Comparing Patient-Reported Outcomes From Sham and Saline-Based Placebo Injections for Knee Osteoarthritis

Data From a Randomized Clinical Trial of Lorecivivint

Jeyanesh R.S. Tambiah,* MD, Ismail Simsek,* MD, Christopher J. Swearingen,* PhD, Sarah Kennedy,* PhD, Brian J. Cole,† MD, Timothy E. McAlindon,‡ MD, and Yusuf Yazici,*§‖ MD
Investigation performed by Biosplice Therapeutics, Inc, San Diego, California, USA

Background: Durable, meaningful symptom responses to intra-articular saline placebo injections are observed in knee osteoarthritis (OA) trials, but it is unclear if these are due to physiological effects.

Purpose: To perform a prospective comparison of patient-reported outcome responses among participants with knee OA who underwent intra-articular injection of saline-based placebo or sham (dry needle).

Study Design: Randomized controlled trial; Level of evidence, 2.

Methods: From a 24-week randomized double-blind trial, participants with moderate to severe knee OA received 2-mL intra-articular injections of saline-based placebo (PBO; 99.45% PBS) or sham (dry needle) to the target knee. Least squares mean differences of changes from baseline to week 24 were compared between the PBO and sham groups for the following: pain Numeric Rating Scale; Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain, stiffness, and function; and patient global assessment. Bang Blinding Index was used to evaluate all-group blinding on day 1 and week 24.

Results: In total, 116 and 117 participants were randomized to the PBO and sham groups, respectively. Within the full trial population, the mean ± SD age and body mass index were 59.0 ± 8.5 years and 28.97 ± 4.01, respectively. An overall 406 (58.4%) were female, and 394 (57.3%) had Kellgren-Lawrence grade 3 target knee OA. The PBO and sham groups demonstrated clinically meaningful improvements (≥10%) from baseline in all patient-reported outcomes at all time points (ie, weeks 4-24). Mean differences (95% CI) at week 24 between the PBO and sham groups were as follows: pain Numeric Rating Scale, –0.10 (–0.79 to 0.59; $P = .78$); WOMAC pain, –2.89 (–9.70 to 3.92; $P = .40$); WOMAC stiffness, –2.37 (–9.37 to 4.63; $P = .51$); and WOMAC function, –1.39 (–8.06 to 5.29; $P = .68$). Bang Blinding Index indicated that blinding was maintained.

Conclusion: PBO and sham groups demonstrated equivalent patient-reported outcomes at all time points through week 24, suggesting that responses attributed to saline were contextual (ie, to the procedure) and not physiological.

Registration: NCT03122860 (ClinicalTrials.gov identifier).

Keywords: knee osteoarthritis; clinical trial; Wnt pathway; patient-reported outcomes; CLK/DYRK inhibitor; knee pain

Knee osteoarthritis (OA) has an estimated worldwide prevalence of 4%. It is characterized by chronic pain and joint degeneration attributed to cartilage degradation and osteophyte formation, leading to impaired function and reduced quality of life. End-stage disease leads to chronic pain management and/or knee replacement surgery.[5] Current drug treatments, such as nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and opioids, only alleviate symptoms. These treatment options have questionable risk/benefit ratios,[4,6,9,12] which highlight an unmet need for safer and/or structure-modifying drugs that may slow the course of knee OA.

A persistent challenge in the development of such treatments is the clinically meaningful and lasting placebo effects observed in trials of intra-articular (IA) injection therapies for knee OA.[3] Published meta-analyses of such trials (>90 studies, >6000 participants with IA placebo) have described consistent improvements over baseline in patient-reported outcomes (PROs) after IA placebo injections (usually saline). These improvements were often larger than the minimal clinically important differences (MCIDs), with onset within a month and with durability of 3 to 6 months.[1,11,14,18] Improvements were observed across a range of PROs, such as pain visual analog scale

The American Journal of Sports Medicine
1–7
DOI: 10.1177/03635465211067201

and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain, function, stiffness, and total scores.[1,11,14] This literature and other studies have raised the question of whether these PRO improvements were due to the physiological effects of saline. If so, such responses observed within a clinical trial, when compared with a test drug, would not isolate the true treatment effect of that drug.

