A Phase 3, 28-week, multicentre, randomised, double-blind, placebo-controlled trial (OA-10) to evaluate the efficacy and safety of a single injection of lorecivivint in the target knee joint of moderately to severely symptomatic osteoarthritis patients

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Abstract

Objective

To assess the efficacy and safety of an intra-articular (IA) CLK/DYRK inhibitor, lorecivivint (LOR), for the treatment of moderate to severe symptomatic knee osteoarthritis (OA).

Methods

This was a Phase 3, 28-week, multicentre, double-blind, placebo-controlled study evaluating the efficacy and safety of a single IA injection of LOR. Patients with ACR-defined knee OA, Kellgren-Lawrence (KL) grades 2–3, and pain Numeric Rating Scale (NRS) ≥4 and ≤8 in the target knee were randomised (1:1) to receive LOR 0.07 mg or vehicle placebo (PBO) on Day 1. The primary endpoint was the change from baseline in Pain NRS at Week 12 between LOR and PBO. Additional outcomes included the change from baseline in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Function, WOMAC Pain, Patient Global Assessment and safety.

Results

498 patients were randomised, and 51.9% had KL Grade 3 severity. In the full analysis set (FAS), LOR failed to meet the primary endpoint when compared to PBO. No significant treatment differences were noted in other efficacy endpoints. A post-hoc analysis demonstrated a positive treatment effect of LOR relative to PBO in the KL Grade 2 subgroup; the difference in weekly Pain NRS between LOR and PBO groups showed nominal statistical significance at Week 4 ($p<0.05$). Incidences, seriousness, and severity of adverse events were similar across the treatment groups.

Conclusion

LOR was well tolerated despite not meeting the primary endpoint. Efficacy signals were identified in patients with less severe structural knee OA disease, suggesting earlier intervention may be more effective.

Key words

lorecivivint, osteoarthritis, CLK/DYRK inhibitor

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Introduction

With ageing populations and increasing rates of obesity and injury, the prevalence of OA is increasing globally. The knee is the most frequently affected joint with a global prevalence of 365 million (1). Knee OA, associated with significant morbidity and mortality, is characterised by cartilage degradation, osteophyte formation, and synovitis leading to pain, disability, and reduced quality of life (2, 3). Unmet need exists to identify disease-modifying OA drugs which slow progression of structural damage while improving symptoms and quality of life. Current OA treatments are limited to relieving symptoms only and have substantial side effects.

The Wnt signalling pathway modulates key biological processes particularly in bone and joints by controlling mesenchymal stem cell (MSC) differentiation into chondrocytes and osteoblasts (4, 5). Preclinical OA models have shown upregulation of the Wnt pathway (6, 7), driving MSCs to differentiate into osteogenic lineage, and increasing metalloproteinase production by chondrocytes resulting in cartilage thinning and destruction (8). Therefore, targeting the Wnt pathway presents a potential strategy for treating knee OA (9)

Lorecivivint (LOR) is a novel intra-articular (IA) inhibitor of the CDC-like kinase 2 (CLK2) and dual-specificity tyrosine phosphorylation-regulated kinase 1 A (DYRK1A), leading to downstream modulation of the Wnt pathway and inflammation (10) In previous trials, LOR was shown to be safe and well tolerated while providing improvements compared with placebo (PBO) for pain and function, patient-reported outcomes (PROs) and medial joint space width (JSW) in patients with predominantly unilateral OA symptoms (11, 12) This Phase 3 study evaluated the efficacy, safety, and tolerability of a single IA LOR 0.07 mg injection for the treatment of knee OA.

Methods

Study design

The OA-10 study was a multicentre, randomised, double-blind, PBO-controlled study of a single LOR 0.07 mg dose injected into the target knee joint of moderately to severely symptomatic OA patients. This study was conducted across 81 investigational sites in the United States between 26 May 2020 and 8 September 2021. Prescreening for OA-10 eligibility occurred concurrently with study OA-11 (56-week trial evaluating PROs and radiographic outcomes), using a pre-screening protocol. Briefly, patients who did not fulfill OA-11 medial JSW criteria (>4 mm or <1.5 mm) but were Kellgren-Lawrence (KL) Grade 2 or 3 and fulfilled pain screening criteria, were held for inclusion in the OA-10 study.

All radiographs were obtained as weight-bearing posterior-anterior views with a positioner providing a 10-degree caudal tilt. These were stored electronically by a blinded central imaging vendor in which KL grading and JSW were measured (13).

