Safety Profile 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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Disclosures

- **Ismail Simsek, MD**: Samumed employee and shareholder
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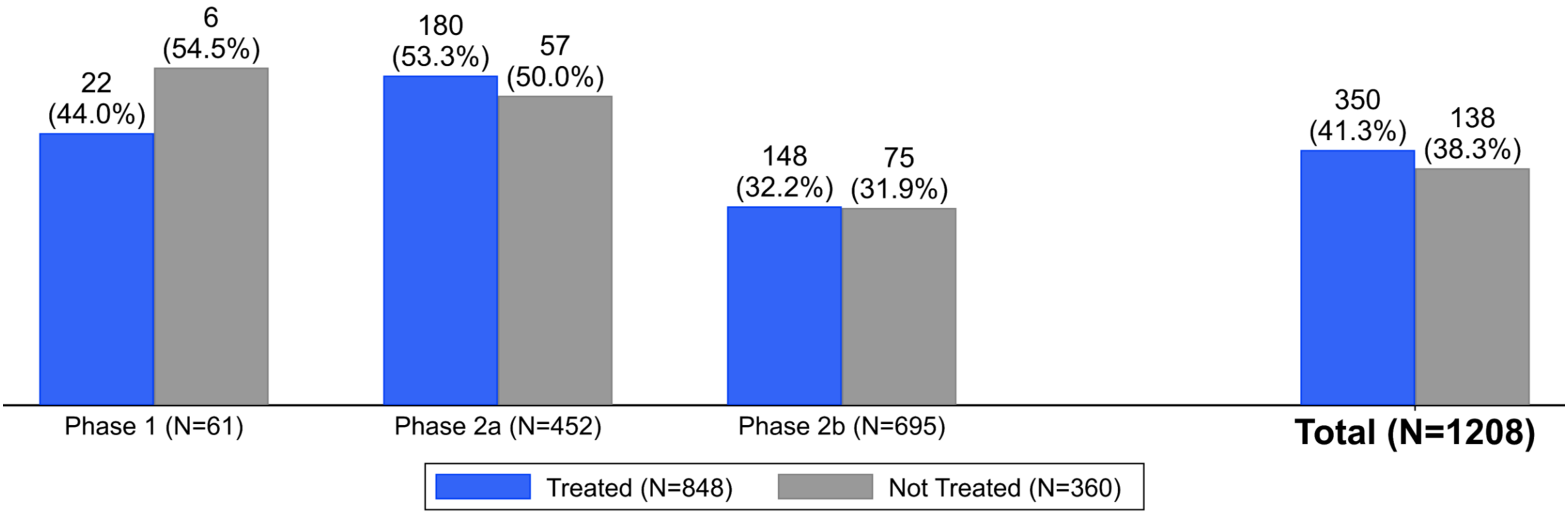
- **Marc Hochberg, MD, MPH**: Bone Therapeutics, Bristol Myers Squibb, Eli Lilly, EMD Serono, Gilead, GlaxoSmithKline, IBSA Institut Biochimique SA, Novartis Pharma AG, Noven Pharmaceuticals Inc., Pfizer Inc., Regenosine, Samumed LLC, Theralogix LLC and Vizuri Health Sciences

Background and methods

- Safety concerns regarding osteoarthritis (OA) pharmacotherapy have reinforced the unmet need for safe and effective OA therapies
- Lorecivivint (LOR), an intra-articular (IA) CLK/DYRK1A inhibitor that modulates the Wnt pathway,[1,2] is in Phase 3 trials as a potential disease-modifying treatment for knee OA
- The safety profile of LOR to date was evaluated by a pooled analysis of 3 completed placebo-controlled trials (Phase 1, 2a, 2b)[3–5]

1. Deshmukh V, et al. *Osteoarthritis Cartilage.* 2017.
2. Deshmukh V, et al. *Osteoarthritis Cartilage.* 2019.
3. https://clinicaltrials.gov (Identification No. NCT02095548).
4. https://clinicaltrials.gov (Identification No. NCT03122860).
5. https://clinicaltrials.gov (Identification No. NCT02536833).

