Lorecivivint (SM04690), an Intra-articular, Small-Molecule CLK2/DYRK1A Inhibitor That Modulates the Wnt Pathway, Provided Cartilage-Protective Effects in an Animal Model of Post-traumatic OA

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biosplice

Disclosures

- All authors are current or former employees of Biosplice Therapeutics, Inc. or its affiliates.

Background

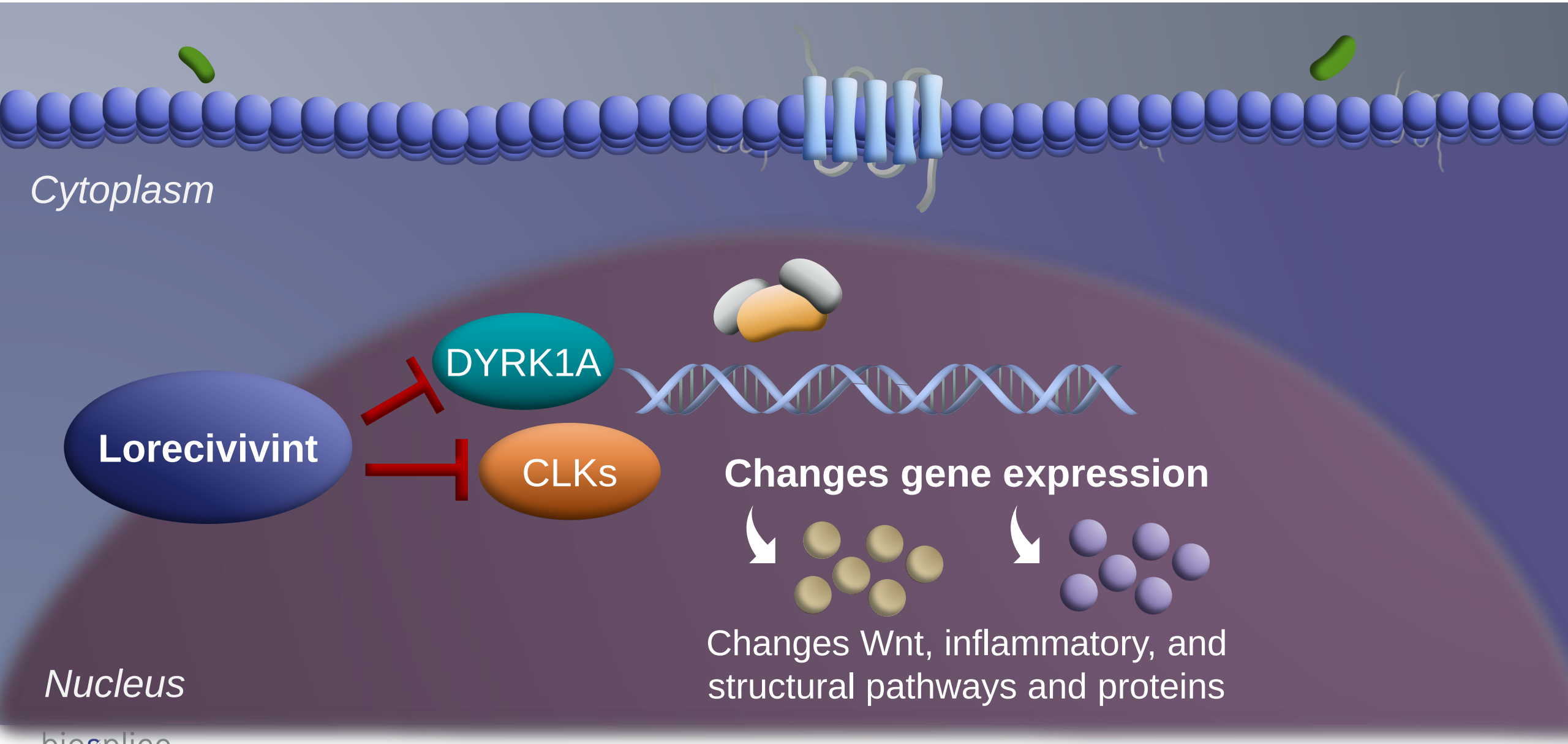
- Osteoarthritis (OA) is characterized by increased cartilage thinning, bone remodeling, and inflammation.
- Post-traumatic OA, which develops after acute direct trauma to the joints, accounts for approximately 12% of all OA cases.
- Current therapeutic options focus on alleviating symptoms and pain rather than structural modification.

Lorecivivint

- Lorecivivint (LOR; SM04690), an intra-articular (IA), small-molecule CLK/DYRK inhibitor that modulates the Wnt pathway, is in development as a potential treatment for knee OA.
  - Clinical trials suggest that a single IA injection of LOR appears to be well tolerated and has potential to improve pain and function and maintain medial joint space width in subjects with knee OA[1-3].
- This study sought to determine the effects of LOR on cartilage in a post-traumatic rat knee OA model when injected after the establishment of cartilage damage.

