Fulcrum Therapeutics

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

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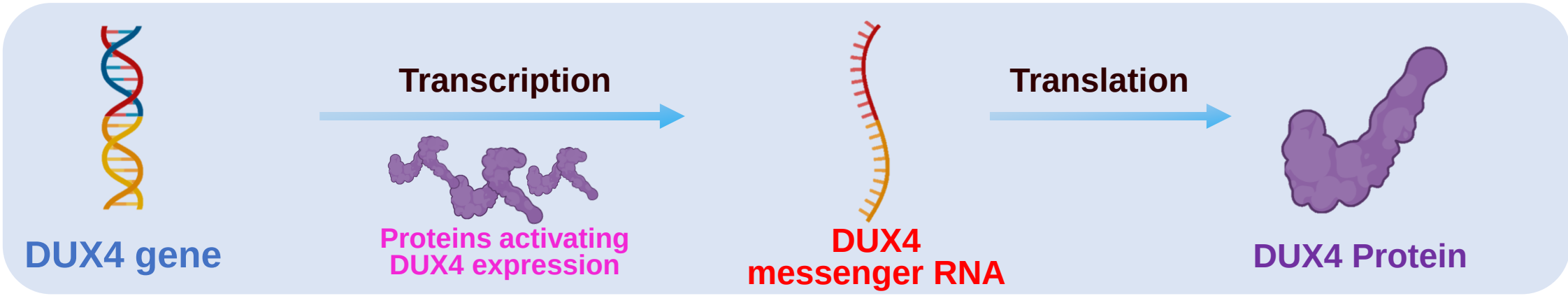
June 2020 – FSHD IRC

Disclosures

- Full-time employee of Fulcrum Therapeutics
- Stock in Fulcrum Therapeutics
- Board certified neurologist with subspecialty training in neuromuscular disease

Therapeutic Strategies Targeting DUX4 Expression

Therapeutic drugs aim to treat FSHD in 3 ways.



Manipulate DNA or RNA (Gene Therapy)

Nationwide Children's
When your child needs a hospital, everything matters.℠

Manipulate gene expression (Small Molecules)

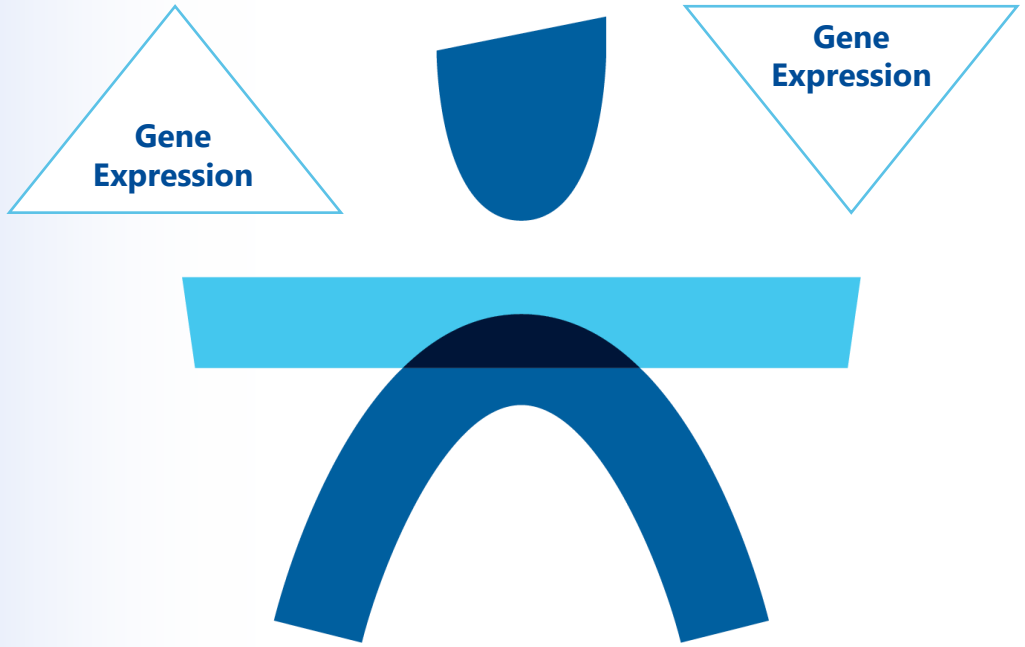
Fulcrum Therapeutics

Manipulate mRNA (RNA Therapy)

