A Phase 3, 56-week, randomised, double-blind, placebo-controlled study (OA-11) utilising patient-reported and radiographic outcomes evaluating the efficacy and safety of a lorecivivint injection in patients with moderate to severe knee osteoarthritis

Y. Yazici[1,2], J.R.S. Tambiah[1], C.J. Swearingen[1], J. Britt[1], S. Kennedy[1], M.S. Fineman[1], I. Simsek[1], E. Solomon[1], T.E. McAlindon[3]

[1]Biosplice Therapeutics, Inc. San Diego, CA; [2]NYU Grossman School of Medicine, New York, NY; [3]UMass Chan Medical School and UMass Memorial Medical Center, Boston, MA, USA.

Abstract

Objective

To determine the efficacy, safety, and tolerability of intraarticular (IA) lorecivivint (LOR) in the treatment of knee osteoarthritis (OA).

Methods

Patients with American College of Rheumatology criteria-defined knee OA, Kellgren-Lawrence (KL) grades 2–3, and medial Joint Space Width (JSW) by radiograph between 1.5 and 4 mm in the target knee were enrolled in this phase 3, 56-week, multicentre, double-blind, placebo-controlled study. Patients were randomised (1:1) to receive a single IA injection of 0.07 mg LOR or vehicle placebo (PBO) on Day 1. The primary endpoint was the change from baseline in pain Numeric Rating Scale (NRS) at Week 12. Additional outcomes included the change from baseline in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Function, WOMAC Pain, Patient Global Assessment, medial JSW, and safety.

Results

513 patients were randomised. Baseline mean medial JSW was 2.61 (±0.7) mm. The mean change from baseline in weekly average of daily Pain NRS at Week 12 was LOR -2.24 (± 0.13) compared with PBO -2.49 (± 0.13); p=0.185, 95% confidence interval (CI) (-0.12, 0.62). No discernable treatment effects of LOR compared with PBO were revealed by the analysis of other endpoints. Neither treatment group showed meaningful medial JSW loss over 52 weeks. Incidences, severity, and relationship to study treatment of AEs were similar between LOR and PBO treatment groups.

Conclusion

In this study, LOR was well tolerated although it did not meet the primary endpoint of change from baseline in target knee Pain NRS at Week 12.

Key words

Lorecivivint, osteoarthritis, CLK/DYRK inhibitor

Yusuf Yazici, MD
Jeyanesh R.S. Tambiah, MBChB
Christopher J. Swearingen, PhD
Jonathan Britt, MS
Sarah Kennedy, PhD
Mark S. Fineman, PhD
Ismail Simsek, MD
Emily Solomon, BSN, RN
Timothy E. McAlindon, MD, MPH

Please address correspondence to:
Yusuf Yazici
Biosplice Therapeutics, Inc.,
9360 Towne Centre Drive,
San Diego, CA 92121, USA.
E-mail: yusuf.yazici@biosplice.com

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Introduction

Osteoarthritis (OA) is the most common joint disease and a major reason for activity limitation in adults (1). Movement limitations are present in approximately 80% of OA patients, and 25% are unable to perform major activities of daily living (2). Non-pharmacological treatments including exercise and weight loss are core in OA management, usually with limited improvements (3), and pharmacological treatments are frequently restricted due to side effects.

Lorecivivint (LOR) is a novel, small-molecule intra-articular (IA) inhibitor of CDC-like kinase 2 (CLK 2) and dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) thought to modulate Wnt and inflammatory pathways (4). Phase 1 and 2 studies showed LOR to be safe, and relative to PBO, improve patient-reported outcomes (PROs) and maintain medial joint space width (JSW) (5, 6). This 56-week phase 3 study (OA-11, NCT03928184), labelled STRIDES-XRAY, evaluated the safety and effectiveness of LOR 0.07 mg via PROs and radiographic assessments in patients with advanced structural knee OA.

