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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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

Changes gene expression

Changes Wnt, inflammatory, and structural pathways and proteins
LOR preclinical development in OA

**In vitro assays and animal models of OA**

- **hMSC assays**
- **Protease assays**
- **Cytokine assays**
- **Animal models**

**Chondrocyte Regeneration**

**Cartilage Protection**

- Chondrocyte Regeneration
- Sustained Local PK

**Protease gene expression**

- Safranin O
- Alcian blue
- Type II collagen

**Cytokine gene expression**

- IL1β
- TNFA
- IL6

**Improved Joint Health**

(Animal models)

- Days
- LOR (nM)
- 0 30 60 90 120 150 180 210
- 0
- 100
- 200
- 300
- 400
- 500
- 600
- Cartilage
- Bone
- Plasma
- Expected therapeutic level (~30 nM)

**Sustained Local PK**

- ACLT + Vehicle
- ACLT + LOR (0.3 µg)

**Anti-inflammation**

- MIA + Vehicle
- MIA + LOR (0.3 µg)
- Sham

**Control**

- (DMSO)

**LOR**

- (30 nM)

**Relative Expression**

- 0.0
- 0.5
- 1.0
- 1.5

**Cytokine Conc. (pg/ml)**

- 0
- 10
- 20
- 30

**Cytokine Conc. (pg/ml)**

- 0
- 20000
- 40000
- 60000
- 80000

**Cytokine Conc. (pg/ml)**

- 0
- 200
- 400
- 600
- 800

**n=10 rats/group, Mean ± SEM, *P<0.05, **P<0.01, ***P<0.001, one-way ANOVA**
Study design

- **ACLT+pMMx**
- **IA Vehicle, LOR**
- **Week 0**
- **Week 2** baseline
- **Week 3** baseline
- **Week 4** baseline
- **12 weeks**
- **Week 14**
  - Histological analysis
  - OARSI score
- **Week 15**
  - Histological analysis
  - OARSI score
- **Week 16**
  - Histological analysis
  - OARSI score
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

Weight Bearing (Week 2 Injection)

- Sham
- Vehicle
- LOR (0.3µg)

% Weight on OA Limb

Day0 Week2 Week8 Week14

Weight Bearing (Week 3 Injection)

- Sham
- Vehicle
- LOR (0.3µg)

% Weight on OA Limb

Day0 Week3 Week9 Week15

Weight Bearing (Week 4 Injection)

- Sham
- Vehicle
- LOR (0.3µg)

% Weight on OA Limb

Day0 Week4 Week10 Week16

Weight Bearing (All Injection Timepoints)

- Vehicle
- LOR (0.3µg)
- Sham

Treated Knee Weight Bearing (%)

Time (weeks)

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