A Phase 3, 28-Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial (OA-10) to Evaluate the Efficacy and Safety of a Single Injection of Lorecivivint Injected in the Target Knee Joint of Moderately to Severely Symptomatic OA Subjects

Yusuf Yazici, MD[1,2], Christopher J. Swearingen, PhD[1], Heli Ghandehari, MS[1], Victor Lopez[1], MS, Ismail Simsek, MD[1], Mark Fineman, PhD [1], Sarah Kennedy, PhD[1], Jeyanesh Tambiah, MD[1], Timothy McAlindon[3]
[1]Biosplice Therapeutics, Inc., San Diego, CA; [2]NYU Grossman School of Medicine, New York, NY; [3] Tufts University, Boston, MA

Background

- Knee osteoarthritis (OA) is a common joint disorder associated with pain, disability, and joint damage with large unmet need for safe and efficacious therapies.
- Lorecivivint (LOR), a novel intra-articular (IA) CLK/DYRK inhibitor thought to modulate Wnt and inflammatory pathways, appeared safe and demonstrated patient-reported outcome (PRO) pain and function improvements compared with placebo (PBO) in a Phase 2b knee OA trial.[1]
- The safety and efficacy of 0.07 mg LOR was evaluated in a Phase 3, 28-week trial (OA-10, NCT04385303) utilizing PROs.

Methods

- Participants with ACR-defined (clinical and radiographic) knee OA, Kellgren-Lawrence (KL) grades 2-3, and Pain Numeric Rating Scale (NRS) [0-10] ≥4 and ≤8 in the target knee and <4 in the contralateral knee, were randomized 1:1 to receive a single intra-articular injection of 2 mL 0.07 mg LOR or vehicle PBO.
- A prescreening protocol was employed to optimize subject recruitment which resulted in more subjects with baseline medial joint space width (mJSW) outside the 1.5-4.0 mm range.
- Primary endpoint was change from baseline in Pain NRS at week 12.

Results

Table 1. Subject Characteristics

Full Analysis Set	PBO	LOR (0.07 mg)	All Subjects
N	239	231	470
Age (Years)*	61.0 (7.9)	61.0 (8.7)	61.0 (8.3)
BMI (kg/m^2)*	29.67 (3.98)	29.94 (3.81)	29.80 (3.90)
Female	148 (61.9)	136 (58.9)	284 (60.4)
Race			
White	181 (75.7)	167 (72.3)	348 (74.0)
African American	45 (18.8)	48 (20.8)	93 (19.8)
Asian	3 (1.3)	3 (1.3)	6 (1.3)
KL Grade 2	115 (48.1)	111 (48.1)	226 (48.1)
Unilateral Symptomatic†	69 (28.9)	82 (35.5)	151 (32.1)

*Mean (SD) reported. Otherwise, n (%) reported.
†Unilateral symptomatic as designated by principal investigator

Table 2. Safety

	LOR N=241	PBO N=251
Adverse Events N (%)	91 (37.8)	85 (33.9)
SAEs* N (%)	4 (1.7)	1 (0.4)
Target-Knee AEs	6 (2.5)	11 (4.4)

*No SAEs deemed related to LOR

Figure 1. Distribution of mJSW across LOR trials

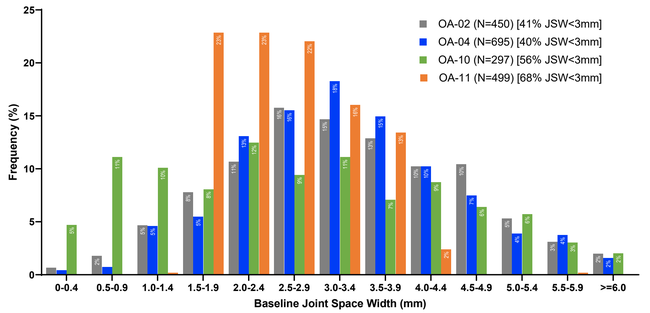


Figure 2. Weekly Average of Daily Pain NRS (FAS)

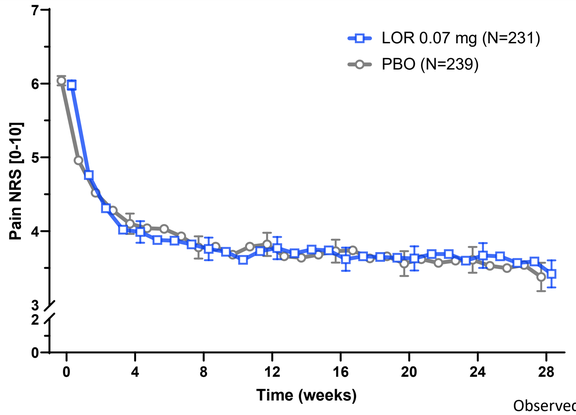
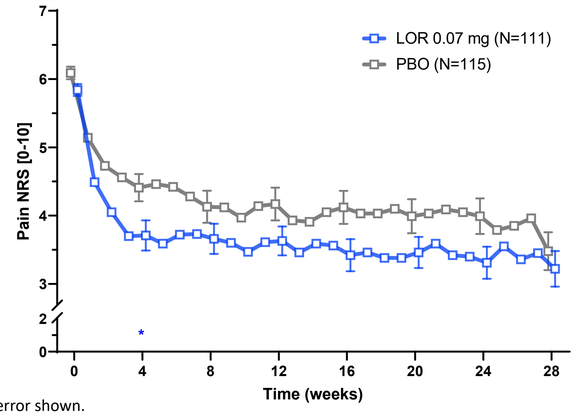


Figure 3. Weekly Average of Daily Pain NRS (KL2)



Observed mean ± standard error shown.
*P<0.05 reported from baseline-adjusted ANCOVA at timepoint comparison

Results

- 498 participants were randomized and 454 completed
- Enrolled participants' baseline mJSW distributions were skewed towards lower mJSWs (56% mJSW < 3 mm). (Figure 1)
- LOR appeared safe and well tolerated (Table 2)
- The trial did not meet its primary endpoint of change from baseline at week 12 in Pain NRS, LOR -2.24 ± 2.21 vs. PBO -2.20 ± 2.32, NS, in the Full Analysis Set (FAS). (Figure 2) There were no meaningful treatment effects observed between LOR and PBO in any FAS PROs.
- Separation was seen in the post hoc KL2 subgroup for all PROs. (Figure 3)

Conclusions

- **LOR appeared safe and well tolerated but did not meet primary or secondary endpoints in this trial.**
- **Efficacy signals were identified in participants with less advanced structural disease, suggesting earlier intervention may be more effective.**
- **This trial was conducted during the COVID pandemic, and while its impact was difficult to quantify, effects on activity levels and pain PROs in knee OA patients have been reported[2,3].**
- **Future trials of LOR in knee OA will target less advanced structural disease.**

References:
1. Yazici et al. *OAC* 2021
2. Larghi et al., *Acta Biomed* 2020
3 Endstrasser et al., *ESSKA* 2020

info@biosplice.com