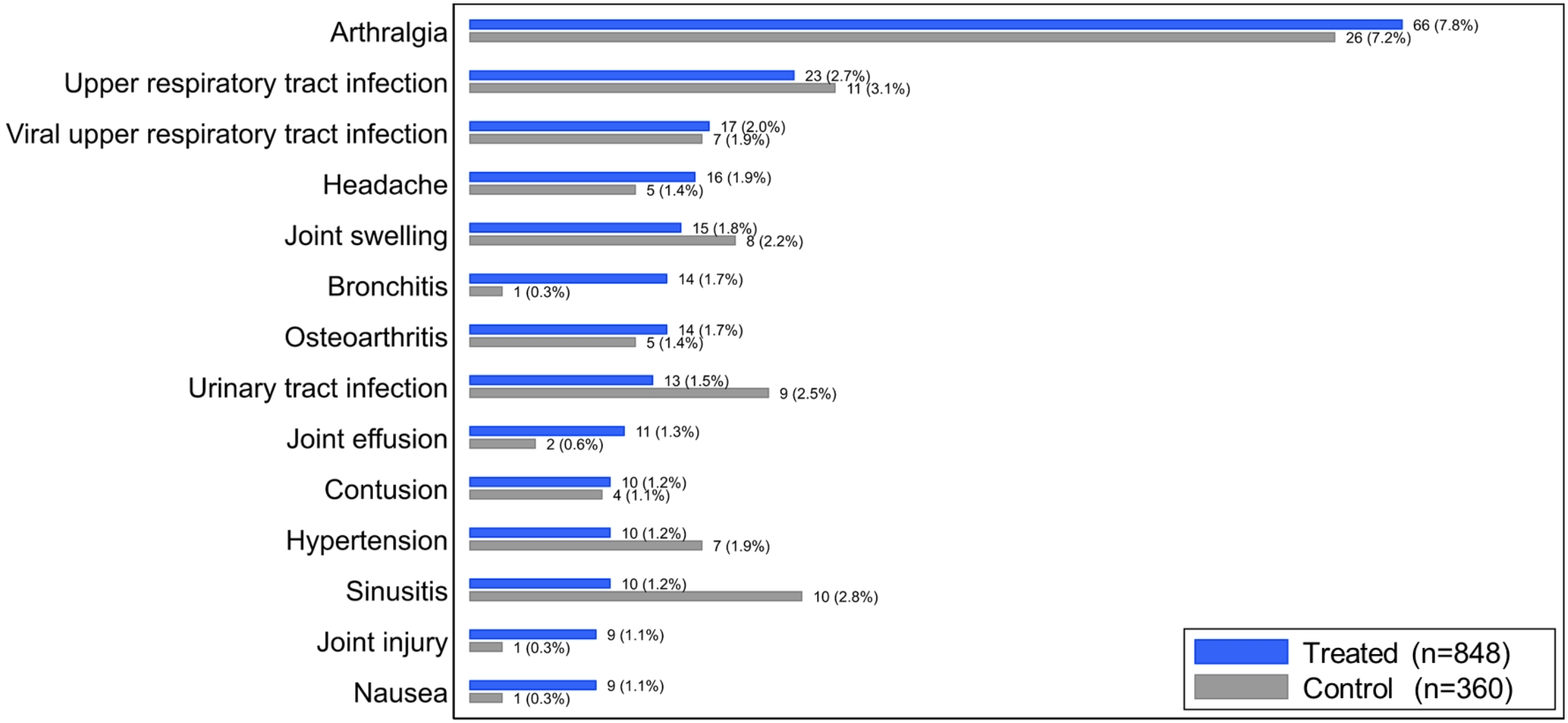
AE rate between control and active subjects consistent across studies and overall



*All subjects received intra-articular procedures.

Integrated safety summary: AEs reported in >1% of treated subjects

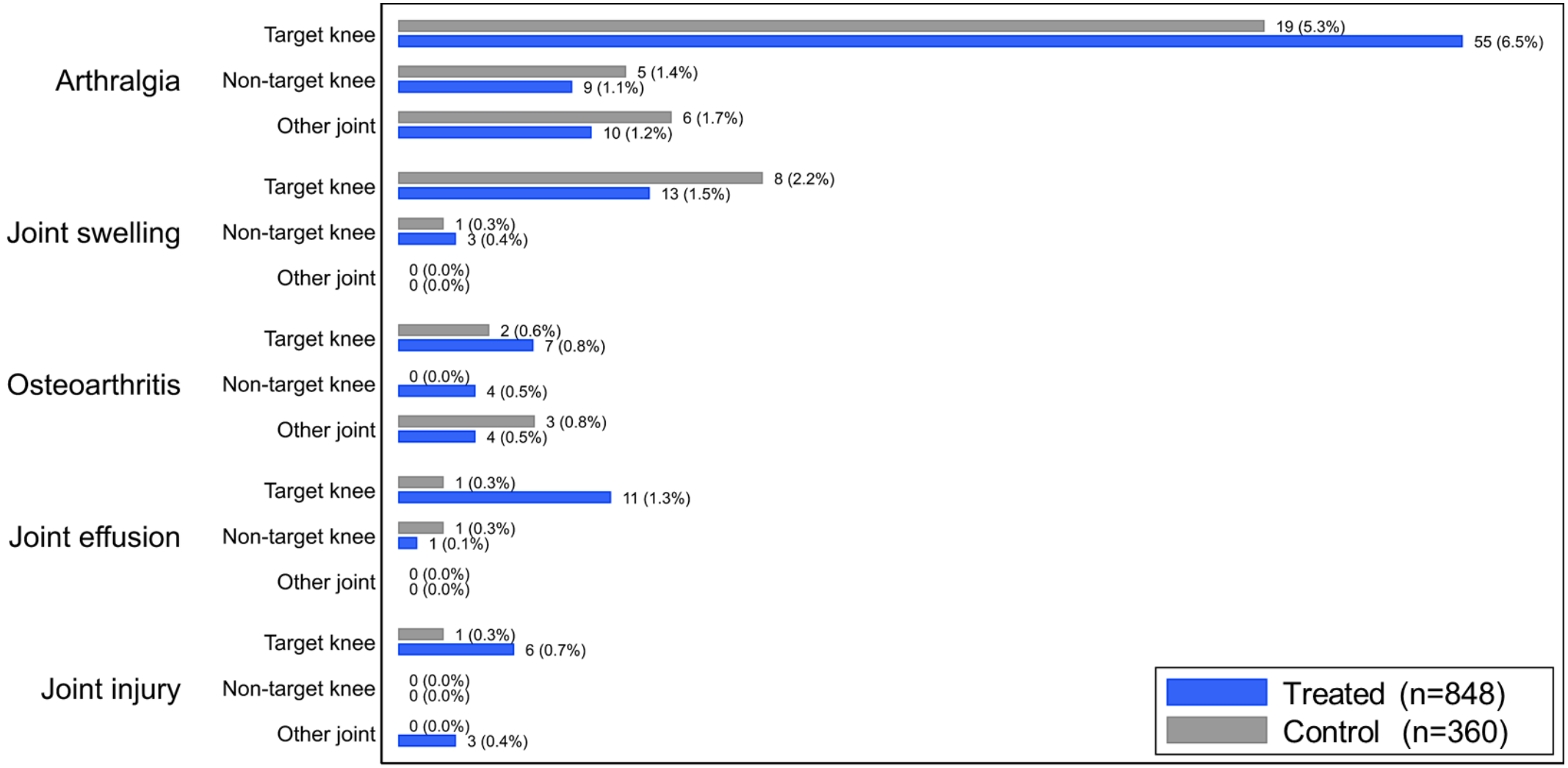
Total clinical trial population (N=1208)