Lorecivivint (LOR) is an IA small molecule drug currently in development for the treatment of knee OA. The drug inhibits CLK2/DYRK1A intranuclear kinases that modulate the Wnt signaling pathway and inflammation, leading to potential benefits in pain and joint structure.[7] As part of a 24-week phase 2 trial (ClinicalTrials.gov, NCT02536833) investigating the safety and tolerability of IA LOR in patients with moderately to severely symptomatic knee OA,[17] improvements in PROs were compared between the control arms: saline-based placebo (PBO) and sham (dry needle).

The comparison of the 2 control arms was a prespecified analysis of an exploratory endpoint within the trial to differentiate the potential contextual (procedural) and physiological effects of the PBO injection from a dry needle. Additionally, a blinding assessment, Bang Blinding Index (BBI), was employed to evaluate if any unblinding occurred, which could confound the study results. The results of the PRO comparisons between the PBO and sham control groups, with the BBI tests, are reported here.

METHODS

Study Design

The 24-week parent study was a phase 2b randomized double-blind trial of 4 doses of LOR injected into the target knee joint of patients with moderately to severely symptomatic knee OA (Kellgren-Lawrence grade 2 or 3 radiographic classification) (Figure 1). The PBO-controlled clinical trial was conducted at 75 US clinical sites between April 2017 and April 2018.[17] The prespecified exploratory endpoint analysis described within this parallel-group trial comprised a prospective comparison between 2 control arms, PBO and sham, for all PROs, as well as an estimation of blinding effectiveness (Appendix, available in the online version of this article). Endpoints included changes from baseline to week 24 in target knee pain per the Numeric Rating Scale (NRS; 0-10 scale), WOMAC pain (Version 3.1; all scores scaled 0-100), WOMAC function, and patient global assessment (0-100 scale; not reported) captured by electronic diary (Rave; Medidata Solutions). WOMAC Stiffness (0-100 scale) was also captured as part of the WOMAC questionnaire. Groupwise statistical comparisons between the PBO and sham arms were made for each PRO.

The trial was conducted in accordance with the Declaration of Helsinki, the International Conference for Harmonisation Good Clinical Practice Guidelines, and applicable regulations. The study protocol was approved by the Advarra Institutional Review Board (Pro00021280) and at each clinic site by an independent ethics committee or institutional review board. All patients provided informed consent before participating in study-related procedures.

Patients

Eligible participants were adults aged 40 to 80 years with a diagnosis of primary femorotibial OA in the target knee according to the clinical and radiographic criteria of the American College of Rheumatology and were otherwise expected to be in generally good health and ambulatory. Participants were excluded if they were receiving any treatments (pharmacological or physical) besides NSAIDs. Participants had knee OA pain for at least 26 weeks before initial screening. The knee designated for injection (target knee) must have been clinically diagnosed as Kellgren-Lawrence grade 2 or 3; it also required a pain intensity score $\geq$4 and $\leq$8 (NRS; 0-10 scale) for at least 4 of 7 days preceding treatment initiation, with a daily score <4 for the nontarget knee. In addition, patients were required to have a WOMAC total score of 96 to 192 (total, 240; normalized, 0-100) for the target knee at baseline, regardless of whether they were taking background oral NSAIDs or acetaminophen. Also, participants were assessed with the Widespread Pain Index and Symptom Severity Scale[16] at screening to evaluate pain and symptoms related to comorbidities.

‖Address correspondence to Yusuf Yazici, MD, Biosplice Therapeutics, Inc, 9360 Towne Centre Dr, San Diego, CA 92121, USA (email: yusuf.yazici@biosplice.com).

*Biosplice Therapeutics, Inc, San Diego, California, USA.

†Midwest Orthopaedics at Rush University, Chicago, Illinois, USA.

‡Tufts Medical Center, Boston, Massachusetts, USA.

§School of Medicine, New York University, New York, USA.

Submitted June 11, 2021; accepted November 1, 2021.