Methods

Study design

OA-11 was a phase 3, multicentre, randomised, double-blind, placebo (PBO)-controlled, parallel-group trial of LOR 0.07 mg dose injected into the target knee of moderately to severely symptomatic knee OA patients on Day 1, and evaluated for 56 weeks. Patients were enrolled via a pre-screening protocol, into either OA-11 or OA-10, a separate 28-week LOR trial. The objective of OA-11 was to determine the efficacy of LOR 0.07 mg for the treatment of knee OA. The primary endpoint was change from baseline in target knee pain assessed by weekly average of daily pain Numeric Rating Scale (NRS, [0–10]) at Week 12. Other endpoints included change from baseline in the following: average daily pain NRS at Weeks 24 and 52; Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Total; WOMAC Function; WOMAC Pain; Patient Global Assessment (PGA), all at Weeks 12, 24 and 52. Use of nonsteroidal anti-inflammatory drugs (NSAIDs)/acetaminophen was assessed by Week 52. Structural progression was evaluated by radiographic medial JSW measurements at screening, Weeks 24 and 52.

Safety outcomes included adverse event (AE) assessments; laboratory and vital signs measures and change from baseline in serum biomarkers concentrations (procollagen type I [P1NP], β-C-terminal telopeptide [β-CTX]), and (cartilage oligomeric matrix protein [COMP]) at Week 56.

Radiographs were evaluated by a blinded radiologist at an independent central imaging vendor. Anterior-posterior radiographs of both knees were obtained and the medial JSW was measured using a landmark-based, fixed-location method with a positioner.

This study was designed, funded, and conducted by Biosplice Therapeutics, Inc. It was conducted in accordance with the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice Guidelines, and applicable regulations. Appropriate independent ethics committee or institutional review board approvals were obtained. All patients provided written informed consent prior to participating in any study related procedures.

Subjects

Eligible patients were adults aged 40-80 years with a diagnosis of primary idiopathic femorotibial OA according to the American College of Rheumatology clinical and radiographic criteria, Kellgren-Lawrence (KL) Grade 2 or 3 and radiographic medial JSW between 1.5–4 mm in the target knee within 12 weeks of the Screening Visit (SV) (8). Patients were excluded from the study if they had: malalignment of target knee anatomical axis (varus or valgus >10°); partial/complete joint replacement in either knee; any bone fracture; a knee brace or surgery in any knee within 26 weeks prior to Day 1. Patients requiring assistive devices ≥50% of the time were excluded.

Patients had pain compatible with OA of the knee(s) for at least 26 weeks prior to the SV and the primary source of pain throughout the body was due to

their target knee OA. Body mass index was ≤40 kg/m^2 at the SV; widespread pain index (WPI) score ≤4 and Symptom Severity Question 2 score ≤2 at the SV and Day 1. Patients had an average Pain NRS intensity score ≥4 and ≤8 on an 11-point [0-10] scale for the target knee and <4 for non-target knee for 4 of 7 days immediately preceding Day 1. Patients were required to have target knee WOMAC Function subscore of 68–136 (max. 170), WOMAC Pain of 20–40 (max. 50) regardless of symptomatic oral treatment and be willing to use a daily electronic diary.

A negative drug test for amphetamines, cocaine, opiates, benzodiazepines, tricyclic antidepressants and others was required, unless any drugs were therapeutically prescribed. Target knee IA injections, including, hyaluronic acid, platelet-rich plasma, and stem cells within 26 weeks, or IA corticosteroids, or aspiration within 12 weeks prior to Day 1 were prohibited. Previous LOR treatment, electrotherapy, acupuncture, chiropractic or physical therapy, ultrasound, and elective surgery for knee OA were prohibited. Patients were excluded if they were receiving opioids >1x per week, centrally acting analgesics, systemic steroids, or anticonvulsants within 12 weeks prior to Day 1 or topical anesthetic agents within 7 days of Day 1. NSAIDs and/or acetaminophen use were allowed if the patient received them at a stable dose for at least 4 weeks prior to Day 1. Participation in another clinical trial within 26 weeks prior to the SV was not allowed. Pregnant women, women of childbearing potential, or male partners of childbearing potential women not willing to use contraception were excluded. Patients with malignancies, active infections, or uncontrolled conditions that could affect study assessments were excluded. Patients with depression or anxiety must have been clinically stable for at least 12 weeks prior to screening.