miRecule
RNA Therapeutics

Fulcrum Overview

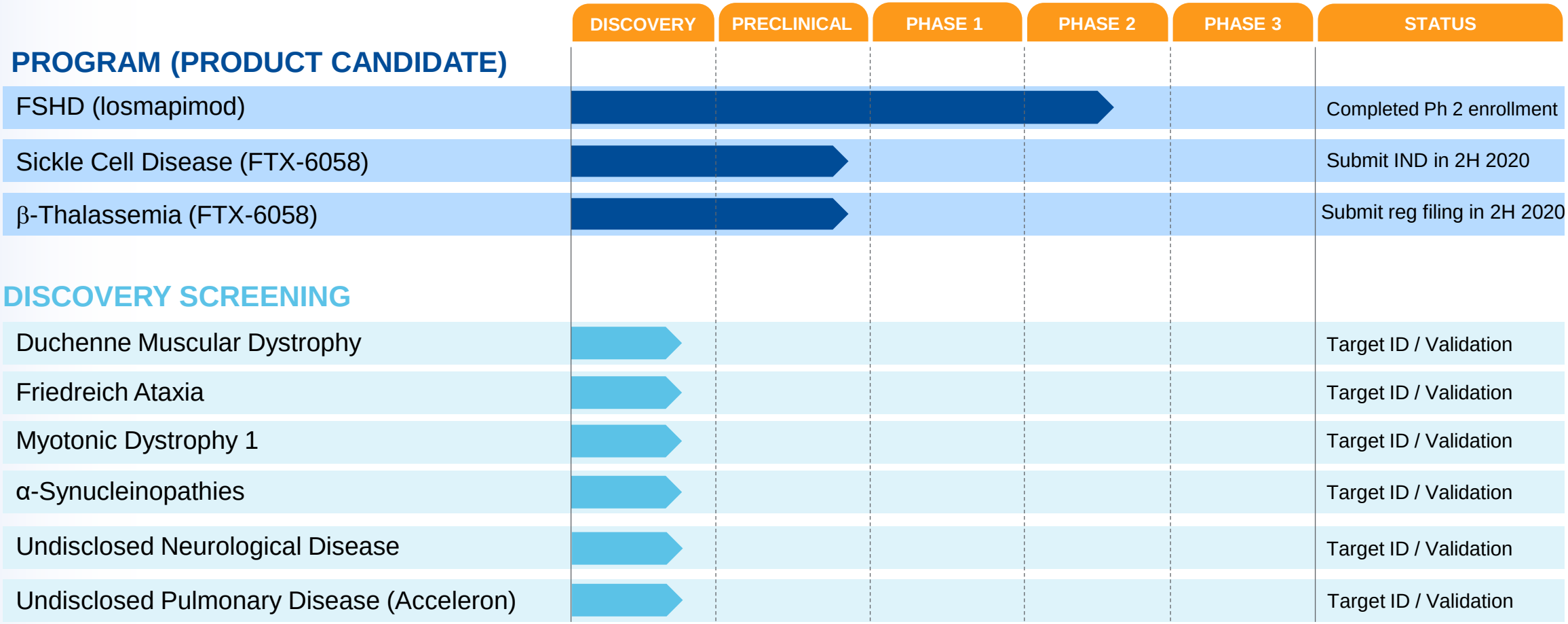
Clinical stage biopharmaceutical company using systematic approach to identify small molecules able to rebalance gene expression



- ~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

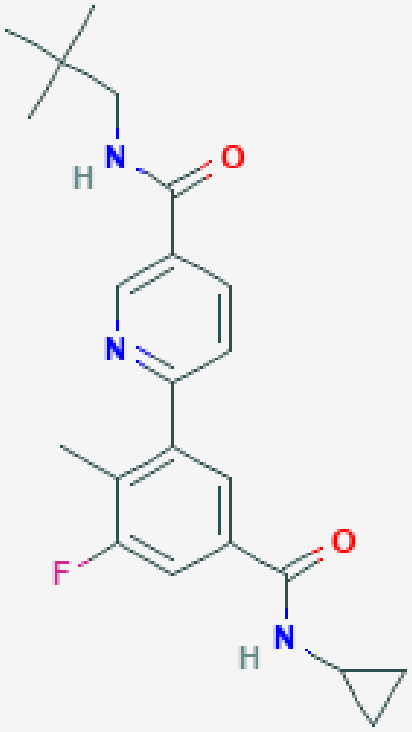
Fulcrum Rare Disease Pipeline



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).
https://www.formularywatch.com/clinical-news/small-molecular-drugs-led-2019-approvals

