJ, van Blitterswijk C. Effects of wnt signaling on proliferation and differentiation of human mesenchymal stem cells. Tissue Eng 2004, https://doi.org/10.1089/107632704323061753.
22. Yano F, Kugimiya F, Ohba S, Ikeda T, Chikuda H, Ogasawara T, *et al*. The canonical Wnt signaling pathway promotes chondrocyte differentiation in a Sox9-dependent manner. Biochem Biophys Res Commun 2005, https://doi.org/10.1016/j.bbrc.2005.06.041. Published online.
23. Thysen S, Luyten FP, Lories RJ. Loss of Frzb and Sfrp1 differentially affects joint homeostasis in instability-induced osteoarthritis. Osteoarthr Cartil 2015, https://doi.org/10.1016/j.joca.2014.10.010.
24. Lories RJU, Peeters J, Bakker A, Tylzanowski P, Derese I, Schrooten J, *et al*. Articular cartilage and biomechanical properties of the long bones in Frzb-knockout mice. Arthritis Rheum 2007, https://doi.org/10.1002/art.23137. Published online.
25. Zhu M, Tang D, Wu Q, Hao S, Chen M, Xie C, *et al*. Activation of β-catenin signaling in articular chondrocytes leads to osteoarthritis-like phenotype in adult β-catenin conditional activation mice. J Bone Miner Res 2009, https://doi.org/10.1359/jbmr.080901. Published online.
26. Yazici Y, McAlindon TE, Gibofsky A, Lane NE, Clauw D, Jones M, *et al*. Lorecivivint, a novel intra-articular CLK2/DYRK1A inhibitor and wnt pathway modulator for treatment of knee osteoarthritis: a phase 2 randomized trial. Arthritis Rheum 2020 Oct;72(10):1694–706.
27. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, *et al*. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. Arthritis Rheum 1986;29(8):1039–49, https://doi.org/10.1002/art.1780290816.

Please cite this article as: Yazici Y et al., A Phase 2b randomized trial of lorecivivint, a novel intra-articular CLK2/DYRK1A inhibitor and Wnt pathway modulator for knee osteoarthritis, Osteoarthritis and Cartilage, https://doi.org/10.1016/j.joca.2021.02.004

28. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Häuser W, Katz RS, *et al*. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: a modification of the ACR preliminary diagnostic criteria for fibromyalgia. J Rheumatol 2011;38(6):1113–22, https://doi.org/10.3899/jrheum.100594.
29. Strand V, Boers M, Idzerda L, Kirwan JR, Kvien TK, Tugwell PS, *et al*. It's good to feel better but it's better to feel good and even better to feel good as soon as possible for as long as possible. Response criteria and the importance of change at OMERACT 10. J Rheumatol 2011, https://doi.org/10.3899/jrheum.110392.
30. Tubach F, Ravaud P, Baron G, Falissard B, Logeart I, Bellamy N, *et al*. Evaluation of clinically relevant states in patient reported outcomes in knee and hip osteoarthritis: the patient acceptable symptom state. Ann Rheum Dis 2005;64(1):34–7, https://doi.org/10.1136/ARD.2004.023028.
31. Ting N. Practical and statistical considerations in designing an early phase II osteoarthritis clinical trial: a case study. Commun Stat Theor Methods 2009;38(18):3282–96, https://doi.org/10.1080/03610920802382619.
32. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Note for guidance on statistical principles for clinical trials. In: ICH Topic E9: Statistical Principles for Clinical Trials 1998.
33. Bretz F, Pinheiro JC, Branson M. Combining multiple comparisons and modeling techniques in dose-response studies. Biometrics 2005;61(3):738–48, https://doi.org/10.1111/j.1541-0420.2005.00344.x.
34. US Food and Drug Administration. Drug development tools: fit-for-purpose initiative, https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tools-fit-purpose-initiative. Accessed June 26, 2020.
35. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP) Qualification Opinion of MCP-Mod as an Efficient Statistical Methodology for Model-Based Design and Analysis of Phase II Dose Finding Studies under Model Uncertainty 2013.
36. Schorning K, Bornkamp B, Bretz F, Dette H. Model selection versus model averaging in dose finding studies. Stat Med 2016;35(22):4021–40, https://doi.org/10.1002/sim.6991.
37. Riddle DL, Stratford PW. Unilateral vs bilateral symptomatic knee osteoarthritis: associations between pain intensity and function. Rheumatology 2013;(September):2229–37, https://doi.org/10.1093/rheumatology/ket291.
38. McAlindon TE, Driban JB, Henrotin Y, Hunter DJ, Jiang GL, Skou ST, *et al*. OARSI Clinical Trials Recommendations: design, conduct, and reporting of clinical trials for knee osteoarthritis. Osteoarthr Cartil 2015, https://doi.org/10.1016/j.joca.2015.03.005. Published online.
39. Felson DT, Goggins J, Niu J, Zhang Y, Hunter DJ. The effect of body weight on progression of knee osteoarthritis is dependent on alignment. Arthritis Rheum 2004, https://doi.org/10.1002/art.20726.
40. Suri P, Morgenroth DC, Hunter DJ. Epidemiology of osteoarthritis and associated comorbidities. PMRJ 2012;4(5):S10–9, https://doi.org/10.1016/j.pmrj.2012.01.007.
41. Barroga C, Hu Y, Deshmukh V, Hood J. Discovery of an intra-articular injection small molecule inhibitor of the wnt pathway (SM04690) as a potential disease modifying treatment for knee osteoarthritis. Arthritis Rheumatol 2015;67(suppl 10).
42. Butoescu N, Jordan O, Doelker E. Intra-articular drug delivery systems for the treatment of rheumatic diseases: a review of the factors influencing their performance. Eur J Pharm Biopharm 2009, https://doi.org/10.1016/j.ejpb.2009.06.009.

Please cite this article as: Yazici Y et al., A Phase 2b randomized trial of lorecivivint, a novel intra-articular CLK2/DYRK1A inhibitor and Wnt pathway modulator for knee osteoarthritis, Osteoarthritis and Cartilage, https://doi.org/10.1016/j.joca.2021.02.004