[1]Yazici Y, et al. *Osteoarthritis Cartilage.* 2017
[2]Yazici Y et al. *Arthritis Rheumatol.* 2020
[3]Yazici Y, et al. *Osteoarthritis Cartilage.* 2021

LOR inhibits CLKs and DYRKs



CLK: CDC-like kinase, DYRK1A: Dual-specificity tyrosine phosphorylation-regulated kinase 1A

LOR preclinical development in OA

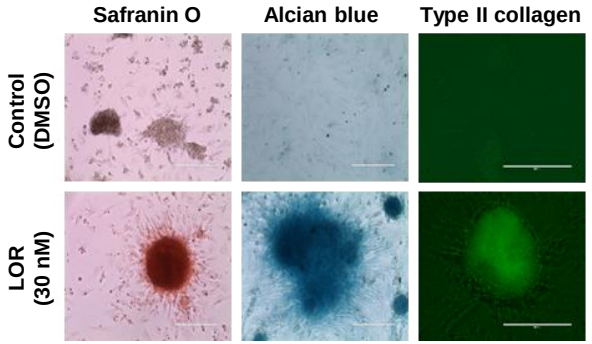
In vitro assays and animal models of OA

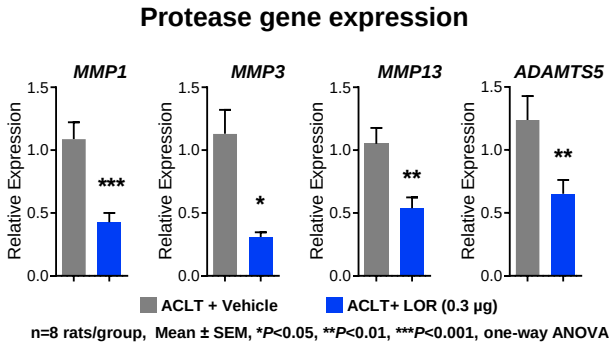
hMSC assays → **Chondrocyte Regeneration**

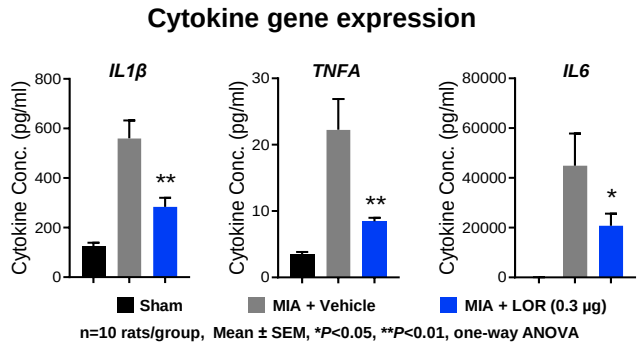
Protease assays → **Cartilage Protection**

