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

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Background: Lorecivivint (LOR; SM04690), an intra-articular (IA), small-molecule CLK/DYRK1A inhibitor that modulates the Wnt pathway, is in development as a potential disease-modifying treatment for knee osteoarthritis (OA). A pooled analysis of safety data from 3 placebo-controlled trials was conducted to obtain an initial safety profile for LOR, including bone health-related adverse events (AEs).

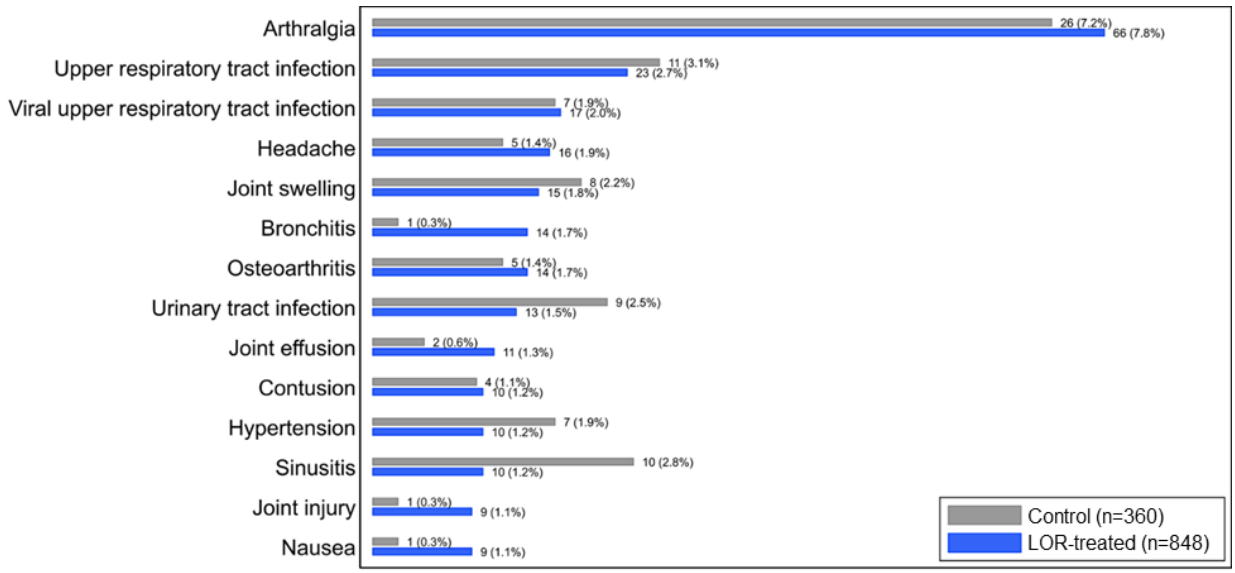
Methods: Safety data were pooled from one Phase 1 (24-week) and two Phase 2 (26- and 52-week) randomized controlled trials evaluating 4 doses (0.03 mg, 0.07 mg, 0.15 mg, 0.23 mg) of a single IA injection of LOR in subjects with moderately to severely symptomatic knee OA. AEs, serious AEs (SAEs), and bone health AEs were categorized by MedDRA classification. Incidence of AEs and SAEs was compared between the combined LOR-treated group and a control group.