- Enter cells easily because they have low molecular weight
- Bind cellular targets to affect disease processes
- Affect other molecules, such as proteins



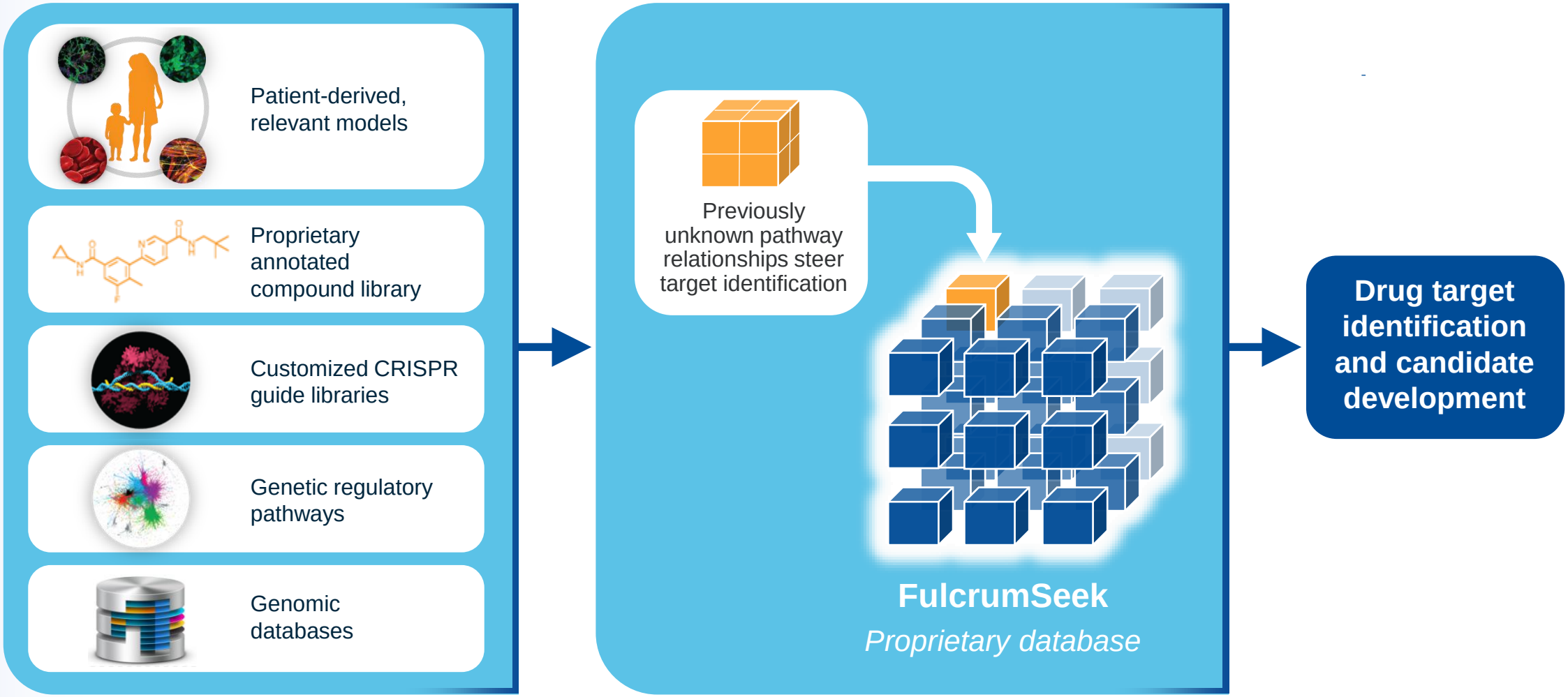
Losmapimod
Molecular weight 383.3 g/mol

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



