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Integrated Safety Summary of the Novel, Intra-articular Agent Lorecivivint (SM04690), a CLK/DYRK1A Inhibitor That Modulates the Wnt Pathway, in Subjects with Knee Osteoarthritis

Ismail Simsek, MD[1], Christopher J. Swearingen, PhD[1], Sarah Kennedy, PhD[1], Jeyanesh Tambiah, MD[1], Cristina Damatarca, MD[1], Yusuf Yazici, MD[1], Nancy E. Lane, MD[2], Marc C. Hochberg, MD[3]

[1]Samumed, LLC, San Diego, CA
[2]University of California Davis, Davis, CA
[3]University of Maryland, Baltimore, MD

Background: Concerns over the safety of available osteoarthritis (OA) treatments have led to revision of treatment guidelines and highlight the need for new therapies. Lorecivivint (LOR; SM04690) is an intra-articular (IA), small-molecule CLK/DYRK1A inhibitor that modulates the Wnt pathway and is in development as a potential disease-modifying treatment for knee OA.[1,2]

Objectives: To evaluate pooled early-phase LOR clinical data for safety, including bone health-related adverse events (AEs).

Methods: Safety data were pooled from 3 randomized controlled trials (one Phase 1, two Phase 2) evaluating 4 doses (0.03 mg, 0.07 mg, 0.15 mg, 0.23 mg) of a single IA injection of LOR in subjects with moderately to severely symptomatic knee OA. Two trials (NCT02095548; NCT03122860) evaluated subjects for 24 weeks and one trial (NCT02536833) for 52 weeks. AEs, serious AEs (SAEs), and bone health AEs were categorized by Medical Dictionary for Regulatory Activities (MedDRA) classification. Incidence of AEs and SAEs was compared between the combined LOR-treated group (subjects who received any dose of LOR) and a control group (subjects not treated with LOR).

Results: This analysis includes 848 LOR-treated and 360 control subjects. The incidence of AEs was similar in LOR-treated (350/848 [41.3%]) and control subjects (138/360 [38.3%]). Incidence of SAEs was 20/848 (2.4%) in LOR-treated and 4/360 (1.1%) in control subjects. The most commonly reported AE in LOR-treated subjects was arthralgia (treated 7.6%, control 7.2%) and was the only AE reported at >5% in either group (Fig. 1). Target-knee arthralgia was the most common joint-specific AE (treated 6.5%, control 5.3%) (Fig. 2). No AEs in other joints exceeded an incidence of 2% in either group. In all categories, individual AEs were reported at similar rates between groups and no SAEs were deemed related to LOR by investigators.

There were 16 bone health-related AEs in 9/848 (1.1%) LOR-treated and 3/360 (0.8%) control subjects. Of the bone health AEs, 2 were osteopenia/osteoporosis in 2 LOR-treated postmenopausal women and 14 were fractures in 10 subjects (7 LOR-treated, 3 control). All fractures (3 patellar [1 target knee, 2 non-target knee], 3 vertebral, 2 foot, 2 wrist, 2 rib, 1 fibula,

1 hand) were adjudicated and determined to be caused by trauma; all healed uneventfully within the expected time frame.

Conclusions: In exposure to date of 848 subjects, IA LOR for the treatment of knee OA appeared to be safe and well tolerated. These data support the continued evaluation of LOR as a potential treatment for knee OA.

Figure 1: Adverse event summary for events occurring in at least 1% of the treated population (N=1208).

