A Multicenter, Observational, Extension Study Evaluating the Safety, Tolerability, and Efficacy of a Single Lorecivivint Injection in Knee OA Subjects

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Background and Objectives

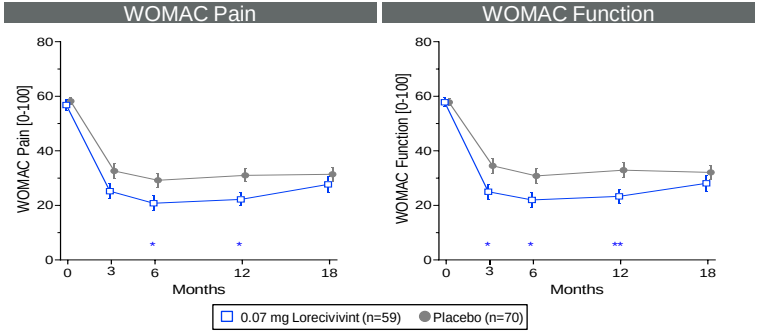
- Lorecivivint (LOR), a novel intra-articular (IA) CLK2/DYRK1A inhibitor that modulates the Wnt pathway, is in development as a knee osteoarthritis (OA) treatment.
- Subjects from two consecutive Phase 2 trials were followed up in a 5-year, pooled, observational study that evaluated the safety and exploratory efficacy of a single LOR injection previously administered into the target knee joint of subjects with moderate to severe knee OA.
- The primary objective evaluated the incidence of serious adverse events (SAEs). Safety data for all doses and a post hoc efficacy analysis for the pivotal dose (0.07 mg LOR) are reported.

Methods

- This was a Phase 3, multicenter, observational, extension study of completer subjects (OA-05; NCT02951026) from two Phase 2 trials of LOR: a 12-month Phase 2a trial (OA-02; NCT02536833)[1] and a 6-month Phase 2b trial (OA-04; NCT03122860)[2].
- Subjects received a single LOR or control (placebo [PBO] or sham) injection at their parent-study baseline visit (OA-02 and OA-04 Visit 0). Pooled data from clinic visits at 6, 12, 24, and 36 months post-injection contributed to the extension-study (OA-05) analysis.
- SAEs, knee-related adverse events (AEs), and AEs of newly diagnosed conditions requiring treatment were collected (**Table 1**).
- Efficacy was assessed by target knee WOMAC Pain and Function subscores (**Figure 1**) and radiographic medial joint space width (mJSW).
- An analysis was performed for 0.07 mg LOR versus PBO to assess responses in a subject subgroup (unilateral symptoms, no wide-spread pain, 18-month post-injection radiograph at study termination). Baseline-adjusted ANCOVA was performed using data from both the current and parent studies at 0, 3, 6, 12, and 18 months.

Results

Figure 1. WOMAC Pain and Function over Time (Unilateral 18-Month Completers)†



†Pooled data from the OA-02, OA-04, and extension study; includes all available data from 3, 6,12, and 18 months after injection. Mean (±SE); *P<0.05, **P<0.01

Table 1. Adverse Events (AEs)

AEs Reported ≥1%	0.03 mg n=131	0.07 mg n=135	0.15 mg n=65	0.23 mg n=135	Other n=29	Control n=208^	All N=703
Total AEs/Unique subjects (%)	50 / 24 (18.3)	28 / 21 (15.6)	25 / 11 (16.9)	64 / 33 (24.4)	10/4 (13.8)	60/44 (21.2)	237 / 137 (19.5)
Osteoarthritis	13 / 9 (6.9)	6 / 6 (4.4)	1 / 1 (1.5)	6 / 5 (3.7)	1 / 1 (3.4)	6/6 (2.9)	33 / 28 (4.0)
Arthralgia	6 / 5 (3.8)	5 / 5 (3.7)	1 / 1 (1.5)	6 / 6 (4.4)	1 / 1 (3.4)	8/7 (3.4)	27 / 25 (3.6)
Meniscus Injury	3 / 3 (2.3)	2 / 2 (1.5)	1 / 1 (1.5)	1 / 1 (0.7)	0 / 0 (0.0)	2/2 (1.0)	9 / 9 (1.3)
Hypertension	2 / 2 (1.5)	0 / 0 (0.0)	2 / 2 (3.1)	2 / 2 (1.5)	0 / 0 (0.0)	6/6 (2.9)	12 / 12 (1.7)
Target Knee AEs (Total)	**22 / 15 (11.5)**	**8 / 7 (5.2)**	**6 / 3 (4.6)**	**11 / 9 (6.7)**	**4 / 1 (3.4)**	**12/11 (5.3)**	**63 / 46 (6.5)**
Osteoarthritis	8 / 8 (6.1)	2 / 2 (1.5)	1 / 1 (1.5)	2 / 2 (1.5)	1 / 1 (3.4)	4/4 (1.9)	18 / 18 (2.6)
Arthralgia	4 / 4 (3.1)	2 / 2 (1.5)	1 / 1 (1.5)	4 / 4 (3.0)	1 / 1 (3.4)	4/4 (1.9)	16 / 16 (2.3)
Meniscus Injury	2 / 2 (1.5)	2 / 2 (1.5)	1 / 1 (1.5)	1 / 1 (0.7)	0 / 0 (0.0)	1/1 (0.5)	7 / 7 (1.0)
Serious AEs							
Subjects Reporting SAEs	14 / 8 (6.1)	8 / 6 (4.4)	8 / 4 (6.2)	32 / 14 (10.4)	1 / 1 (3.4)	5/5 (2.4)	68 / 38 (5.4)

#AE / #subjects (%) reported.
Other: All subjects treated with anything other than the protocol-specified dose of LOR
^Includes 2 PBO subjects with dose of PBO not specified by protocol

Conclusions

- **From these data, LOR appeared to be safe and well tolerated.**
  - The most common AEs were osteoarthritis and arthralgia; incidence was similar between LOR and control groups. No SAEs were considered to be related to treatment by investigator.
- **A post hoc-analyzed subset of completer subjects treated with a single 0.07 mg LOR injection reported durable symptom improvements in WOMAC Pain and Function for up to at least 12 months versus PBO subjects**.

Limitations

- Subjects from LOR and control groups were "completers," therefore, more likely to be responders.
- Subjects could have been on any medication or treatment in the extension study.
- Other limitations include small sample size and the post hoc nature of the analysis.

References

1. Yazici Y, et al. *Arthritis Rheumatol*. 2020.
2. Yazici Y, et al. *Osteoarthritis Cartilage*. 2021.

IS, CJS, HG, SK, JT and YY are employees and shareholders of Biosplice Therapeutics, Inc. NS is a consultant of Biosplice Therapeutics, Inc.

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