The objective of this study was to determine the efficacy, safety, and tolerability of IA LOR 0.07 mg for the treatment of knee OA. The primary endpoint was the change from baseline in target knee OA pain as assessed by weekly average of daily Pain Numeric Rating Scale (Pain NRS) at Week 12. Secondary / exploratory endpoints included the change from baseline in the following: Pain NRS at Week 24, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Function and Pain subscores, WOMAC Total score, Patient Global Assessment (PtGA) at Weeks 12 and 24, and non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen usage for target knee OA pain. Safety analyses are described in the *Statistical analysis* section.

This study was designed, funded and conducted by Biosplice Therapeutics Inc., 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 institutional review board. All patients provided written informed consent prior to participating in any study related procedures. The study was registered at ClinicalTrials.gov (NCT04385303).

Subjects

Eligible patients were aged 40-80 years with a diagnosis of primary femorotibial OA according to the American College of Rheumatology (ACR) clinical and radiographic criteria and KL Grade 2–3 in the target knee within 24 weeks of the Screening Visit (14). All radiographs were assessed and scored by an independent central imaging vendor blinded to patients' treatments.

Assistive devices (*e.g.* walkers, canes) were allowed if needed <50% of time. Patients had pain compatible with knee OA for at least 26 weeks prior to the Screening Visit and the primary source of bodily pain was due to their OA. Patients had target knee Pain NRS intensity score ≥4 and ≤8, and <4 for the non-target knee, on an 11-point [0–10] scale for 4 of 7 days preceding treatment Day 1. Body mass index (BMI) was ≤35 kg/m^2 at the Screening Visit, Widespread Pain Index (15) score ≤4 and Symptom Severity Question 2 (SSQ2) score ≤2 at the Screening Visit and Day 1. Patients were required to have a WOMAC Function subscore of 68 to 136 (out of 170) for the target knee at baseline regardless of symptomatic oral treatment and were willing to use a daily electronic diary. A negative drug test for amphetamine, cocaine, opiates, barbiturates, benzodiazepine, tricyclic antidepressants amongst others was required, unless these were prescribed for a specific diagnosis. Patients with depression or anxiety must have been clinically stable for at least 12 weeks prior to screening.

Patients were excluded from the study if they had significant target knee joint malalignment (>10°), effusion, any joint replacement in either knee, used a lower extremity prosthesis, a structural knee brace or had surgery in any knee within 26 weeks prior to Day 1. Therapeutic IA injections into the target knee including hyaluronic acid, platelet-rich plasma, and stem cell therapies within 26 weeks prior to Day 1, or corticosteroids or aspiration of the target knee within 12 weeks prior to Day 1 were prohibited. Previous target knee treatment with LOR, electrotherapy, acupuncture, chiropractic or physical therapy, therapeutic ultrasound, or planned surgery were also prohibited. Pregnant women, woman of childbearing potential or a male partner not willing to use contraception were excluded. Patients were excluded if they received opioids, systemic steroids, analgesics or anticonvulsants within 12 weeks prior to Day 1 or topical anesthetic agents within 7 days of Day 1. Patients with malignancies, active infections or comorbid conditions including inflammatory arthritis were also excluded.

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. The test drug or PBO was administered in the clinic on Day 1 by an unblinded investigator through lateral or medial approaches based on their standard practice. Although not required, the injections may have been guided by ultrasound or fluoroscopy. Because LOR drug product is a suspension, prior aspiration of synovial fluid into the syringe containing the injectate was avoided to prevent trapping of particles within synovial aspirate/cellular content residues. Only topical anesthetics were allowed prior to study medication injection. The patient was blinded to the injection procedure and then followed-up by blinded personnel. The LOR dose of 0.07 mg was selected based on evidence from non-clinical studies and 3 completed human clinical studies (SM04690-01 [OA-01], SM04690-OA-02 [OA-02], and SM04690-OA-04 [OA-04]).

Statistical analysis

From aggregated data and Monte Carlo simulations, a sample size of approximately 500 patients was estimated to yield 225 evaluable patients per treatment group assuming a 10% dropout rate. Power was estimated to be 94.3%, assuming a treatment difference of -0.8 between LOR and PBO and a correlation of 0.25 between baseline and follow up.