One or more of the authors has declared the following potential conflict of interest or source of funding: Biosplice Therapeutics, Inc, 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. J.R.S.T., I.S., C.J.S., S.K., and Y.Y. own stock or stock options in Biosplice Therapeutics, Inc (formerly Samumed, LLC). B.C. has received honoraria from Vericel; support for education from Medwest and Endo Pharmaceuticals; hospitality payments from GE Healthcare; consulting fees from Acumed, Aesculap Biologics, Bioventus, Flexion Therapeutics, Geistlich Pharma, Smith & Nephew, Vericel, Zimmer Biomet, Endo Pharmaceuticals, Samumed, Arthrex, and Regentis; research support from Aesculap, Arthrex, the National Institutes of Health, and Regentis; speaking fees from Arthrex, Pacira, Terumo BCT, and Lifenet Health; and royalties from Arthrex and DJO. B.C. also owns stock or stock options in Bandgrip, Ossio, and Regentis. T.E.M has received consulting fees from Lilly USA, Anika Therapeutics, Genzyme, Roche, Chugai Pharmaceutical, Sanofi-Aventis, Upsher-Smith Laboratories, Samumed, Astellas, Flexion, Pfizer, Regeneron, and Seikugaku; hospitality payments from Noven Therapeutics; honoraria from Upsher-Smith; and research support from Samumed. AOSSM checks author disclosures against the Open Payments Database (OPD). AOSSM has not conducted an independent investigation on the OPD and disclaims any liability or responsibility relating thereto.