Treatment protocol

Eligible patients were randomised in a 1:1 ratio to receive LOR 0.07 mg in a 2 mL injectable suspension or vehicle PBO. Only a single knee was treated for each patient. LOR or PBO was administered in the clinic on Day 1 by an unblinded investigator through lateral or medial approaches based on their standard practice. The injections may have been guided by ultrasound or fluoroscopy according to investigators' usual practice, however this information was not tracked. Because LOR drug product is a suspension, prior aspiration of synovial fluid into the injectate syringe was avoided to prevent particle trapping within synovial aspirate/cellular content residues. Only topical anesthetics were allowed prior to study injection. Patients were blinded to observation of the treatment/injection procedure and were followed-up for 56 weeks by blinded personnel.

The LOR 0.07 mg dose was selected from nonclinical evidence and 3 completed human clinical studies (SM04690-01 [OA-01], SM04690-OA-02 [OA-02], and SM04690-OA-04 [OA-04]) (5, 6, 9).

Statistical analysis

Efficacy analyses are described based on the full analysis set (FAS), defined as all patients who received a study injection. A mixed-effects model for repeated measures (MMRM) was used to estimate changes from baseline for primary, and other endpoints (pain NRS, WOMAC, PGA, medial JSW and SF-36 scores), using treatment group, week, treatment × week interaction and baseline value as covariates. Unadjusted 95% confidence interval (CIs) and *p*-values were also reported. Three sensitivity analyses were specified for primary and secondary endpoints. Analysis of Covariance (ANCOVA) was used to estimate the least squares difference in change in primary and secondary endpoints in the FAS, first adjusting for baseline values, second adjusting for baseline values and NSAID/acetaminophen usage and lastly, adjusting for baseline values only for the Per-Protocol Analysis Set represented by FAS patients study completers with no major protocol deviations impacting evaluation of outcomes. Logistic regression analyses were implemented for evaluating 30%, 50% and 70% improvements in all endpoints.

Safety analyses are described for the Safety Analysis Set (SAS), denoted by all patients who received a study injection. ANCOVA was used to analyse the

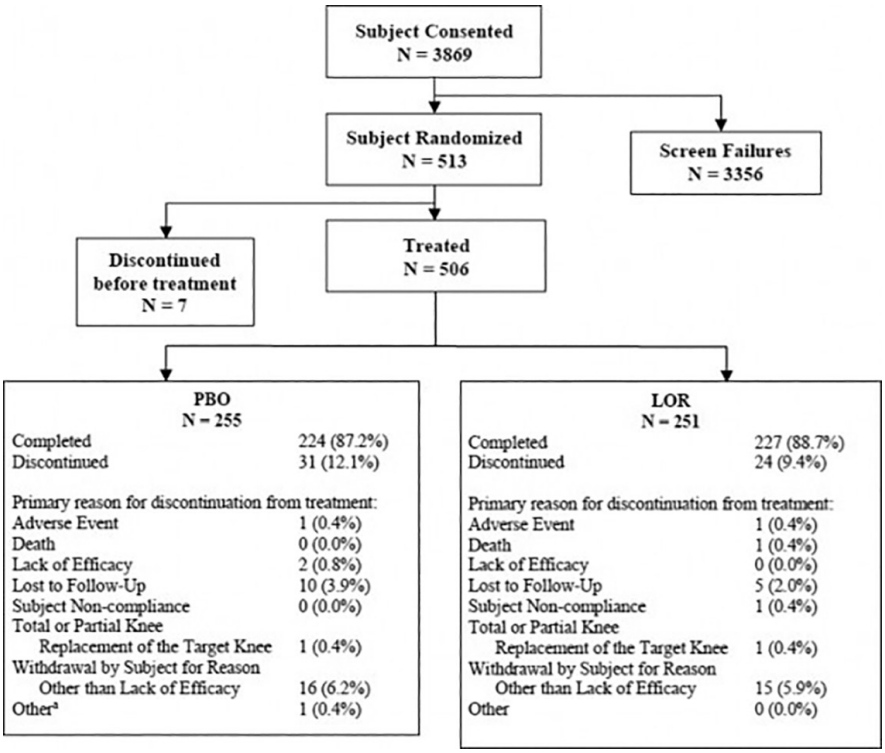

Fig. 1. Patients' disposition.
PBO: placebo; LOR: Lorecivivint

change from baseline expression of serum (P1NP, and β-CTX) and cartilage (COMP) biomarkers at Week 56.