Efficacy analyses are described based on the full analysis set (FAS), defined as all patients who were randomised and received a study injection. A mixed-effects model for repeated measures (MMRM) was used to estimate changes from baseline in primary, secondary and exploratory outcomes, using treatment group, week, treatment × week interaction, and baseline values as covariates. Unadjusted 95% confidence intervals (CIs) and *p*-values are reported. Three sensitivity analyses were specified for the primary and secondary endpoints. Analysis of Covariance (ANCOVA) was used to estimate the least squares difference in change in primary and secondary endpoints for 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 who completed the study with no major protocol deviations impacting the evaluation of efficacy outcomes. No sensitivity analysis using imputation was performed on the *post-hoc* analysis.

NSAID information was recorded at visits and computed by converting all concomitant medications into an equivalent dose of diclofenac 150 mg (16) . Safety analyses are described for the Safety Analysis Set (SAS), denoting all patients who received a study injection. Statistical analyses were performed using SAS v. 9.4 (Cary, NC).

Results

Of 1107 patients consented, 498 were randomised. Two patients from the PBO group discontinued prior to dosing; one randomised in error but did not receive study drug, one withdrew consent. Therefore, 243 patients were treated with LOR 0.07 mg (LOR group) and 253 with vehicle (PBO group) (Fig. 1).

Mean (±standard deviation [SD]) age and BMI at enrolment were 61.0 (±8.3) years and, 29.80 (±3.90) kg/m^2, respectively. More patients were female (284 [60.4%]), White (348 [74.0%]) and not Hispanic or Latino (355 [75.5%]). At enrolment, 226 (48.1%) patients had OA severity KL Grade 2 and 244 (51.9%) KL Grade 3. Mean (±SD) medial JSW was 2.77 (±1.52) mm. Patients' baseline characteristics were similar across the 2 treatment groups (Table I). Nine subjects (PBO 6 [2.4%]

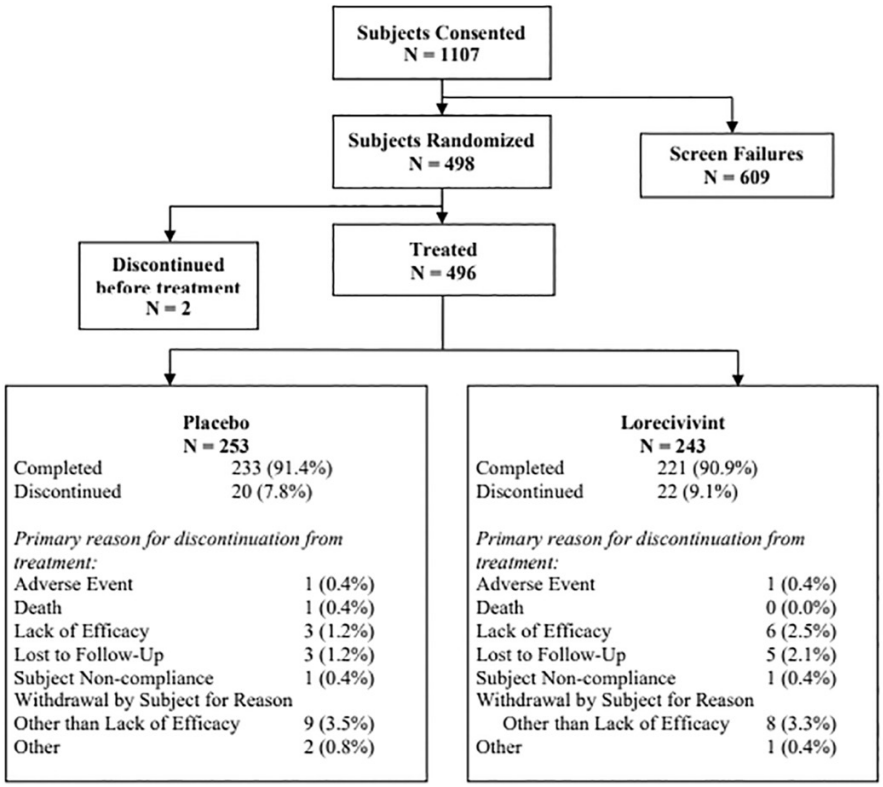

Fig. 1. Subject disposition and primary reasons for discontinuation from study treatment.

Table I. Demographic and baseline characteristics.