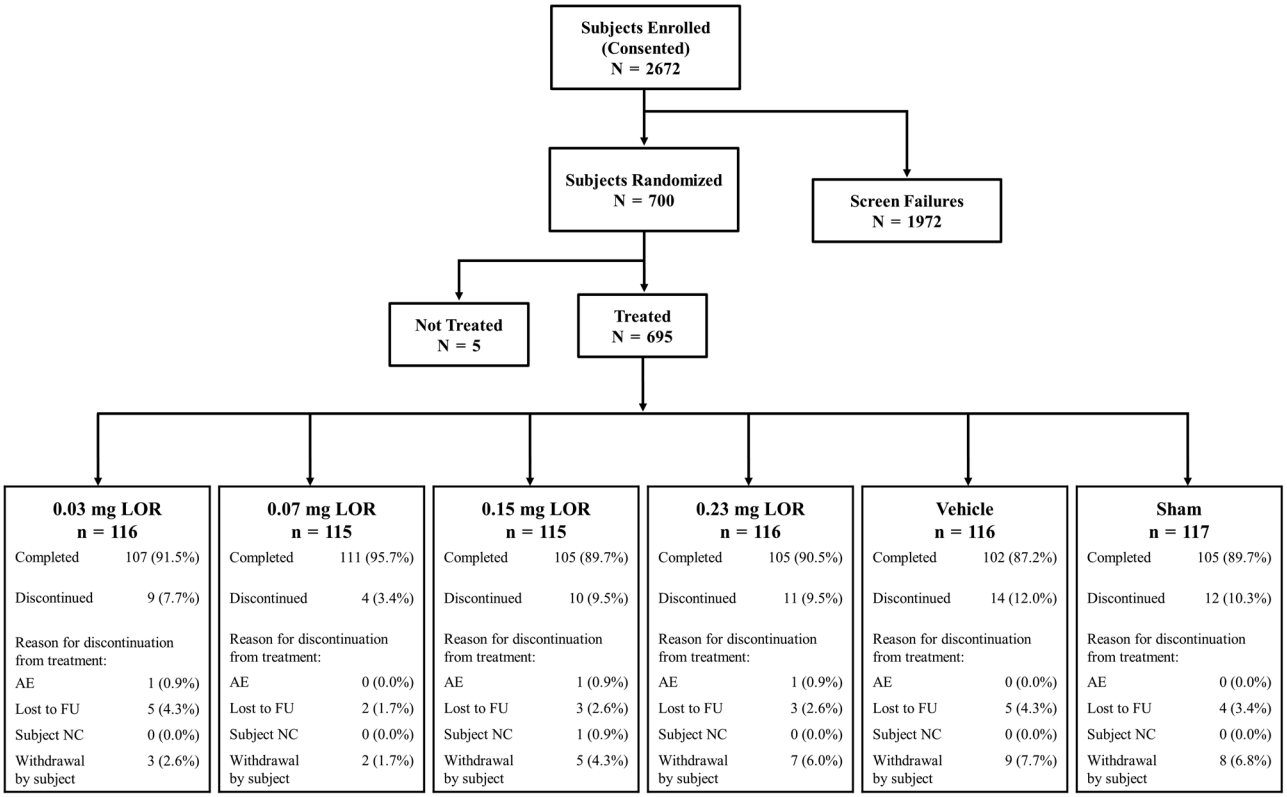

Figure 1. Patient disposition and reasons for discontinuation. The number and percentage are provided for all treatment groups. The numbers are based on the planned treatment. AE, adverse event; FU, follow-up; LOR, lorecivivint; NC, noncompliance.

Study Protocol

Eligible participants were randomized into 6 treatment groups: 1 of 4 LOR doses, PBO, or sham. All except the sham group received a 2.0-mL IA injection into the target knee on day 0. The procedural approach to injection administration was determined by the injector's usual practice. In all cases, joint aspiration was prohibited, but a fluid backflush (0.3-0.5 mL) was allowed to verify needle insertion into the joint cavity. The PBO consisted of pH 7.4 phosphate-buffered saline with 0.5% carboxymethylcellulose sodium and 0.05% polysorbate 80, which was identical to the LOR drug product with the active ingredient withheld. For the sham injection, a dry-needle syringe was held in place in the joint using the same duration and applied pressure as the PBO and drug injections.

Study investigators and participants were blinded to treatment assignments; unblinded personnel prepared medication and performed injections. All unblinded personnel were instructed to minimize contact with participants and were not allowed to perform study assessments. Blinding of participants was accomplished by requiring them to wear a blindfold before and throughout the injection procedure; they remained blindfolded until all injection-related materials had been removed.

Participant characteristics, medical history, and body mass index were collected at screening. Participants were required to complete an electronic diary (ERT) to assess daily pain NRS, NSAID usage, and monthly completion of the WOMAC and patient global assessment. The following changes were assessed over 24 weeks: weekly averages of daily pain NRS scores for the target knee; monthly WOMAC pain, stiffness, and function subscores; and monthly patient global assessment scores. Data were evaluated by baseline-adjusted analysis of covariance using the full analysis set, which comprised all patients who were randomized and treated. All analyses were conducted using SAS 9.4M3 (Cary, NC). Groupwise comparisons between the LOR and PBO groups and the PBO and sham groups, expressed as least squares mean difference (95% CI), were made for each PRO at every time point.

In addition, on day 1 and at week 24, participants were asked to identify which treatment they believed they had received: "study drug injection," "injection of 2 mL inactive vehicle substance," "needle insertion into the knee with no vehicle substance injected," and "do not know." Responses were compared via BBI,[2] which estimated the extent of unblinding beyond that created by chance. BBI generated a value between -1 (implying completely incorrect guessing, indicative of a maintained blind) and $+1$ (implying completely correct guessing, indicative of complete unblinding); a BBI of 0 was indicative of random guessing. BBI values (day 1 and week 24) were determined for the combined LOR-treated, PBO, and sham groups, but they were not statistically compared. Similarly, changes in PROs against the MCID ($\geq$10% improvement in score[15]) were descriptive only.

TABLE 1
Baseline Characteristics for the Vehicle Placebo and Dry-Needle Sham Injection Groups[a]

	Placebo (n = 116)	Sham (n = 117)
Age at consent, y	60.1 ± 9.0	59.0 ± 8.0
Body mass index	28.6 ± 4.3	29.0 ± 3.8
Female	64 (55.2)	70 (59.8)
Race		
White	90 (77.6)	86 (73.5)
Black	17 (14.7)	24 (20.5)
Asian	6 (5.2)	3 (2.6)
Kellgren-Lawrence grade 3	72 (62.1)	58 (49.6)
Unilateral symptomatic	61 (52.6)	62 (53.0)
No widespread pain[b]	93 (80.2)	94 (80.3)

[a]Values are presented as mean ± SD or No. (%).
[b]Widespread Pain Index <4.

