Development of Losmapimod, A Small Molecule, to Regulate Gene Expression to Treat the Root Cause of FSHD

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Disclosures

- Full-time employee of Fulcrum Therapeutics
- Stock in Fulcrum Therapeutics
- Board certified neurologist with subspecialty training in neuromuscular disease
Therapeutic drugs aim to treat FSHD in 3 ways.

**Therapeutic Strategies Targeting DUX4 Expression**

**Transcription**
- Manipulate DNA or RNA (Gene Therapy)
  - Proteins activating DUX4 expression

**Translation**
- Manipulate mRNA (RNA Therapy)
  - DUX4 messenger RNA
  - DUX4 Protein

**Manipulate gene expression** (Small Molecules)
- Fulcrum Therapeutics
- miRecule

**Image Descriptions**
- DNA double helix
- RNA strand
- Protein structure
- Small molecules
- Therapeutic logos
Fulcrum Overview

Clinical stage biopharmaceutical company using systematic approach to identify small molecules able to rebalance gene expression

- ~7,000 genetically defined diseases today
- We are building on decades of research highlighting gene expression role in disease
- High-throughput product engine designed to rapidly identify and validate drug targets that can modulate gene expression – and treat disease at its root cause
- Focus on small molecules as therapeutic modality

Our vision is to treat genetically defined diseases by addressing their root cause
## Fulcrum Rare Disease Pipeline

<table>
<thead>
<tr>
<th>PROGRAM (PRODUCT CANDIDATE)</th>
<th>DISCOVERY</th>
<th>PRECLINICAL</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
<th>STATUS</th>
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</thead>
<tbody>
<tr>
<td>FSHD (losmapimod)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Completed Ph 2 enrollment</td>
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<tr>
<td>Sickle Cell Disease (FTX-6058)</td>
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<td>Submit IND in 2H 2020</td>
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<td>Submit reg filing in 2H 2020</td>
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</tbody>
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### DISCOVERY SCREENING

- Duchenne Muscular Dystrophy: Target ID / Validation
- Friedreich Ataxia: Target ID / Validation
- Myotonic Dystrophy 1: Target ID / Validation
- α-Synucleinopathies: Target ID / Validation
- Undisclosed Neurological Disease: Target ID / Validation
- Undisclosed Pulmonary Disease (Acceleron): Target ID / Validation

Additional screens & FulcrumSeek planned for 2020
What is a small molecule?

Nearly 90% of therapies on the market are small molecules. In 2019, small molecules accounted for more than 70% novel drug approvals by the US Food and Drug Administration (FDA).


• Enter cells easily because they have low molecular weight

• Bind cellular targets to affect disease processes

• Affect other molecules, such as proteins

Losmapimod
Molecular weight 383.3 g/mol
Characteristics of Small Molecule Therapies

- Usually oral route of administration
  - Drug absorption
  - Drug elimination
- Manufacturing usually less complex
- Need to consider:
  - Off-target effects
  - Drug-Drug interactions
  - Special Populations
• Targets identified using proprietary probe library
• Fulcrum product engine identified p38α (MAPK) as key regulator of DUX4 expression
• p38α (MAPK) validated using genomic and chemogenomic tools across multiple cells
• Compounds identified that reduced DUX4 expression
• Disease modeled using patient-derived myotubes
• Phase 1: Clinical Safety, Tolerability, Dose (PK)
• Phase 2: Clinical Proof of Concept
• Phase 3: Confirmation of Clinical Benefit
Identification of a Target

Previously unknown pathway relationships steer target identification

Drug target identification and candidate development

FulcrumSeek
Proprietary database

- Patient-derived, relevant models
- Proprietary annotated compound library
- Customized CRISPR guide libraries
- Genetic regulatory pathways
- Genomic databases
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p38 \(\alpha/\beta\) protein kinase

- p38\(\alpha/\beta\) kinases are members of a family of proteins that modify other proteins and modulate their function in response to extracellular signals.
DUX4 activity reduced by multiple small molecules targeting p38

- Diverse p38 compounds inhibit a common target
- Dose dependent reduction of MBD3L2 with no effect on MYOG

- SMI activity was phenocopied with p38 specific silencing siRNA (light blue)
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Losmapimod is a p38 Inhibitor

- Losmapimod was found to reduce levels of DUX4 in patient-derived muscle cells.