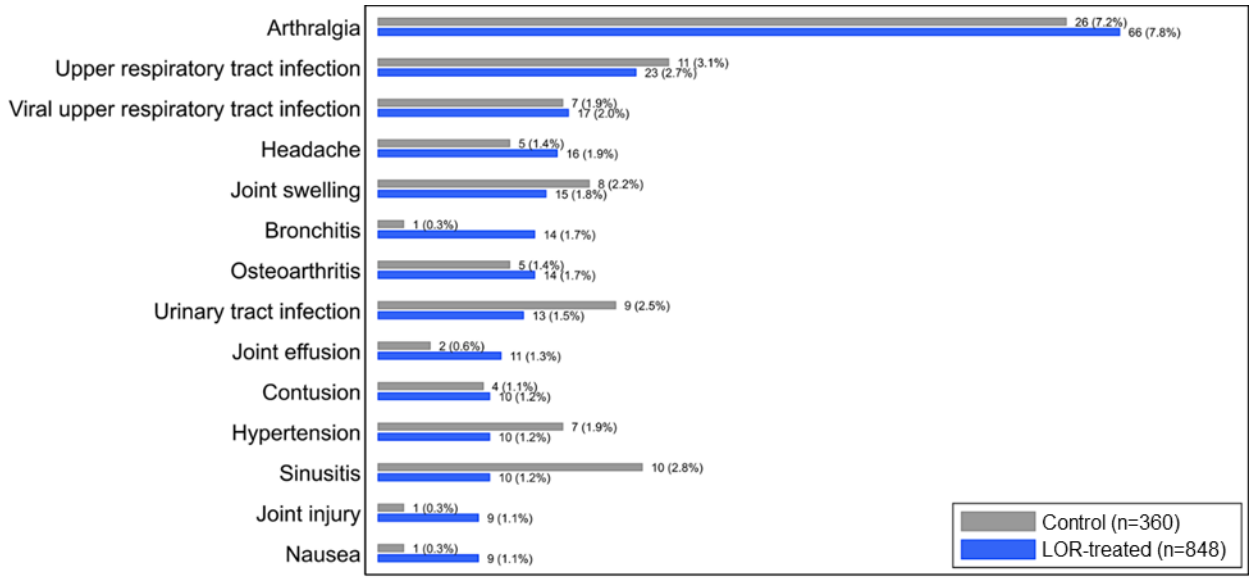
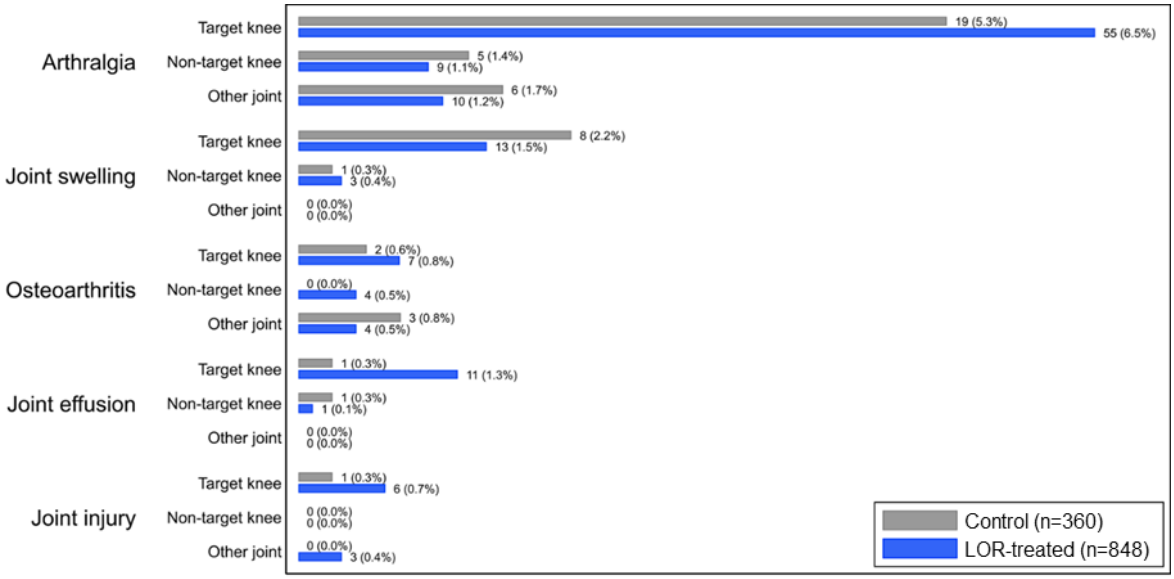


Figure 2: Joint-specific adverse event summary, subcategorized by affected joint, for events occurring in at least 1% of the treated population (N=1208).



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1. Deshmukh V, et al. *Osteoarthritis Cartilage*. 2017.
2. Deshmukh V, et al. *Osteoarthritis Cartilage*. 2019.