Based on Monte Carlo simulations, estimated sample size was selected to yield at least 225 evaluable patients per treatment group assuming 10% dropout. The proportion of statistically significant results at α=0.05 was estimated as the approximate power for a sample size of 225 subjects per group. All statistical analyses were performed using SAS v. 9.4 (Cary, NC).

Results

A total of 513 patients were randomised at 100 investigational centres in the United States between May 2019 and August 2021. Seven patients discontinued prior to dosing; 5 LOR patients were randomised by error and 2 PBO patients withdrew consent. Therefore 251 patients were treated with LOR 0.07 mg (LOR group) and 255 with vehicle (PBO group). A total of 451/506 (89.1%) patients receiving study treatment completed the study (Fig. 1).

Key mean (± standard deviation [SD]) patient enrolment demographics included: age 60.9 (8.3) years; medial JSW 2.61 (0.72) mm; BMI 31.54 (4.69) kg/m^2. Other characteristics included: White race, n=346 (69.1%); female, n=328 (65.5%); target knee KL Grade 2, n=258 (51.5%); KL Grade 3 n=243 (48.5%). There were no considerable differences in demographic and baseline characteristics between LOR and PBO treatment groups (Table I).

Table I. Demographic and baseline characteristics.

Parameter	Statistic	Planned treatment		All subjects
		Placebo	Lorecivivint	
Number of patients (n)		n=253	n=248	n=501
Age at consent [years]	Mean (SD)	61.0 (8.7)	60.8 (8.0)	60.9 (8.3)
Weight [kg]	Mean (SD)	88.82 (18.35)	90.14 (16.75)	89.47 (17.57)
Height [cm]	Mean (SD)	167.7 (10.8)	168.5 (9.8)	168.1 (10.3)
Body Mass Index [kg/m^2]	Mean (SD)	31.41 (4.83)	31.66 (4.55)	31.54 (4.69)
Widespread Pain Index	Mean (SD)	0.9 (1.1)	0.9 (1.0)	0.9 (1.1)
Symptom severity question 2	Mean (SD)	0.3 (0.6)	0.4 (0.7)	0.4 (0.7)
Medial joint space width [mm] in the target knee	Mean (SD)	2.61 (0.69)	2.61 (0.74)	2.61 (0.72)
Sex				
Female	n (%)	163 (64.4)	165 (66.5)	328 (65.5)
Male		90 (35.6)	83 (33.5)	173 (34.5)
Race	n (%)			
White		175 (69.2)	171 (69.0)	346 (69.1)
Black or African American		65 (25.7)	66 (26.6)	131 (26.1)
Asian		7 (2.8)	6 (2.4)	13 (2.6)
Native Hawaiian or Other Pacific Islander		1 (0.4)	3 (1.2)	4 (0.8)
American Indian or Alaska Native		1 (0.4)	1 (0.4)	2 (0.4)
Other		4 (1.6)	1 (0.4)	5 (1.0)
Ethnicity	n (%)			
Not Hispanic or Latino		199 (78.7)	202 (81.5)	401 (80.0)
Hispanic or Latino		54 (21.3)	46 (18.5)	100 (20.0)
Kellgren-Lawrence grade in the target knee	n (%)			
2		134 (53.0)	124 (50.0)	258 (51.5)
3		119 (47.0)	124 (50.0)	243 (48.5)
OA Symptom laterality	n (%)			
Bilateral		171 (67.6)	168 (67.7)	339 (67.7)
Unilateral		82 (32.4)	80 (32.3)	162 (32.3)

SD: standard deviation; OA: osteoarthritis; PBO: placebo.

Efficacy results

The study did not meet the primary endpoint of change in OA pain in the target knee. Based on the main analysis, the mean (standard error [SE]) change from baseline in Pain NRS at Week 12 was LOR -2.24 (0.13) compared with PBO -2.49 (0.13); p=0.185, 95% CI (-0.12, 0.62) (Fig. 2).

No discernable treatment effects of LOR compared with PBO were revealed by the main analysis of other endpoints (change from baseline in Pain NRS at Week 24 and Week 52); WOMAC Function at Weeks 12, 24,52; PGA at Weeks 12, 24, 52; and average daily NSAID usage at any timepoint.