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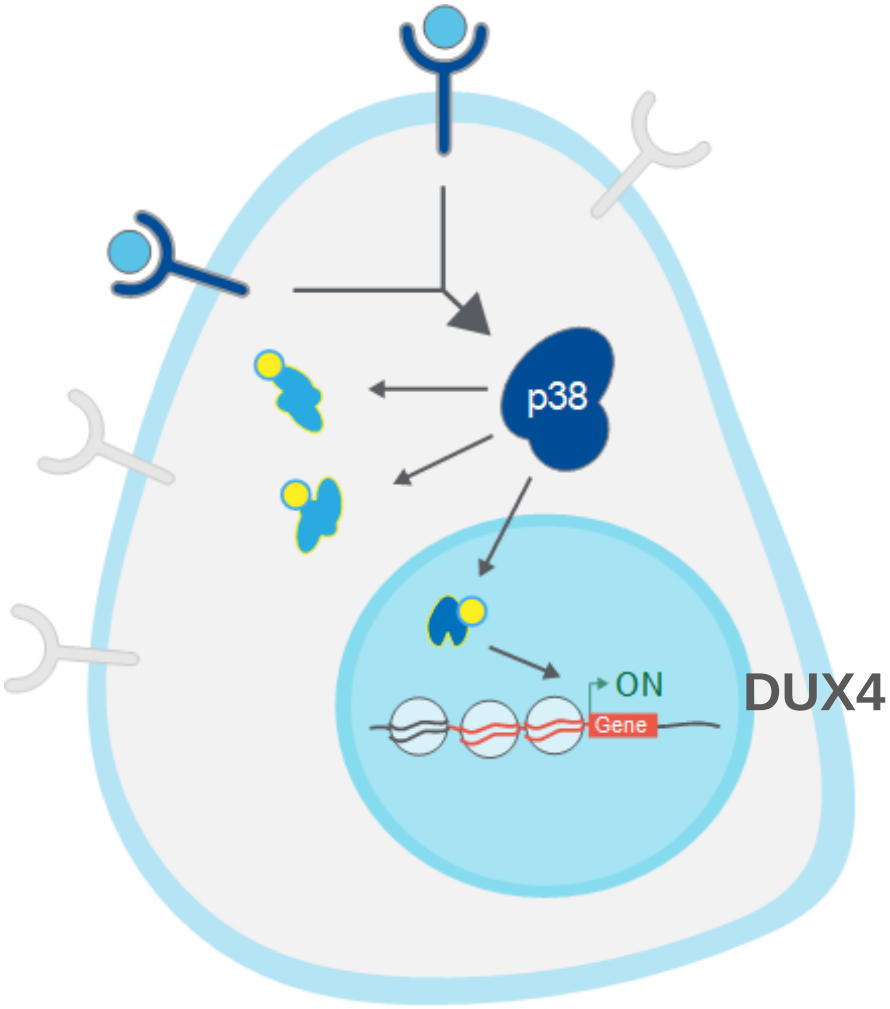
p38 α/β protein kinase

- p38α/β kinases are members of a family of proteins that modify other proteins and modulate their function in response to extracellular signals

