A Phase 2, 104-Week Study of Repeat Lorecivivint Injections Evaluating Safety, Efficacy, and Bone Health Utilizing Quantitative Computed Tomography (QCT) in Knee Osteoarthritis (OA-06)

Yusuf Yazici, MD[1,2], Christopher J. Swearingen, PhD[1], Heli Ghandehari, MS[1], Jon Britt[1], MS, Ismail Simsek, MD[1], Mark Fineman, PhD [1], Sarah Kennedy, PhD[1], Jeyanesh Tambiah, MD[1], Nancy E. Lane[3]
[1]Biosplice Therapeutics, Inc., San Diego, CA; [2]NYU Grossman School of Medicine, New York, NY; [3] University of California, Davis, CA

Background

- Knee osteoarthritis (OA) is a common joint disorder associated with pain, disability, and joint damage.
- There is a large unmet need for safe and efficacious treatments for treatment of symptoms and structural modification.
- Lorecivivint (LOR), an intra-articular (IA) CLK/DYRK inhibitor thought to modulate Wnt and inflammatory pathways, is in development as a potential treatment for knee OA.
- The primary objective of this trial was to assess the safety and tolerability of repeated 6-month dosing of LOR in a 104-week trial (OA-06, NCT03727022).
- This trial also sought to characterize juxta-articular bone health using quantitative computed tomography (QCT) and regional bone health via dual energy x-ray absorptiometry (DXA).

Methods

- Participants with ACR-defined clinical and radiographic OA, aged 40-80, and Kellgren-Lawrence (KL) grades 2-3 were randomized 1:1 to receive IA injections of 2 mL 0.07 mg LOR or vehicle PBO at baseline, 24 weeks, 52 weeks, and 72 weeks (4 injections total).
- The trial was conducted in two 52-week phases, part A (baseline - week 52) and part B (week 53 - week 104), with A completers invited to B. General safety was assessed by physical examinations, clinical laboratory tests, and collection of adverse events (AEs) and serious AEs (SAEs).
- Bone safety assessments included target and non-target knee QCT (standardized by calibration phantom), bone and cartilage biomarkers, and DXA of hip and spine.
- Exploratory efficacy was assessed by patient-reported outcomes (PROs). For bone imaging endpoints, change from baseline was estimated using baseline-adjusted ANCOVA.

Results

Figure 1. Total Target Knee BMD over 104 weeks

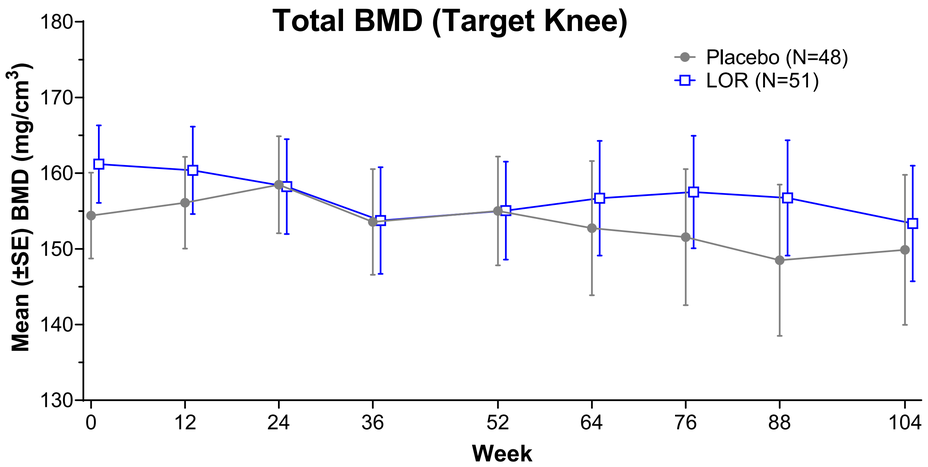

Figure 1. Total Target Knee BMD over 104 weeks. Change from baseline using ANCOVA

Table 1A and 1B

Phase A	# Events / # Participants Reporting	
	LOR (N=50)	PBO (N=51)
Adverse Events (AE)	52/25	52/24
Serious AE	5/2	3/2
Target Knee AE	7/6	4/3

Phase B	# Events / # Participants Reporting	
	LOR (N=33)	PBO (N=32)
Adverse Events (AE)	19/8	15/11
Serious AE	2/2	0/0
Target Knee AE	2/1	0/0

Results

- 101 participants (mean age 60.9±9.1 years, BMI 28.6±3.7 kg/m^2, female 59.4%, KL2 52.5%) were enrolled. 77 participants completed part A and 53 completed part B.
- AE rates were similar between PBO and LOR, and no SAEs were deemed related to treatment.
- There were no clinical signals for change in bone health, with no fractures, accelerated OA, or osteoporosis observed in LOR or PBO. Observed target knee BMD values as assessed by QCT were similar between LOR and PBO (Figure 1).
- There were no effects of repeated injection on rates of change in BMDs; the change from baseline in BMD at Week 104 was -7.08 (12.34) mg/cm^2 in LOR and -2.95 (8.65) mg/cm^2 in PBO, (estimated difference -4.05 [95% CI -11.21, 3.11], not significant).
- There were no significant differences between LOR and PBO in females and age [65-80] (those with potentially higher risk of decreased bone density) in target knee nor total hip or spine BMD.
- There were no meaningful differences in PRO changes between LOR and PBO groups.
- A trial conduct limitation was the small number of QCT-enabled sites in the US. Potential confounding factors included baseline imbalances in sex (PBO 68.0% vs. LOR 51.0% female), KL grade (PBO 62.0% vs LOR 42.1% KL 2), and site randomization.

Conclusions

- **The incidence of AEs was similar between treatment groups and not affected by repeated injections of LOR.**
- **Multiple injections of LOR over 2 years did not appear adversely affect bone health locally around the knee or regionally at spine or hip.**

info@biosplice.com