RESULTS

Baseline characteristics are provided for the PBO and sham groups (Table 1) and for the LOR treatment groups (Appendix Table A1, available online). Within the full trial population, 406 (58.4%) patients were female and 289 (41.6%) were male; 517 (75.5%) were White; and 394 (57.3%) had Kellgren-Lawrence grade 3 radiographic disease in the target knee. Mean ± SD age and body mass index were 59.0 ± 8.5 years and 28.97 ± 4.01, respectively. No statistically significant differences in baseline characteristics were identified between groups (Appendix Table A1, available online).

The PBO and sham groups comprised 116 and 117 randomized participants, respectively (Figure 1). The full trial results are published elsewhere (Appendix Figure A1, available online).[17] The PBO and sham groups demonstrated improvements (MCID ≥10%) from baseline to week 24 in all tested PROs at all time points (Figure 2; Appendix Figure A2, available online). No mean differences (95% CI) in the degree of improvement were found between the PBO and sham groups in any PRO at any time point: week 24 pain NRS, −0.10 (−0.79 to 0.59; P = .78); WOMAC pain, –2.89 (–9.70 to 3.92; P = .403); WOMAC stiffness, −2.37 (−9.37 to 4.63; P = .505); and WOMAC function, −1.39 (–8.06 to 5.29; P = .682). BBI values for the PBO and sham groups were negative at day 1 (−0.216 and −0.282, respectively) and week 24 (−0.373 and −0.429) (Table 2).

DISCUSSION

This phase 2b trial demonstrated that in the primary PRO analyses, all types of treatment, including PBO and sham, produced clinically meaningful (MCID ≥10%)[15] improvements over baseline. These improvements were achieved by week 4, reached a maximum by week 12, and were maintained throughout the 24-week trial.[17] All PROs in the PBO and sham groups were virtually superimposable in magnitude at all time points. Finally, the negative BBI values for the PBO and sham groups indicated that participants remained blinded throughout the study.

The results for the PBO and sham arms were similar to results for saline placebos from meta-analyses and systematic reviews of other IA therapy-based knee OA studies.[1,3,11,14,18] These studies also demonstrated clinically meaningful and durable PRO improvements from baseline, raising the hypothesis that these responses could be due to saline. Zhang et al[18] published a systematic review in 2008 that examined placebo effects in OA across different joints and included 122 knee OA studies (with 10,300 participants). The review concluded that placebos (including those with non-IA routes of administration) had overall moderate effects (effect size, 0.54 [95% CI, 0.49-0.55]) on pain and other subjective outcomes. Drivers of these effects were concluded to be baseline pain, active treatment expectations, study sample size, and route of delivery. In a 2016 meta-analysis, Altman et al[1] assessed 38 randomized controlled trials of knee OA for the effects of IA saline placebos on pain. In 32 of 38 studies (participant 1705), statistically significant improvements in outcomes, as compared with baseline, lasted for up to 6 months. While acknowledging that substantial heterogeneity across studies was a confounding factor, the authors concluded that IA saline may have physiological effects beyond those of a true placebo. This result was replicated in a meta-analysis of 14 trial groups involving IA saline placebo for knee OA (n = 1076) by Saltzman et al,[14] which identified clinically and statistically significant PRO improvements from baseline that continued for up to 6 months after injection; it was hypothesized that these effects were due to the biological properties of saline and potentially to dilution of inflammatory mediators. In addition, Previtali et al[11] recently published a meta-analysis of 50 trials (including 4076 participants) that examined the effects of IA saline placebo injections for knee OA, confirming statistically significant PRO improvements near or above MCIDs from study baselines, which persisted for up to 6 months. The specified PROs were pain visual analog scale, WOMAC subscores, and evaluator global assessments. The authors calculated a mean Outcome Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) responder rate of 56% at 6 months from studies that had this measure. The authors proposed that some of these effects were procedure and patient related, and they similarly noted that placebo effect size appeared to correlate with that of the test product. They also postulated that there could be a contribution from the biological effects of IA saline. However, they noted no apparent evidence that differing saline injectate volumes affected either patient responses or physiological effects, thereby bringing into question the inflammatory mediator dilution hypothesis. In summary, the potential therapeutic benefits of saline have been hypothesized to be mechanistically due to inflammatory mediator dilution, changes in nociceptive responses, and alterations of biophysical joint properties, among others.[1,11,14] Saltzman et al and Previtali et al acknowledged that to truly test these potentially therapeutic saline effects, a prospective trial is needed with a null comparator group (sham injection).