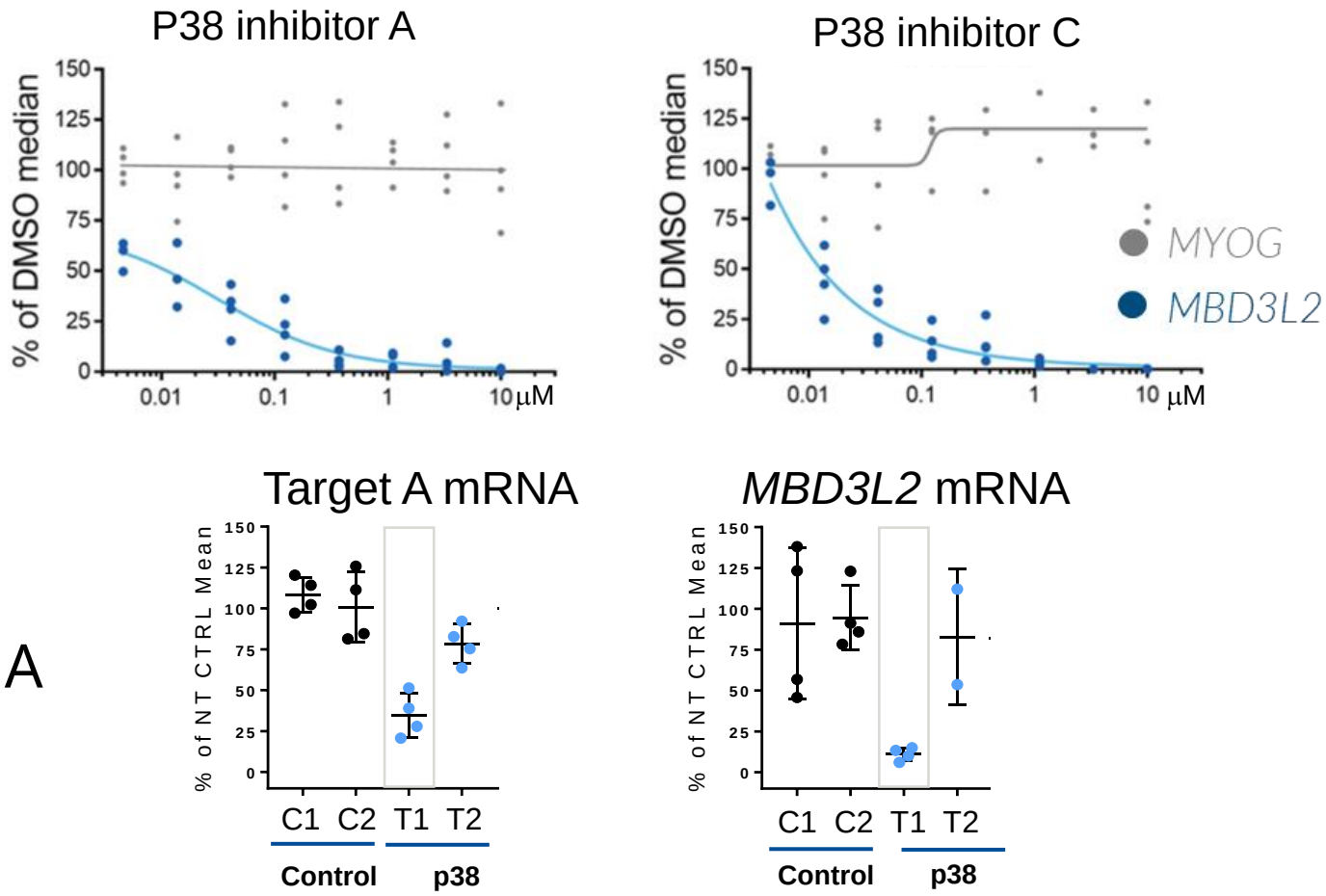


DUX4 activity reduced by multiple small molecules targeting p38

- 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)