- A treatment that reduces or prevents aberrant DUX4 activity in skeletal muscles may stop or prevent functional impairment and accumulation of disability and could potentially enable improved repair of damaged muscles.
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Establishing Pre-Clinical Efficacy

Losmapimod reduces DUX4 in FSHD muscle cells

HSP27 is a target of p38 MAP kinase pathway

**MBD3L2** is a DUX4-target gene

Active Caspase-3 measures cell death

Losmapimod inhibits p38, reduces DUX4, a DUX4 target gene and prevents FSHD muscle cells from dying
Predicting Effective Exposures

Increasing concentrations of losmapimod reduce DUX4 expression in FSHD1 and FSHD2

11 FSHD patient-derived cells
8 FSHD1 with different n of repeats
3 FSHD2 with different SMCHD1 mutations

50-70% Reduction of DUX4 activity in vitro
30 and 100 nM are clinically relevant concentrations

Losmapimod reduces DUX4 in FSHD1 and FSHD2 muscle cells
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Phase 1 Key Questions

Did losmapimod show initial evidence of safety and tolerability in FSHD patients?

Can losmapimod be detected in muscle at clinically relevant doses?

Does losmapimod engage the drug target, p38 MAPK, in blood and in muscle?
Phase 1 study: Study design

PART A

Cross Over Design

<table>
<thead>
<tr>
<th>Single dose</th>
<th>Single dose</th>
</tr>
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<tbody>
<tr>
<td>8 losmapimod 7.5 mg: 2 Placebo</td>
<td>8 losmapimod 15 mg: 2 Placebo</td>
</tr>
</tbody>
</table>

Wash-out

PART B

Randomized Controlled Design

<table>
<thead>
<tr>
<th>Muscle biopsy</th>
<th>Losmapimod 7.5 mg twice daily (n=6)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Losmapimod 15 mg twice daily (n=6)</td>
</tr>
<tr>
<td></td>
<td>Placebo twice daily (n=3)</td>
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</tbody>
</table>

14-day Placebo Controlled Treatment Period

PART C

Open Label Design

<table>
<thead>
<tr>
<th>Muscle biopsy</th>
<th>Losmapimod 15 mg twice daily (n=5)</th>
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</thead>
</table>

14-day Open Label Treatment Period
Adverse Events Summary

- **No serious adverse events**
  - Most Adverse Events were not considered related to study drug administration

- **No discontinuations due to AEs**

- **Mild Severity**
  - No clinically significant changes in vital signs, laboratory analyses, ECG or urinalysis

- **Most common**
  - Headache
  - Dizziness
  - Somnolence
  - GI disorders
Drug Levels in Muscle

![Bar chart showing drug levels in muscle](chart.png)
Losmapimod was generally safe and well tolerated in FSHD patients.

Achieved clinically relevant, dose-dependent concentrations in muscle.

Exposures in plasma and muscle were at concentrations that showed efficacy in pre-clinical evaluations in multiple labs.

15 mg PO BID dose showed sustained and robust target inhibition.
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Phase 2 Key Questions

1. Does losmapimod show evidence of an effect on the root cause of disease?

2. Is there evidence of safety and tolerability during chronic dosing?

3. Does losmapimod show an emerging affect on muscle health and selected clinical endpoints?
ReDUX4 clinical trial summary

80
FSHD subjects enrolled
Placebo vs losmapimod at 15 mg twice daily dose

17
Sites participating
12 in the USA, 2 in Canada and 3 in the EU

DUX4
Reduction of aberrant DUX4-driven gene expression in affected skeletal muscle cells (the target tissue) primary endpoint

Other endpoints:
• MRI, lean muscle and fat infiltration/fraction volumes
• Clinical outcomes: RWS, TUG, Dynamometry, PROs
• Drug levels and p38 inhibition in blood and muscle
Day 1 & Week 16 or 36: Muscle Biopsy (MBx)
  DUX4-driven gene expression in skeletal muscle needle biopsy

Visit 1, Week 12, Week 24**, Week 48: MRI
  Lean skeletal muscle volume; skeletal muscle fat fraction

Day 1, Weeks 4, 12, 16, 24, 36, 48: Clinical assessments
  PK; safety; Reachable Work Space; FSHD-Timed Up & GO, Muscle function measures, dynamometry and Patient Reported Outcomes
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✓ p38α (MAPK) validated using genomic and chemogenomic tools across multiple cells

✓ Compounds identified that reduced DUX4 expression

✓ Disease modeled using patient-derived myotubes

✓ Initial Safety, Tolerability, Dose (PK)
  • Clinical Proof of Concept, Safety
  • Confirmation of Clinical Benefit, Safety
Acknowledgements

Healthy volunteers and FSHD patients participating in these studies

Fulcrum’s phase 1 study, ReDUX4 and OLS management teams

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Patient groups

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Thank you