Parameter	Statistic	Planned treatment		All patients
		Placebo (n=239)	Lorecivivint (n=231)	(n=470)
Age at consent (years)	Mean (SD)	61.0 (7.9)	61.0 (8.7)	61.0 (8.3)
Weight (kg)	Mean (SD)	85.81 (15.14)	86.80 (15.21)	86.29 (15.17)
Height (cm)	Mean (SD)	169.8 (9.9)	170.0 (10.7)	169.9 (10.3)
Body Mass Index (kg/m^2)	Mean (SD)	29.67 (3.98)	29.94 (3.81)	29.80 (3.90)
Widespread Pain Index	Mean (SD)	0.9 (0.9)	1.0 (1.1)	0.9 (1.0)
Symptom severity question 2	Mean (SD)	0.3 (0.6)	0.4 (0.7)	0.3 (0.6)
Medial joint space width (mm)[b]	Mean (SD)	2.74 (1.47)	2.79 (1.57)	2.77 (1.52)
Sex	Female (%)	148 (61.9)	136 (58.9)	284 (60.4)
	Male (%)	91 (38.1)	95 (41.1)	186 (39.6)
Race	White (%)	181 (75.7)	167 (72.3)	348 (74.0)
	Black or African American (%)	45 (18.8)	48 (20.8)	93 (19.8)
	American Indian or Alaska Native (%)	3 (1.3)	3 (1.3)	6 (1.3)
	Asian (%)	3 (1.3)	3 (1.3)	6 (1.3)
	Native Hawaiian or Other Pacific Islander (%)	3 (1.3)	3 (1.3)	6 (1.3)
	Other[a] (%)	4 (1.7)	7 (3.0)	11 (2.3)
Ethnicity	Not Hispanic or Latino (%)	184 (77.0)	171 (74.0)	355 (75.5)
	Hispanic or Latino (%)	55 (23.0)	60 (26.0)	115 (24.5)
Kellgren-Lawrence Grade[b]	2 (%)	115 (48.1)	111 (48.1)	226 (48.1)
	3 (%)	124 (51.9)	120 (51.9)	244 (51.9)
Symptomatic OA[c]	Bilateral (%)	170 (71.1)	149 (64.5)	319 (67.9)
	Unilateral (%)	69 (28.9)	82 (35.5)	151 (32.1)

LOR: lorecivivint; OA: osteoarthritis; PBO: placebo; n: number
[a]Including multiple of the above; [b]Target knee; [c]Based on investigator's assessment.

LOR 3 [1.2%]) reported concomitant drug treatments for osteopenia or osteoporosis.

Efficacy results

The trial did not meet the primary efficacy endpoint of change from baseline in target knee OA pain at Week 12. Based on the main (MMRM) efficacy analysis, the mean (standard error [SE]) change from baseline in weekly average of daily Pain NRS at Week 12 was LOR -2.22 (0.14) compared with PBO -2.15 (0.14); p=0.703; 95% CI (-0.46, 0.31) (Fig. 2A). Additionally, no significant treatment effects of LOR relative to PBO were demonstrated by analysis of key secondary endpoints.

Sensitivity analyses of primary and secondary endpoints similarly did not demonstrate any differences between treatment groups. Logistic regression of patient-reported percent improvements in Pain NRS at Week 12 revealed no additional efficacy trends of LOR relative to PBO.

A *post-hoc* analysis of KL subgroups indicated trends towards positive efficacy of LOR relative to PBO in the KL Grade 2 subgroup when compared to the KL Grade 3 subgroup. Among KL Grade 2 patients, sustained separation in Pain NRS (Fig. 2B) and additional efficacy endpoints (WOMAC function, WOMAC pain, and PGA) were observed between LOR and PBO treatment groups throughout the study time course (Supplementary data). At Week 12, the mean (SE) change from baseline in Pain NRS was LOR -2.31 (0.23) compared with PBO -1.86 (0.22); p=0.155, 95% CI (-1.09, 0.17). The difference in weekly Pain NRS between LOR and PBO groups showed nominal statistical significance at Week 4 (p<0.05) and trended towards statistical significance at Weeks 16 and 24 (p<0.1) (Fig. 2b).

In contrast, in the KL Grade 3 subgroup, patients treated with LOR compared with PBO had smaller reductions relative to baseline in Pain NRS and additional PROs.