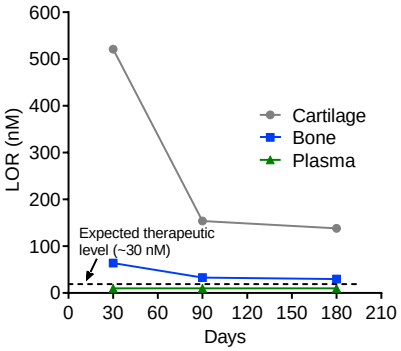
Cytokine assays → **Anti-inflammation**

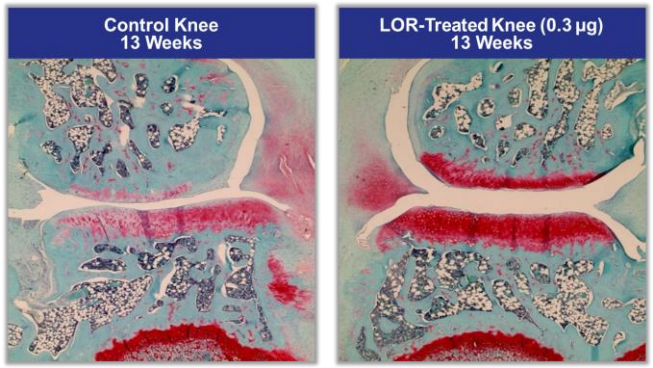
Animal models → **Sustained Local PK**





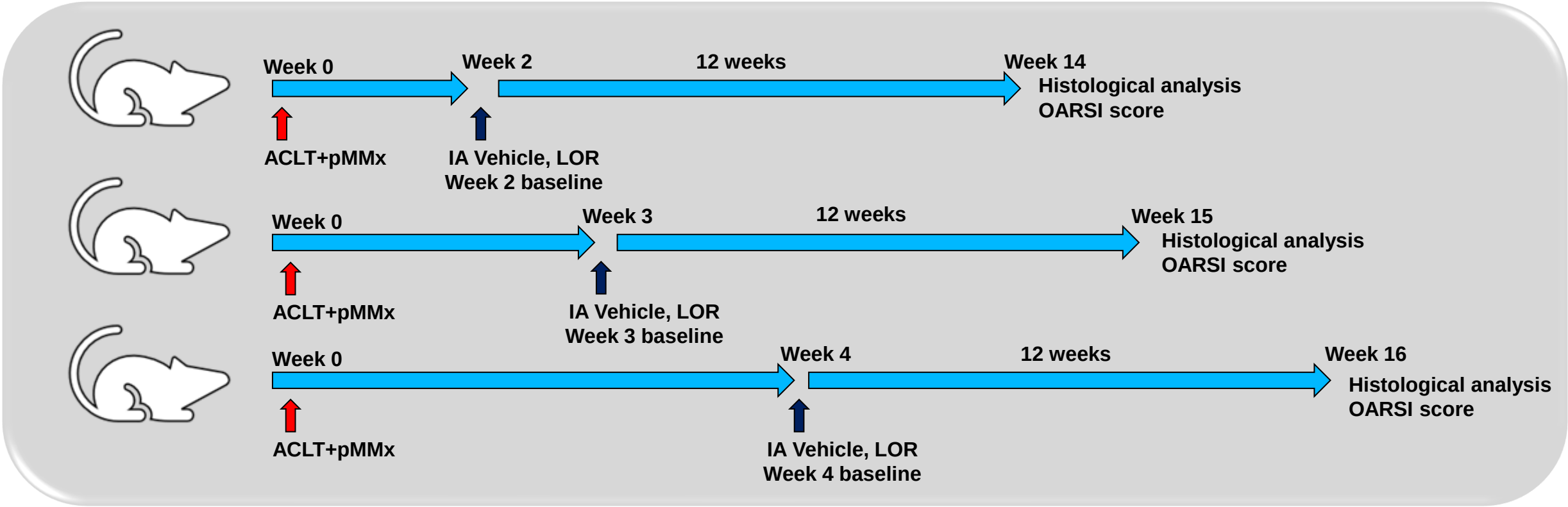




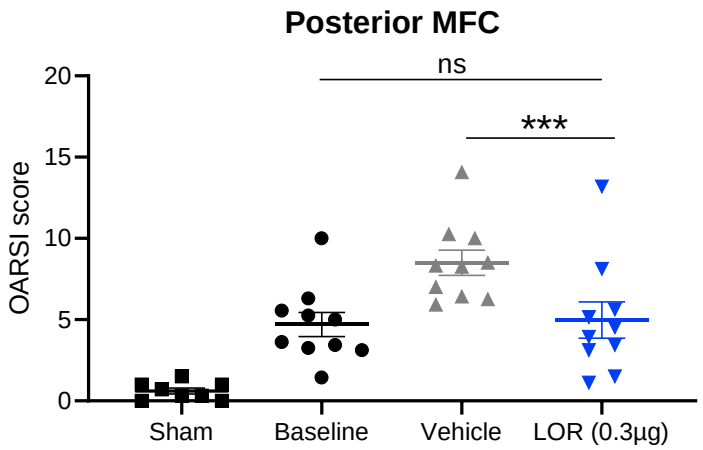


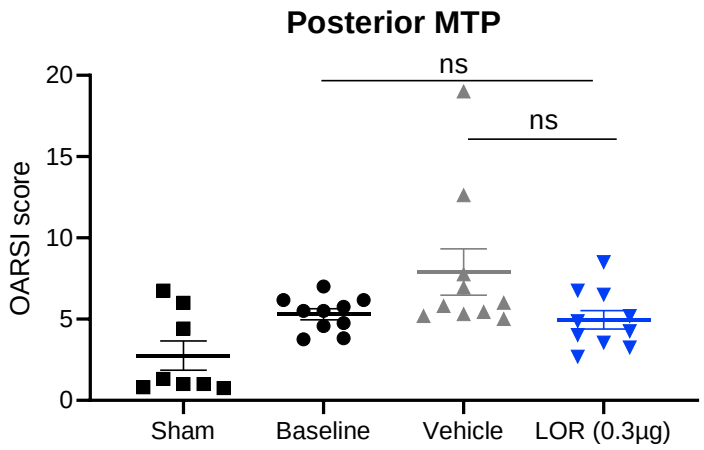
Improved Joint Health
(Animal models)