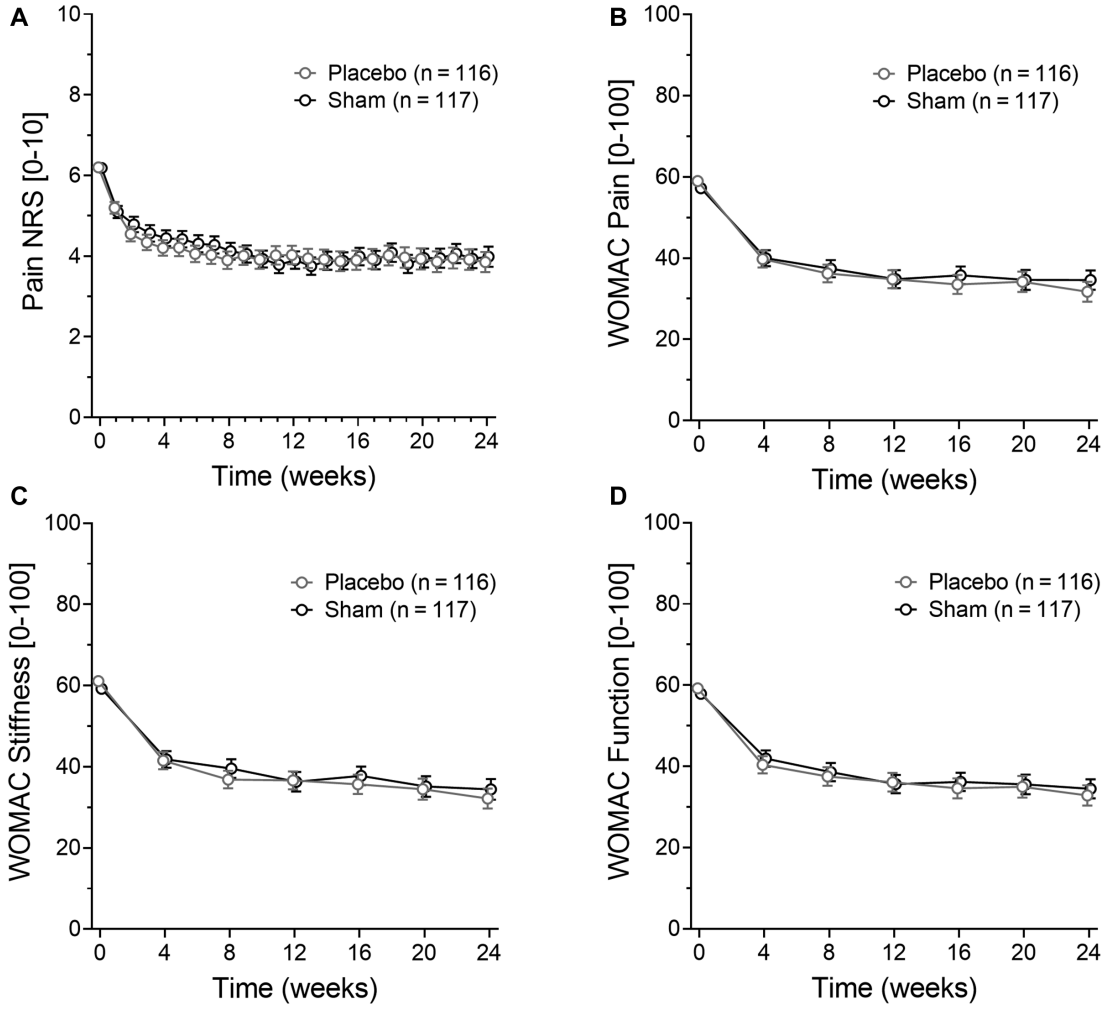

Figure 2. Changes in PROs from baseline to each time point for the trial control groups: (A) pain NRS and (B-D) WOMAC pain, stiffness, and function. Gray line, intra-articular vehicle (placebo); black line, dry-needle injection (sham). Lower scores represent symptom improvement. Values are presented as mean ± SD. All PROs demonstrated clinically meaningful improvements from baseline (≥10%), but no between-group differences were found at any time point. NRS, numeric rating scale; PRO, patient-reported outcome; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