Sensitivity analyses of primary and other endpoints did not demonstrate any clinically meaningful differences in LOR treatment outcomes relative to the main efficacy analyses. Logistic regression of primary and other endpoints did not reveal further efficacy trends or statistically significant differences between LOR and PBO groups.

No significant treatment differences between LOR and PBO groups were indicated by analyses of other endpoints; change from baseline in WOMAC Total at Weeks 12, 24, 52; WOMAC Pain at Weeks 12, 24, 52; medial JSW at Week 52.

The mean (SE) change from baseline in medial JSW at Week 52, as evaluated by radiographs of the target knee, was LOR -0.10 (0.03) compared with PBO -0.07 (0.03); p=0.533; CI (-0.13, 0.07) (Fig. 3).

A *post-hoc* subgroup analysis performed to compare PROs in KL Grades 2 and 3 patients showed no discernable treatment effects of LOR relative to PBO on primary or other endpoints.

Safety and other results

In general, AE incidences, severity, and relationship to study treatment were similar between LOR and PBO groups. A total of 618 AEs were reported in 261 (52.1%) patients; 311 in 136 LOR and 307 in 125 PBO patients. Most AEs (603 [97.6%]) were not related to study treatment and 95.1% were mild to moderate severity. The most frequently reported LOR group AEs were arthralgia, urinary tract infection, back pain, and COVID-19, while PBO group were most commonly arthralgia, urinary tract infection, hypertension and headache (Table II).

Knee-related AEs were reported in 52 (10.4%) patients; 18 (7.2%) in the LOR group, and 12 (4.8%) in PBO, none were considered serious. Thirty-four

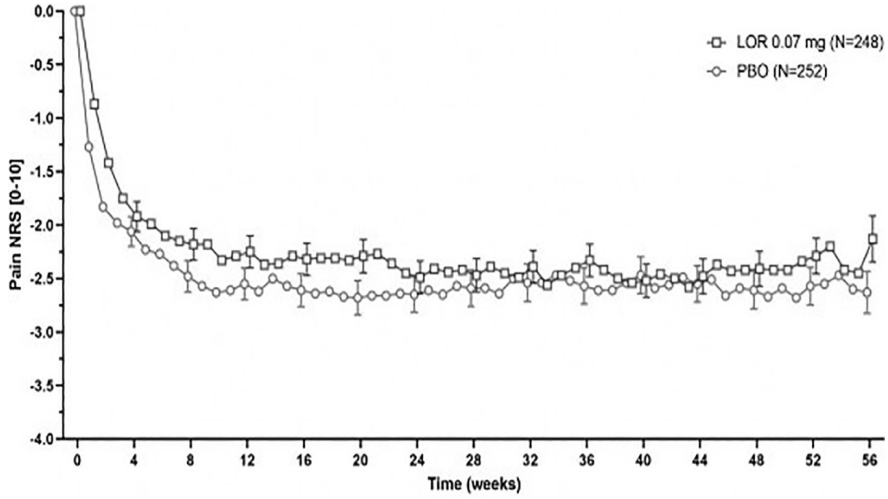

Fig. 2. Pain NRS change from baseline over time.
LOR: Lorecivivint; NRS: numeric rating score; PBO: placebo. Change from baseline means ± standard errors shown.
p-values were reported from baseline-adjusted mixed-model repeated measures marginal estimation at timepoint.