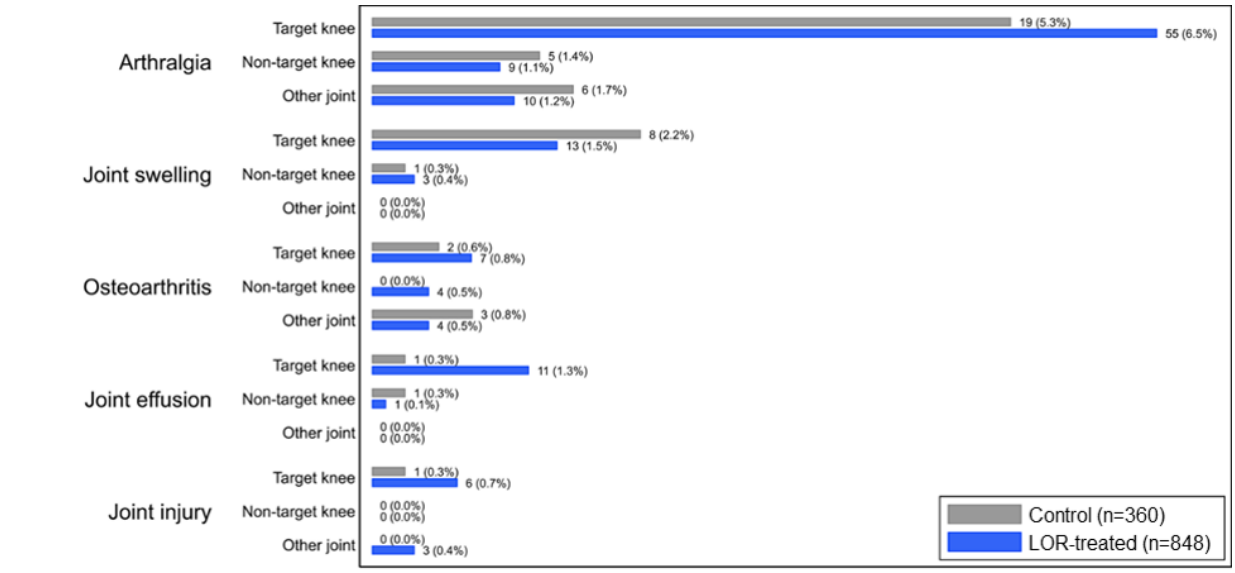
Results: The incidence of AEs was similar in LOR-treated (350/848 [41.3%]) and control subjects (138/360 [38.3%]). Incidence of SAEs was 20/848 (2.4%) in LOR-treated and 4/360 (1.1%) in control subjects. Arthralgia was the most common AE in LOR-treated subjects (treated 7.6%, control 7.2%). Target-knee arthralgia was the most common joint-specific AE (treated 6.5%, control 5.3%). 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. Two AEs were osteopenia/osteoporosis in 2 LOR-treated postmenopausal women. Fourteen were trauma-induced fractures in 10 subjects (7 LOR-treated, 3 control). All fractures (3 patellar [1 target, 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.

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

Figures:


Arthralgia
Upper respiratory tract infection
Viral upper respiratory tract infection
Headache
Joint swelling
Bronchitis
Osteoarthritis
Urinary tract infection
Joint effusion
Contusion
Hypertension
Sinusitis
Joint injury
Nausea
26 (7.2%)
66 (7.8%)
11 (3.1%)
23 (2.7%)
7 (1.9%)
17 (2.0%)
5 (1.4%)
16 (1.9%)
8 (2.2%)
15 (1.8%)
1 (0.3%)
14 (1.7%)
5 (1.4%)
14 (1.7%)
9 (2.5%)
13 (1.5%)
2 (0.6%)
11 (1.3%)
4 (1.1%)
10 (1.2%)
7 (1.9%)
10 (1.2%)
10 (2.8%)
10 (1.2%)
1 (0.3%)
9 (1.1%)
1 (0.3%)
9 (1.1%)
Control (n=360)
LOR-treated (n=848)


Arthralgia
Joint swelling
Osteoarthritis
Joint effusion
Joint injury
Target knee
Non-target knee
Other joint
19 (5.3%)
55 (6.5%)
5 (1.4%)
9 (1.1%)
6 (1.7%)
10 (1.2%)
8 (2.2%)
13 (1.5%)
1 (0.3%)
3 (0.4%)
0 (0.0%)
0 (0.0%)
2 (0.6%)
7 (0.8%)
0 (0.0%)
4 (0.5%)
3 (0.8%)
4 (0.5%)
1 (0.3%)
11 (1.3%)
1 (0.3%)
1 (0.1%)
0 (0.0%)
0 (0.0%)
1 (0.3%)
6 (0.7%)
0 (0.0%)
0 (0.0%)
0 (0.0%)
3 (0.4%)
Control (n=360)
LOR-treated (n=848)