Safety results

A total of 318 AEs were reported in 176 (35.8%) patients; 164 AEs in 91 (37.8%) LOR patients and 154 AEs in

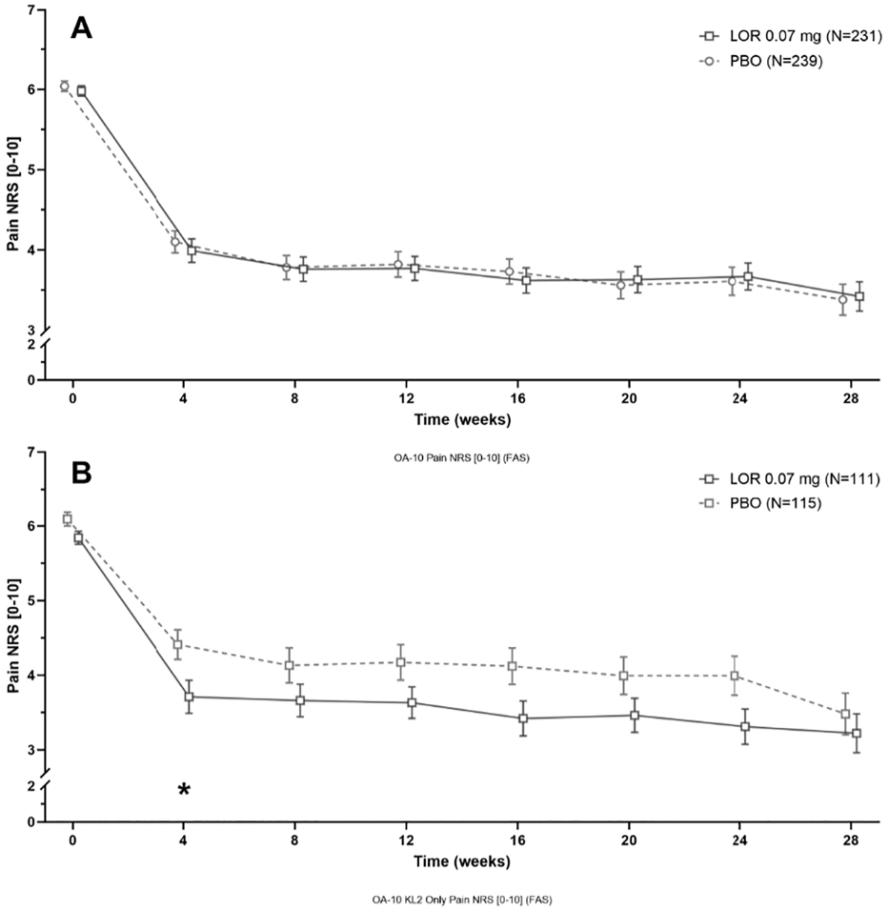

Fig. 2. Change from baseline in Pain NRS over time for **A**) all patients and **B**) KL Grade 2 patients. KL: Kellgren and Lawrence (OA classification system); LOR: lorecivivint; NRS: numerical rating score; PBO: placebo; N: number.
**p*<0.05 LOR *vs*. PBO from baseline-adjusted ANCOVA at timepoint.
Change from baseline in weekly average of daily Pain NRS (0-10) (means ± standard errors) shown.

Table II. Adverse event with an incidence of ≥ 2% in either treatment group.

Preferred term	Number (%) of patients with at least 1 event actual treatment		
	Placebo n=251	Lorecivivint n=241	All patients n=492
Urinary tract infection	7 (2.8)	9 (3.7)	16 (3.3)
COVID-19	8 (3.2)	8 (3.3)	16 (3.3)
Hypertension	3 (1.2)	8 (3.3)	11 (2.2)
Arthralgia	14 (5.6)	7 (2.9)	21 (4.3)
Headache	5 (2.0)	2 (0.8)	7 (1.4)
Ligament sprain	6 (2.4)	0 (0.0)	6 (1.2)

COVID-19: Coronavirus Disease 2019; LOR: lorecivivint; PBO: placebo.
Sorted by decreasing incidence for lorecivivint-treated patients.

85 (33.9%) PBO patients. Most AEs (97.5%) were considered unrelated to the study treatment and 97.5% were of mild to moderate intensity. Incidences, seriousness, severity, and relationship to study treatment of AEs were similar across the treatment groups (Table II).
Target-knee related AEs were noted in 17 (3.5%) patients; 6 (2.5%) LOR patients and 11 (4.4%) PBO patients. The most frequently reported target-knee AEs were arthralgia (5 patients) and synovial cysts (3 patients), none were serious. Six serious adverse events (SAEs) were reported in 5 (1.0%) patients; 5 SAEs in 4 (1.7%) LOR patients and 1 SAE in 1 (0.4%) PBO patient. In the LOR group, SAEs included 2 COVID-19 events, one chronic cholecystitis, one cerebrovascular accident and one hypertension. One PBO group patient died on Day 181 following a SAE of COVID-19 pneumonia, which was considered unrelated to the study medication.
Two patients discontinued the study due to AEs; one PBO patient reported arthralgia, and one LOR patient experienced substance abuse. Both events were considered non-serious and unrelated to study treatments. No clinically relevant shifts in laboratory assessments were observed between the treatment groups.