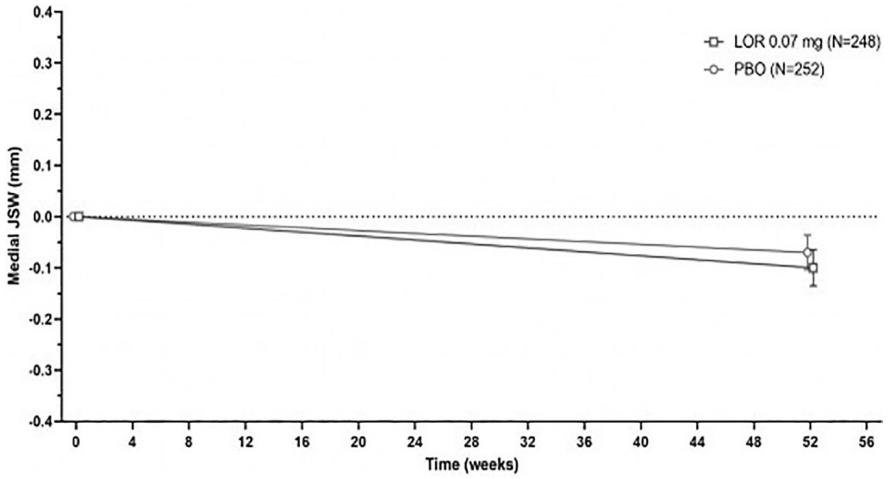

Fig. 3. Medial JSW change from baseline over time.
LOR: Lorecivivint; PBO: placebo; medial JSW: medial joint space width.
Change from baseline means ± standard errors shown.
p-values were reported from baseline-adjusted ANCOVA at all timepoints.

Serious Adverse Events (SAEs) were reported in 25 (5.0%) patients, all considered unrelated to study treatment. One LOR patient died of a myocardial infarction, considered unrelated to the treatment. Two (0.4%) patients discontinued the study due to AEs; a PBO patient experienced a mild seizure; a LOR patient developed an intraductal proliferative breast lesion. Both events were considered non-serious and unrelated to the study treatment. No trends or differences in clinically relevant shifts in chemistry, haematology, or urinalysis laboratory assessments were observed between treatment groups. No clinically important changes from baseline in vital signs were observed in either group. Change in biomarker expression from baseline at Week 56 were as follows: COMP (Difference [SE] 6.4% [2.7]; p=0.016, CI [1.2, 11.7]), β-CTX (Difference [SE] -2.9% [5.4]; p=0.586, 95% CI [-13.5, 7.6]) and P1NP (Difference [SE] -0.2 %[4.0]; p=0.96, 95% CI [-8.1, 7.6]).

Discussion

Study OA-11 was a phase 3, 56-week, multicenter, randomised, double-blind, PBO-controlled, parallel-group trial investigating the safety and efficacy of IA LOR 0.07 mg for the treatment of moderately to severely symptomatic knee OA patients (STRIDES-XRAY Study). Regarding safety outcomes, LOR demonstrated a similar profile to those of previous trials, with low rates of AEs. No SAEs were deemed related to LOR and no new safety concerns were identified. Regarding efficacy outcomes, LOR did not meet the primary endpoint of change from baseline in target knee Pain NRS at Week 12. In addition, no meaningful treatment effects of LOR relative to PBO were demonstrated based on the analyses of other endpoints.

These efficacy findings are contrary to evidence generated during phase 2 development of LOR. Trial OA-02 showed that a pre-defined subpopulation (with unilateral symptomatic knee OA and without Widespread Pain), treated with LOR 0.07 mg, demonstrated statistically significantly improved WOMAC Pain and Function subscores compared to equivalent controls at 26 and 52 weeks (10). This subpopulation also demonstrated statistically significant maintenance of radiological medial JSW compared to controls at one year. Consequently, a population with similar characteristics was tested *a priori* in OA-04, a phase 2b randomised controlled trial (RCT), designed to evaluate symptomatic PROs (6). In this trial, the LOR 0.07 mg dose arm successfully met its primary endpoint at 24 weeks compared to vehicle PBO for Pain NRS. Additional characterisation of the Pain NRS data showed significant treatment effect starting as early as Week 5, with significant improvement maximising at Week 12 and persisting until Week 24.

An ensuing phase 3 programme consisted of 2 RCTs; OA-10, a 26-week trial designed to assess symptoms; and OA-11, a 56-week trial designed to evaluate symptom and structure outcomes. To this end the OA-11 trial population, in addition to specified unilateral knee pain and WPI inclusion criteria, was enriched with patients more likely to experience structural progression (measured by radiographic medial JSW) over one year. This 'progressor' population was defined by restricting baseline medial JSW inclusion criteria

Table II. Adverse events with an incidence of 2% or higher in either treatment group.