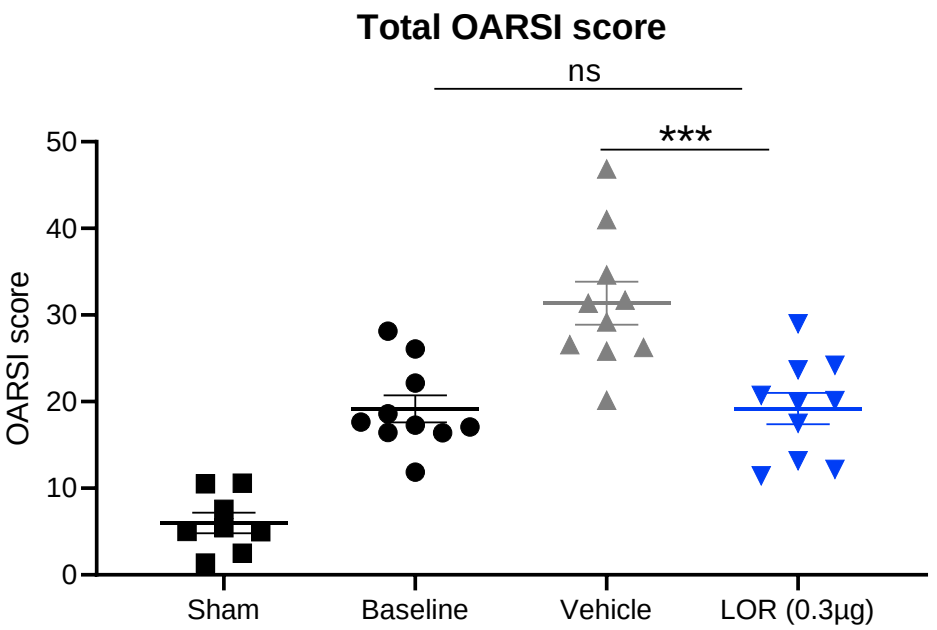
Study design

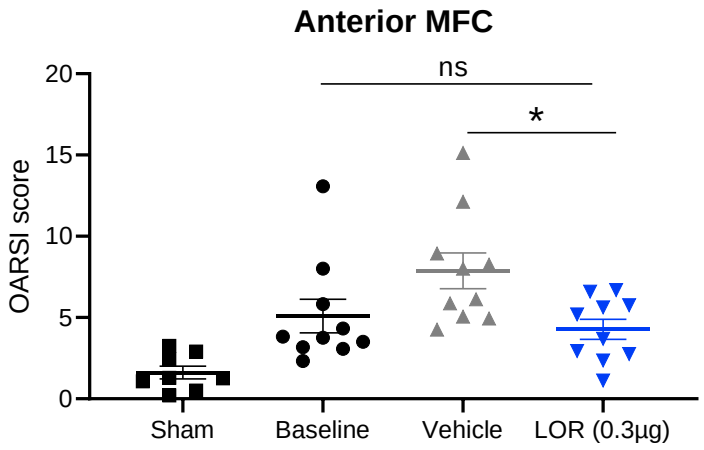


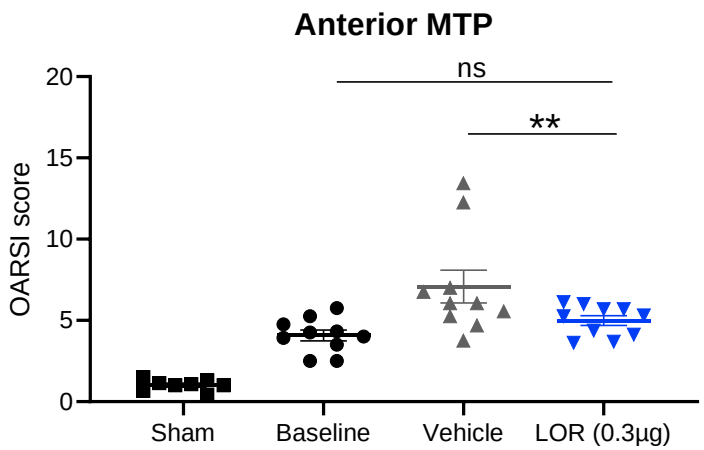
LOR decreased OARSI scores when injected at Week 2