TABLE 2
Participants' Identification of Their Treatment Groups and Accuracy According to Bang Blinding Index[a]

	Response, No.[b]					
Visit: Treatment Group	LOR	PBO	Sham	Do Not Know	Total	BBI[c]
Day 1						
LOR[d]	111	17	13	321	462	0.175
PBO	23	2	4	87	116	−0.216
Sham	29	7	3	78	117	−0.282
Total	163	26	20	486	695	NA
Week 24						
LOR[d]	193	50	37	147	427	0.248
PBO	47	16	7	32	102	−0.373
Sham	43	13	11	38	105	−0.429
Total	283	79	55	217	634	NA

[a]BBI, Bang Blinding Index; LOR, lorecivivint; PBO, vehicle placebo.
[b]Participants were asked to identify which type of treatment they received. "I do not know" was an allowed response.
[c]Scored on a scale of −1 (completely incorrect guessing) to +1 (completely correct guessing [complete unblinding]) with 0 indicating random guessing.
[d]Comprises all dose groups combined.

Interestingly, this trial was not the first report of sham injections compared against saline-based placebos. Two studies from the 1950s were reported.[8,10] In particular and remarkable in design for its time, Miller et al[10] incorporated randomization and blinding of participants and assessors. The authors tested 10-mL IA injections of lactic acid, novocaine, saline, and hydrocortisone against "mock" needle injections in 181 patients with primary knee OA under a protocol in which unblinded injectors administered the 5 allocated IA treatments every 2 weeks. Outcomes were evaluations of patient-reported symptoms ("improved," "unchanged," or "worsened") and objective findings captured by clinician examinations. Approximately 87% of patients indicated "improved" at 6 months with no between-group statistical differences, including the mock injection group. The authors ascribed these results to "procedural ritual and psychological causes."[10] The other study, by Desmarais,[8] consisted of allocated osteoarthritic hip and knee case cohorts, tested with IA treatments of lactic acid, procaine, saline, and dry-needle sham injection (considered the control group). PROs of "no change," "slight improvement," or "marked improvement" were recorded before injection, after treatment, and at 3 and 6 months after treatment. A group of 21 knees was treated with saline, and a group of 18 knees was treated with sham injection. The author noted similar improvements for the saline and sham knee injection groups lasting through 6 months. At 3 months, statistical testing showed no significant between-group differences for any treatment. The author noted, "The improvement in pain obtained in all groups, including the control group, observed immediately after treatment suggests the psychological effect on the patient of a new treatment," and he concluded that IA injections in the treatment of OA were of "very limited value."[8]

Our study reproduced these results employing modern trial design techniques, by testing a saline-based PBO and sham injection within a population that underwent thorough prescreening for target knee OA pain, multicenter randomization, and assessment by more sensitive and validated PRO instruments (multi-item, multidimensional, volunteered response [not elicited]). Overall, the results from this and earlier studies refute the concept of saline being physiologically active and instead support the existence of strong contextual true placebo effects within IA injection trials for knee OA. Contextual effects are defined as physical, psychological, and social factors that form the components of a therapeutic encounter between patient and health care provider. The ritual of undergoing an IA procedure, including factors such as aseptic preparation and needle injection, is interpreted by the patient (or clinical trial participant) in such a way to produce emotions and expectations that then influence the treatment outcome.[13] These appear to be causal for the responses observed. The negative BBI values for the PBO and sham groups in this trial support this conclusion, indicating that participants had no perception of whether they were administered a dry-needle injection or a fluid bolus into their knee joints.

A potential limitation to interpreting these data was the use of a saline-based PBO vehicle containing 0.55% excipients (ie, not pure saline). This was designed to ensure that the true LOR drug effect was assessed in the parent study. However, on testing, the PBO viscosity was the same as that of saline. Furthermore, in a previous phase 2a trial of LOR that used saline as the placebo,[7] improvements from baseline were similar in magnitude to this trial's PBO group, suggesting that the additional components did not alter PBO significantly from saline.