	Number (%) of subjects with at least 1 event		
	Actual treatment		
Adverse event	Placebo n=252	Lorecivivint n=249	All subjects n=501
Arthralgia	17 (6.7)	20 (8.0)	37 (7.4)
Urinary tract infection	13 (5.2)	16 (6.4)	29 (5.8)
Back pain	8 (3.2)	13 (5.2)	21 (4.2)
COVID-19	7 (2.8)	11 (4.4)	18 (3.6)
Joint swelling	4 (1.6)	7 (2.8)	11 (2.2)
Nasopharyngitis	4 (1.6)	7 (2.8)	11 (2.2)
Headache	10 (4.0)	6 (2.4)	16 (3.2)
Upper respiratory tract infection	5 (2.0)	6 (2.4)	11 (2.2)
Sciatica	2 (0.8)	6 (2.4)	8 (1.6)
Contusion	5 (2.0)	5 (2.0)	10 (2.0)
Osteoarthritis	2 (0.8)	5 (2.0)	7 (1.4)
Gastroesophageal reflux disease	1 (0.4)	5 (2.0)	6 (1.2)
Sinusitis	6 (2.4)	4 (1.6)	10 (2.0)
Hypertension	11 (4.4)	3 (1.2)	14 (2.8)
Toothache	5 (2.0)	3 (1.2)	8 (1.6)
Bronchitis	5 (2.0)	2 (0.8)	7 (1.4)
Ligament sprain	5 (2.0)	2 (0.8)	7 (1.4)

between 1.5–4.0 mm. Previous data has postulated that such medial JSW baseline restriction in disease-modifying OA drug trials reduces measurement variability, optimising statistical power to detect change beyond measurement error (10). However, the degree of disease progression observed in OA-11 across both PBO and LOR arms was much lower than the anticipated 0.1–0.2 mm per year, hence this outcome could not be objectively evaluated (11).

Regarding LOR effects on symptomatic PROs, further anomalous findings occurred in this trial compared to previous LOR data. *Ad-hoc* analysis from OA-10 and OA-04 trials showed that LOR demonstrated greater relative efficacy in KL Grade 2 OA patients compared to KL Grade 3 patients. In contrast, no such treatment effects of LOR relative to PBO were discernable in this trial between KL Grade 2 and 3 patients.

Multiple reasons for the observed discrepancies in outcomes between OA-11 and other LOR trials described were investigated and proposed (7). Due to the restrictive baseline medial JSW inclusion criteria, the cohort of patients enrolled into OA-11 were found to have the most advanced knee OA observed of any LOR trial, with 68% having baseline medial JSW <3 mm. To compare, OA-10 and OA-04 trials had 56% and 40% of such patients, respectively. This skewed OA-11 population resulted from unforeseen effects of the prescreening OA-15 protocol employed to optimise recruitment efficiency across OA-10 and OA-11 trials. This advanced stage of knee OA therefore could have impacted the OA-11 trial results. One hypothesis is that these more advanced knee OA patients may require higher, and/or more frequent LOR doses to achieve symptomatic or structural benefits. This hypothesis is being tested in an ongoing extension trial of OA-11 (OA-07, NCT04520607), which will assess the effects of a second and third annual LOR injection on PROs and medial JSW.

In addition, the OA-11 trial was conducted during the COVID-19 pandemic, and while its impact was difficult to quantify, its confounding effects on knee OA patients' activities and PROs have been reported (12). A study has shown decreased physical activity and increased sedentary time (13). Another showed negative impacts on WOMAC Pain and Function, as well as on Visual Analogue Scale pain scores during lockdown environments (14). Patients' activities of daily living in this OA-11 trial were almost certainly disrupted, probably affecting OA progression rates and PRO responses. Operationally, pandemic travel restrictions affected site access and patient ability to attend scheduled visits. These trial conduct issues also introduced unforeseen confounding factors. Notably, the pandemic effects on clinical trial conduct in general have been accepted as being widespread and significant (15). However, it must be noted that objectively proving these pandemic effects on this trial are difficult and should be, therefore, regarded as a limitation to this report.

Regarding serum biomarkers, no changes were observed between LOR and PBO arms for β-CTX and P1NP levels, however there was a significant difference in COMP expression noted for LOR over PBO at Week 56. The clinical relevance of this observed difference is unknown.

In summary, a combination of patients with structurally advanced knee OA along with unpredicted pandemic effects probably contributed towards the unsuccessful outcomes of this trial. Of note initial results from the extension trial OA-07 do appear to confirm the earlier hypothesis that these advanced OA patients benefit from repeat LOR doses, as shown by PRO improvements and reduced medial JSW loss compared to patients on PBO (16). The final results from this trial will confirm or refute our hypothesis.

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