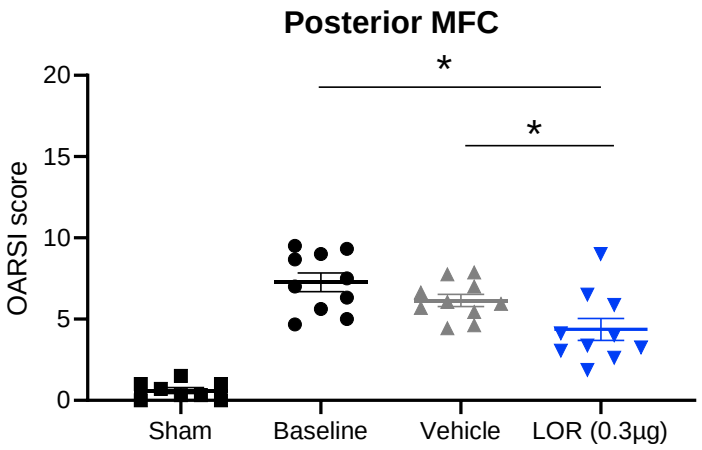


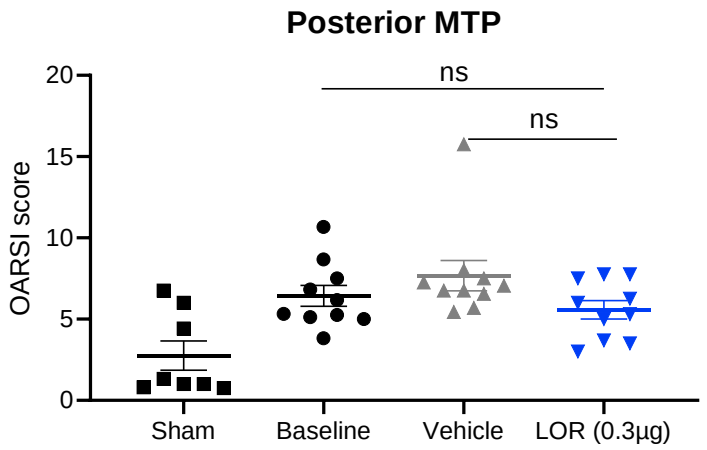


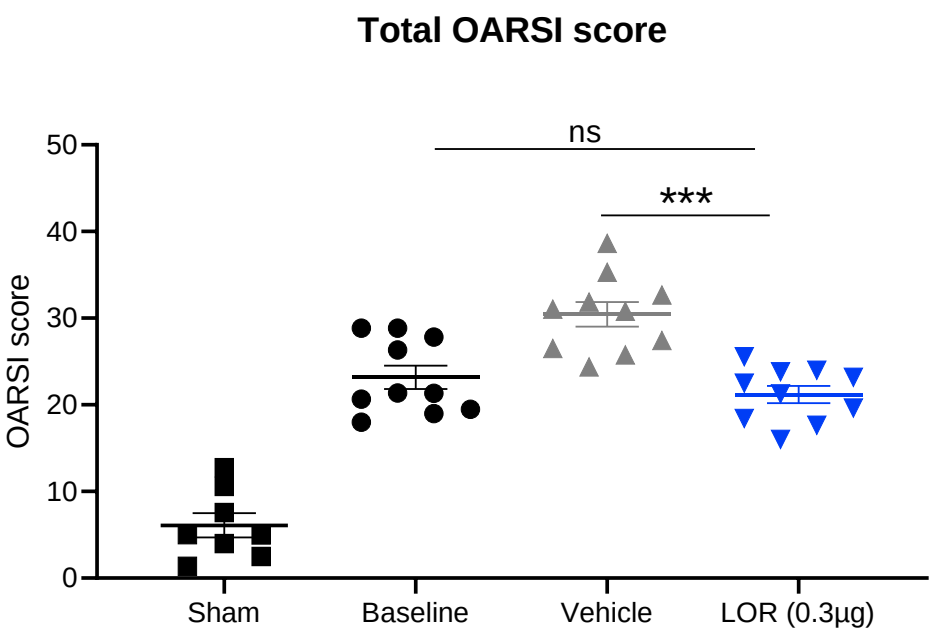


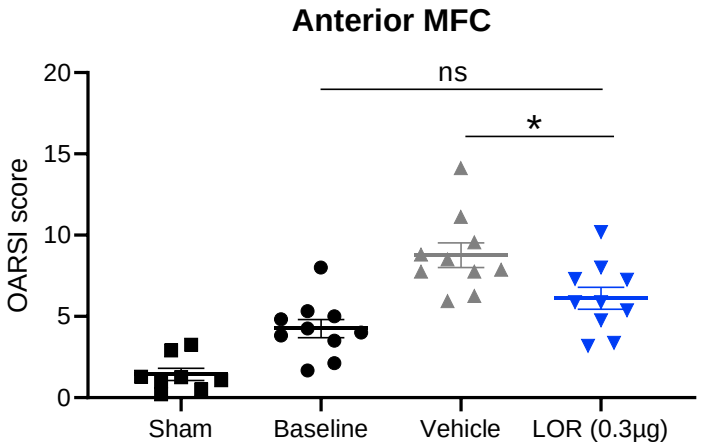
N=10 rats/group for treatment and N=8 for Sham, Mean±SEM, *P<0.05, **P<0.01, ***P<0.001, one-Way ANOVA with Dunnett's multiple comparisons test

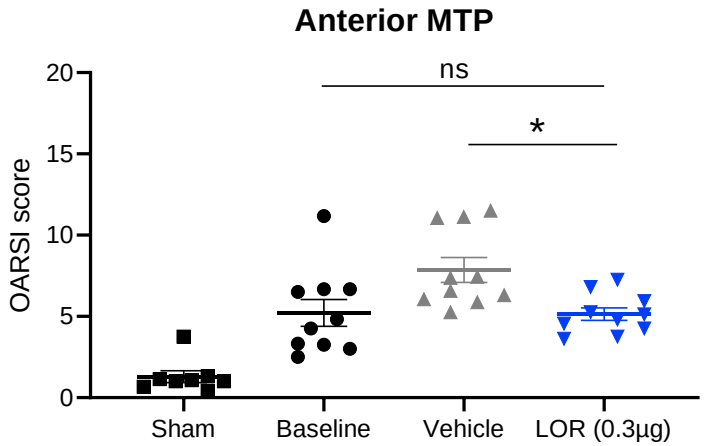
LOR decreased OARSI scores when injected at Week 3