Discussion

Study OA-10 was a Phase 3, 28-week, multicentre, randomised, double-blind, PBO-controlled trial evaluating the safety and efficacy of a single IA LOR 0.07 mg injection compared with PBO in the target knee joint of moderate to severe symptomatic knee OA patients. LOR appeared to be safe and well tolerated, demonstrating a safety profile consistent with previous studies. In this trial LOR did not meet the primary endpoint of change from baseline in target knee Pain NRS at Week 12. Similarly, no clinically meaningful treatment effects of LOR relative to PBO were demonstrated from assessments of key secondary efficacy endpoints. However, *post-hoc* subgroup analysis based on knee OA structural severity demonstrated a clear trend of improved LOR efficacy in KL Grade 2 patients relative to KL Grade 3 (Fig. 2B). Interestingly, the treatment effect noted in this subanalysis was made up in part by a lower response in the PBO arm compared to that observed in the FAS. This lower PBO response observed in earlier stage knee OA may indicate a more discriminative pain response in these patients possibly due to activation of fewer pain pathways compared to later disease stages. These *post-hoc* observations need to be confirmed prospectively.
The efficacy results from this study differ with the earlier Phase 2b trial, (OA-04, NCT03122860) (11). This trial had a similar design and inclusion criteria to OA-10, but patients were randomised into Vehicle PBO, IA sham injection,

LOR 0.03 mg, 0.07 mg, 0.15 mg or 0.23 mg doses (randomisation ratio 1:1:1:1:1:1) arms. Treatment with LOR 0.07 mg (estimate -0.70, 95% CI [-1.34, -0.06], p=0.031) and 0.23 mg (estimate -0.82, 95% CI [-1.51, -0.12], p=0.022) resulted in statistically significant improvements in pain over Vehicle PBO, as measured by Pain NRS at Week 24 (primary endpoint), Week 12 and other timepoints. LOR 0.07 mg, as lowest efficacious dose, was chosen for further development.

The efficacy differences observed between OA-10 and OA-04 trial results might be attributed to patients´ baseline characteristics. Due to the prescreening protocol previously described, patients enrolled into OA-10 met the same pain screening criteria as OA-11 patients but did not fulfill its restricted medial JSW limits (medial JSW 1.5–4 mm). Consequently, 115 of 496 OA-10 patients (25%) had a baseline medial JSW <1.5 mm, resulting in a reduced trial population average baseline medial JSW than observed in the OA-04 trial (47 of 695 patients with medial JSW <1.5 mm [6.8%]). Therefore, this OA-10 population had more severe baseline structural knee OA compared with OA-04; (baseline mean (±SD) medial JSW in OA-10 = 2.77 (±1.52) mm; in OA-04 = 3.30 (±1.19) mm) and may have impacted patients' responses to LOR. These data are supportive of previous work showing such associations between radiographic knee OA severity and knee pain based on an analysis from the Multicenter Osteoarthritis Study and the Framingham Osteoarthritis Study (18). The literature also supports the concept that early-stage, symptomatic knee OA may present a 'window of opportunity' for intervention, which can slow or possibly arrest disease progression (14).

Several barriers exist for designing early-stage OA trials, including the absence of validated clinical and imaging classification criteria that permit the identification and selection of patients at high risk of osteoarthritis progression (19).

In relation to study limitations, the authors acknowledge that the study was conducted during the COVID-19 pandemic. Studies have shown meaningful differences in WOMAC pain and function, as well as in Visual Analogue Scale pain scores in knee OA patients among pre- and post-lockdown environments. Decreased physical activity levels and increased anxiety are also thought to have been confounding factors for pain and function reporting (20, 21). Finally, the operational conduct of clinical trials generally was highly impacted by the pandemic (22). Unfortunately, objective assessment of the limitations these confounding factors caused to this study were not possible to make.

The increasing prevalence of OA, the lack of pharmacological therapies that can prevent, halt, or delay the disease progression in association with their long-term safety, makes OA a major public health concern worldwide (2, 23). LOR may still represent a promising treatment option for patients with less advanced structural knee OA despite the current trial, with its relatively advanced knee OA population not meeting its primary endpoint.

Biosplice is conducting an additional, confirmatory Phase 3 study, OA-21, in primarily KL Grade 2 knee OA patients to further evaluate the efficacy and safety of LOR.

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