CONCLUSION

This prospective randomized trial demonstrated that sham injections (dry needle) resulted in durable and meaningful PRO improvements in patients with knee OA that were identical to those from saline-based vehicle injections. These data support a contextual true placebo response attributed to IA procedures rather than to the physiological effects of saline. Therefore, for an IA knee OA treatment to demonstrate efficacy, achievement of a treatment effect over this true placebo response is required.

ACKNOWLEDGMENT

The authors gratefully acknowledge and thank the study participants, investigators, and associated research professionals who contributed their time and efforts to these clinical studies. The authors also thank Andrew Ray and Elizabeth Orient for critical revision of this manuscript and the Biosplice team for its contributions to these clinical studies. All studies described in this report and the preparation of this manuscript were funded by Biosplice Therapeutics, Inc.

REFERENCES

1. 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):151-159. doi:10.1016/J.SEMARTHRIT.2016.04.003
2. Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. *Control Clin Trials*. 2004;25(2):143-156. doi:10.1016/J.CCT.2003.10.016
3. Bannuru RR, McAlindon TE, Sullivan MC, Wong JB, Kent DM, Schmid CH. Effectiveness and implications of alternative placebo treatments: a systematic review and network meta-analysis of osteoarthritis trials. *Ann Intern Med*. 2015;163(5):365-372. doi:10.7326/M15-0623
4. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis. *Ann Intern Med*. 2015;162(1):46-54. doi:10.7326/M14-1231
5. Cross M, Smith E, Hoy D, 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):1323-1330. doi:10.1136/annrheumdis-2013-204763
6. da Costa BR, Reichenbach S, Keller N, et al. Effectiveness of nonsteroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. *Lancet*. 2017;390(10090):e21-e33. doi:10.1016/S0140-6736(17)31744-0
7. Deshmukh V, O'Green AL, Bossard C, 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. *Osteoarthritis Cartilage*. 2019;27:1347-1360. doi:10.1016/j.joca.2019.05.006
8. Desmarais MHL. Value of intra-articular injections in osteo-arthritis: a controlled series. *Ann Rheum Dis*. 1952;11(4):277-281.
9. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage*. 2014;22(3):363-388. doi:10.1016/j.joca.2014.01.003
10. Miller JH, White J, Norton TH. The value of intra-articular injections in osteoarthritis of the knee. *J Bone Joint Surg Br*. 1958;40(4):636-643.
11. Previtali D, Merli G, Di Laura Frattura G, Candrian C, Zaffagnini S, Filardo G. The long-lasting effects of ''placebo injections'' in knee osteoarthritis: a meta-analysis. *Cartilage*. Published online March 18, 2020. doi:10.1177/1947603520906597
12. Roberts E, Nunes VD, Buckner S, et al. Paracetamol: not as safe as we thought? A systematic literature review of observational studies. *Ann Rheum Dis*. 2016;75(3):552-559. doi:10.1136/annrheumdis-2014-206914
13. Rossettini G, Carlino E, Testa M. Clinical relevance of contextual factors as triggers of placebo and nocebo effects in musculoskeletal pain. *BMC Musculoskelet Disord*. 2018;19(1):27. doi:10.1186/S12891-018-1943-8
14. Saltzman BM, Leroux T, Meyer MA, et al. The therapeutic effect of intra-articular normal saline injections for knee osteoarthritis: a meta-analysis of evidence level 1 studies. *Am J Sports Med*. 2017;45(11):2647-2653. doi:10.1177/0363546516680607
15. Strand V, Boers M, Idzerda L, 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;38(8):1720-1727. doi:10.3899/jrheum.110392
16. Wolfe F, Clauw DJ, Fitzcharles MA, 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):1113-1122. doi:10.3899/jrheum.100594
17. Yazici Y, McAlindon TE, Gibofsky A, et al. A phase 2b randomized trial of lorecivivint, a novel intra-articular CLK2/DYRK1A inhibitor and Wnt pathway modulator for knee osteoarthritis. *Osteoarthritis Cartilage*. 2021;29(5):654-666. doi:10.1016/j.joca.2021.02.004
18. Zhang W, Robertson J, Jones AC, Dieppe PA, Doherty M. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. *Ann Rheum Dis*. 2008;67(12):1716-1723. doi:10.1136/ard.2008.092015