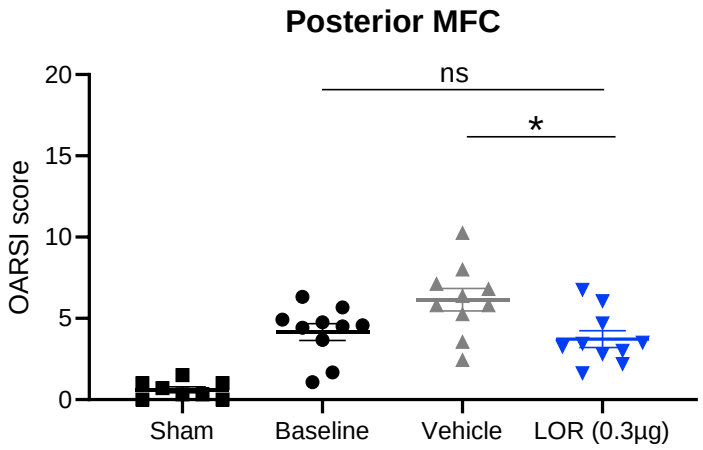


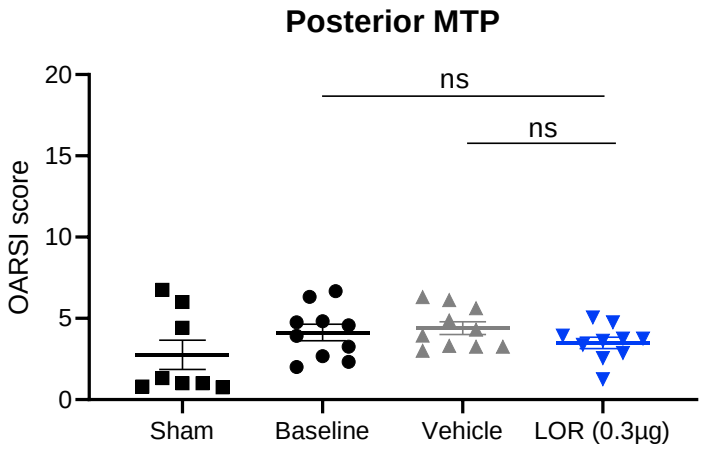


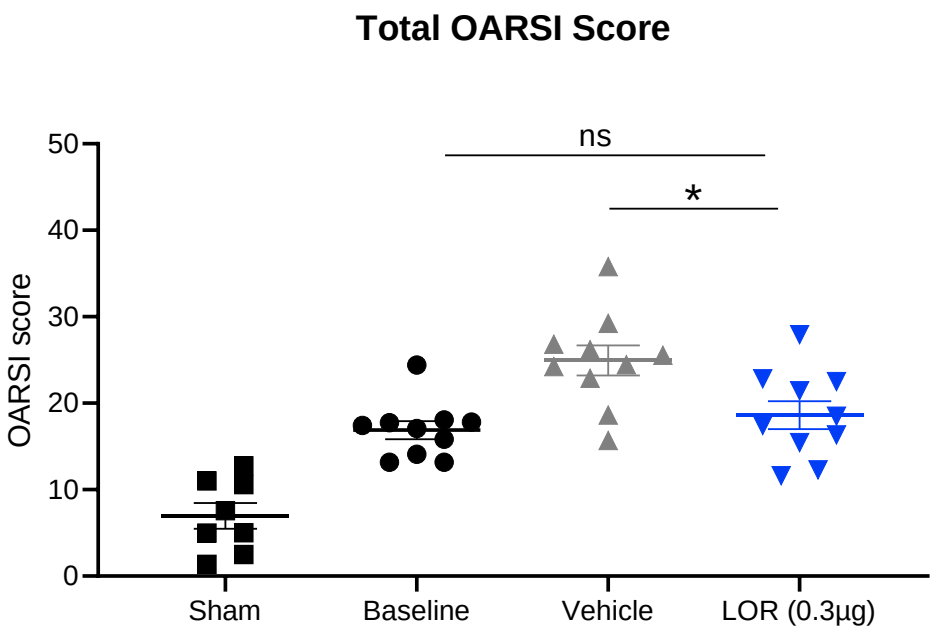


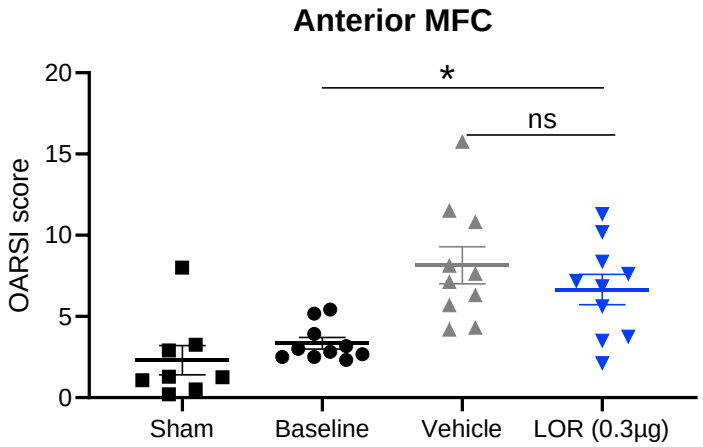
N=10 rats/group for treatment and N=8 for Sham, Mean±SEM, *P<0.05, ***P<0.001, one-Way ANOVA with Dunnett's multiple comparisons test

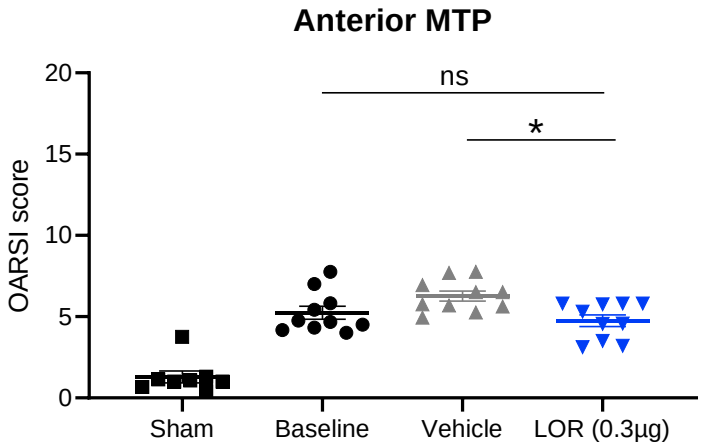
LOR decreased OARSI scores when injected at Week 4