Safety data from completed trials. All subjects received intra-articular injections.

Integrated safety summary: Joint-related AEs

Total clinical trial population (N=1208)



Safety data from completed trials. All subjects received intra-articular injections.

Integrated safety summary: Bone health-related AEs

Total clinical trial population (N=1208)

- 16 bone health-related AEs in 12/1208 (1.0%) subjects
  - 2 osteopenia/osteoporosis in 2 LOR-treated postmenopausal women
  - 14 fractures in 10 subjects (7 LOR-treated, 3 control)
    - 3 patellar (2 non-target knee, 1 target knee), 3 vertebral, 2 foot, 2 wrist, 2 rib, 1 fibula, 1 hand

- All fractures were adjudicated by the medical monitors and determined to be caused by trauma; all healed uneventfully within the expected time frame

Serious adverse event summary

From Safety Review: 2018-10-23	Lorecivivint (LOR)				
	0.03 mg (N=234)	0.07 mg (N=235)	0.23 mg (N=226)	All LOR* (N=801)	Placebo (N=353)
Total SAEs (%)	**9 (3.8)**	**13 (5.6)**	**7 (3.1)**	**29 (3.5)**	**4 (1.1)**
Cardiac Disorders	**2 (0.8)**	**4 (1.6)**	0 (0.0)	**6 (0.7)**	**1 (0.3)**
Infections	**3 (1.2)**	**2 (0.8)**	**1 (0.4)**	**6 (0.7)**	0 (0.0)
Renal / Urinary Disorders	**1 (0.4)**	**1 (0.4)**	**1 (0.4)**	**3 (0.4)**	0 (0.0)
Vascular Disorders	**1 (0.4)**	**2 (0.8)**	0 (0.0)	**3 (0.4)**	0 (0.0)
Injury / Procedural Complications	0 (0.0)	0 (0.0)	**2 (0.8)**	**2 (0.2)**	**1 (0.3)**
Neoplasms	0 (0.0)	**1 (0.4)**	**1 (0.4)**	**2 (0.2)**	0 (0.0)
Reproductive System Disorders	0 (0.0)	**1 (0.4)**	**1 (0.4)**	**2 (0.2)**	0 (0.0)
Congenital / Genetic Disorders	0 (0.0)	**1 (0.4)**	0 (0.0)	**1 (0.1)**	0 (0.0)
Gastrointestinal Disorders	**1 (0.4)**	0 (0.0)	0 (0.0)	**1 (0.1)**	0 (0.0)
Hepatobiliary Disorders	0 (0.0)	**1 (0.4)**	0 (0.0)	**1 (0.1)**	0 (0.0)
General Disorders / Administration Site Condition	0 (0.0)	0 (0.0)	**1 (0.4)**	**1 (0.1)**	0 (0.0)
Nervous System Disorders	**1 (0.4)**	0 (0.0)	0 (0.0)	**1 (0.1)**	0 (0.0)
Musculoskeletal / Connective Tissue Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.3)**
Respiratory Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	**1 (0.3)**

There were no deaths. All SAEs were deemed unrelated to LOR by investigator.

*The LOR 0.15 mg (N=106) group had no SAEs. Formulation errors not reported.

Conclusions

- Based on AEs observed in completed trials (N=1208), IA LOR for the treatment of painful knee OA appeared to be safe and well tolerated
- Individual AEs were reported at comparable rates between groups
- Incidence of bone health-related AEs was similar between groups
- No SAEs were deemed related to LOR by investigators
- Clinical development of LOR as a treatment for knee OA is ongoing

Thank you