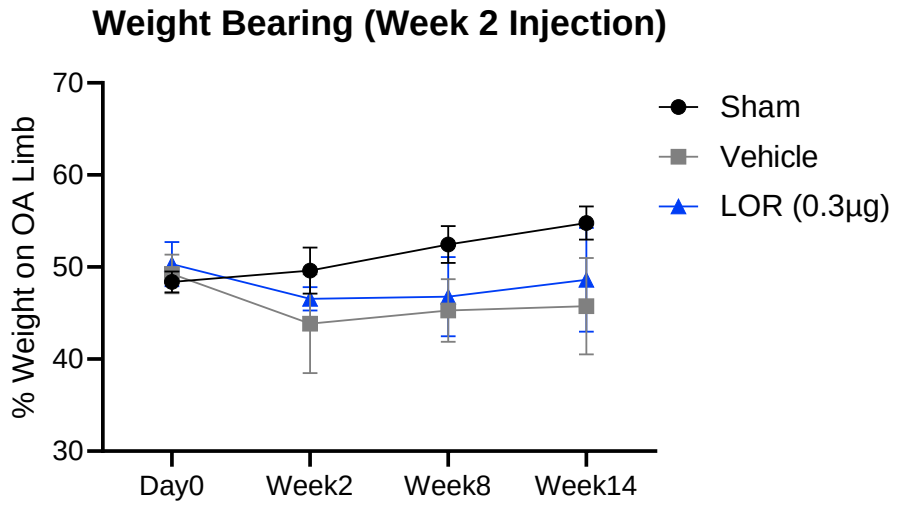


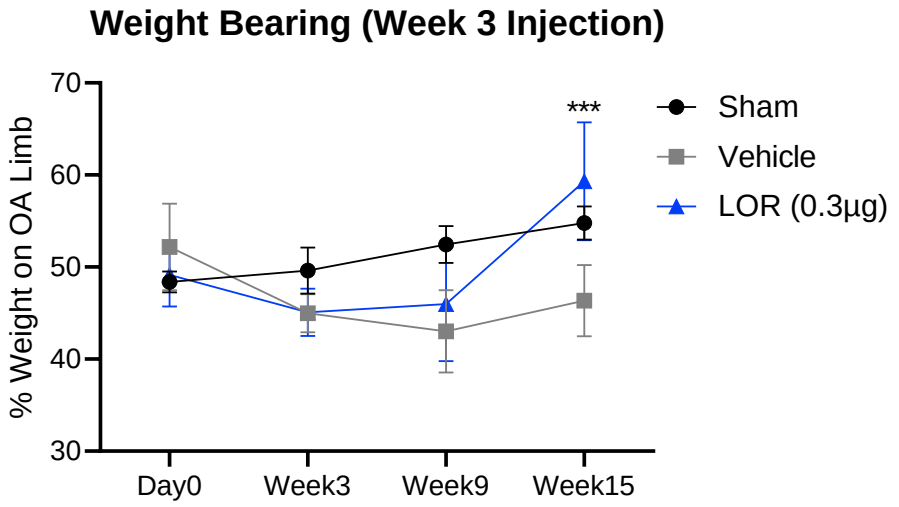


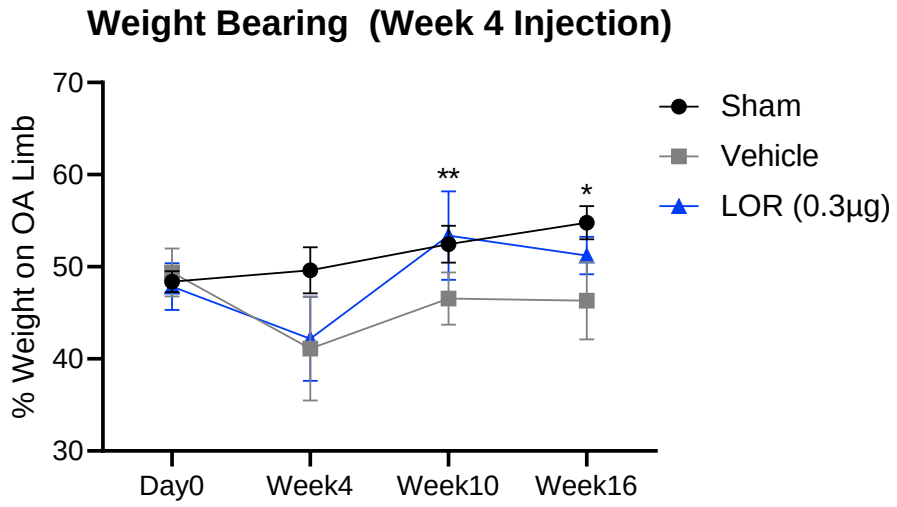


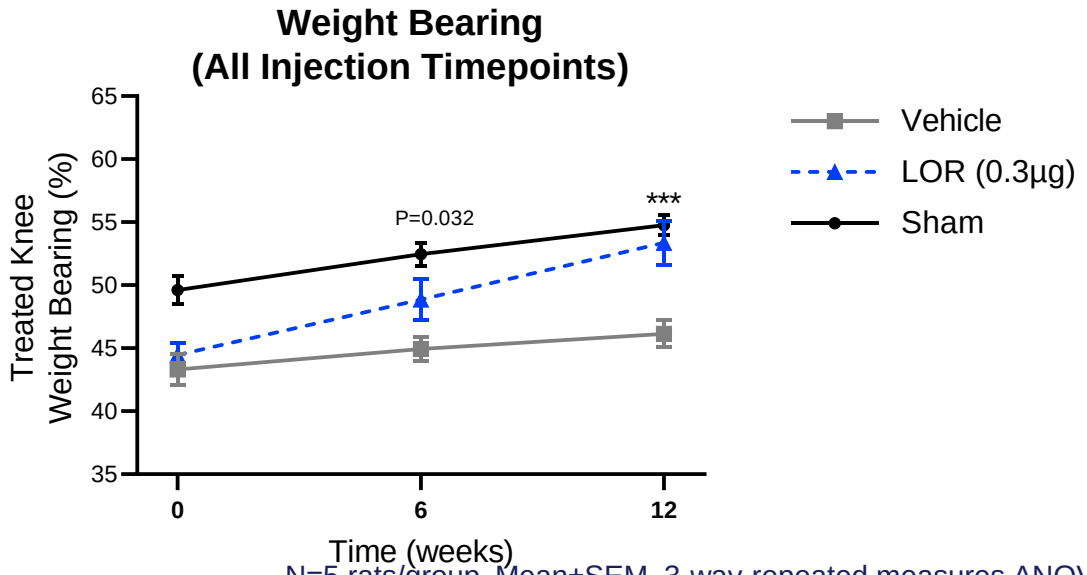
N=10 rats/group for treatment and N=8 for Sham, Mean±SEM, *P<0.05, one-Way ANOVA with Dunnett's multiple comparisons test

LOR improved weight bearing when injected at week 3 or 4









N=5 rats/group, Mean±SEM, 3-way-repeated measures ANOVA
N=5 rats/group, Mean±SEM, 2-way-repeated measures ANOVA
Mean±SEM, **P*<0.05, ***P*<0.01, ****P*<0.001
(overall treatment effect correcting for time from injection)

Conclusions and significance

- Compared to vehicle, lorecivivint treatment after OA induction:
  - slowed OA histological progression when injected at weeks 2, 3, or 4
  - Improved weight bearing in the injured joint when injected at weeks 3 or 4

- Lorecivivint protected cartilage in a post-traumatic OA animal model

- These data support the potential of LOR as a treatment for symptomatic and structural benefit in knee OA

Thank you

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