MBD3L2 gene surrogate for DUX4



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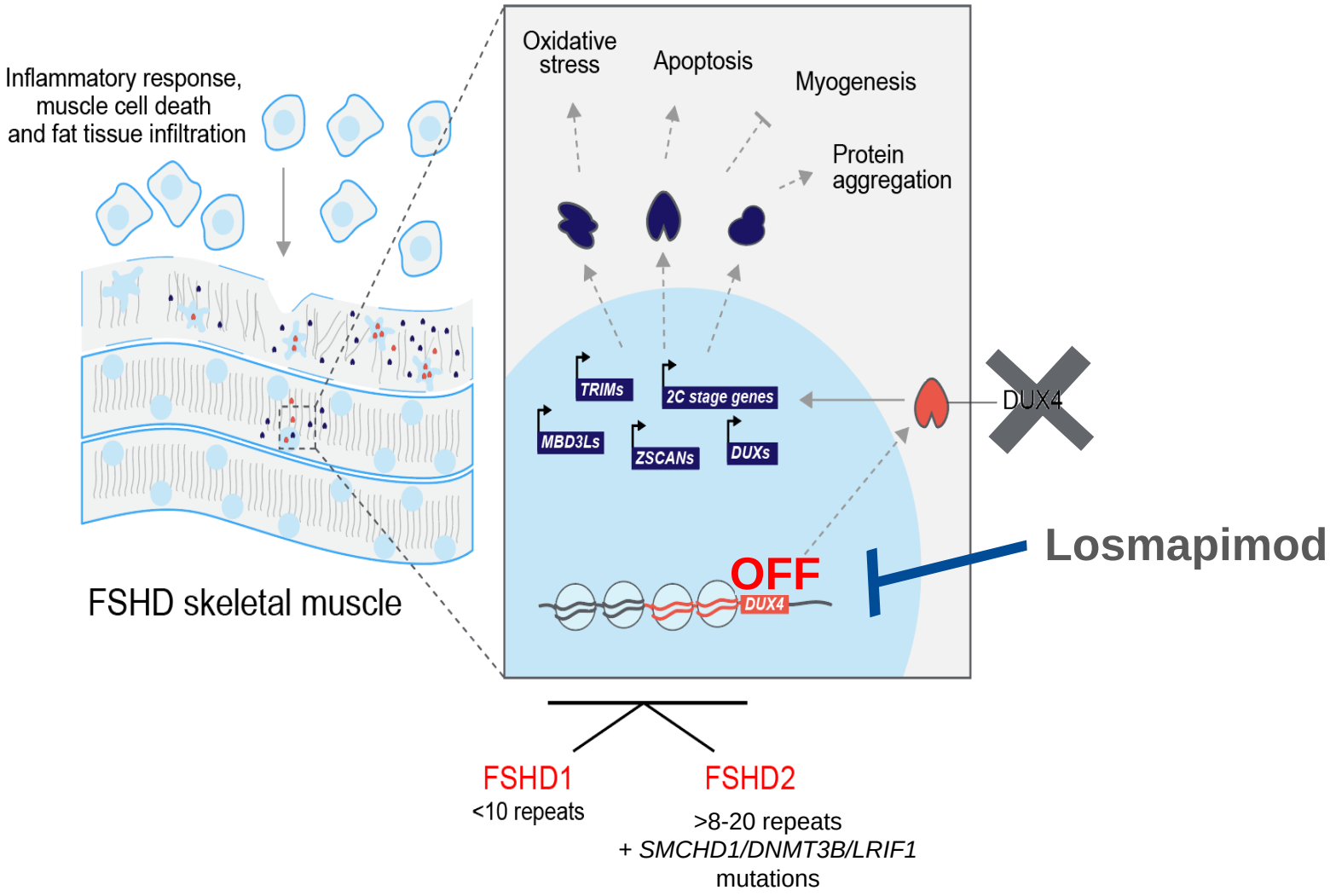
Losmapimod is a p38 Inhibitor



- 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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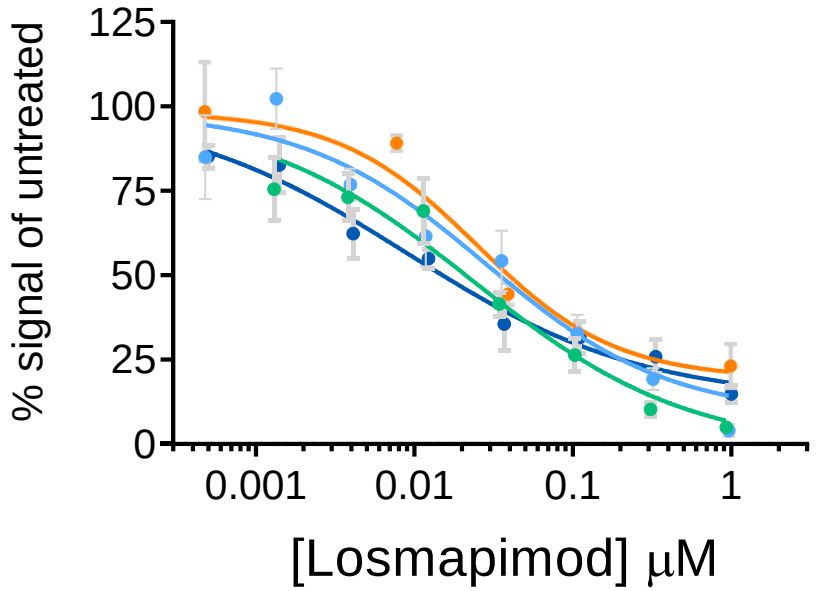
Establishing Pre-Clinical Efficacy

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

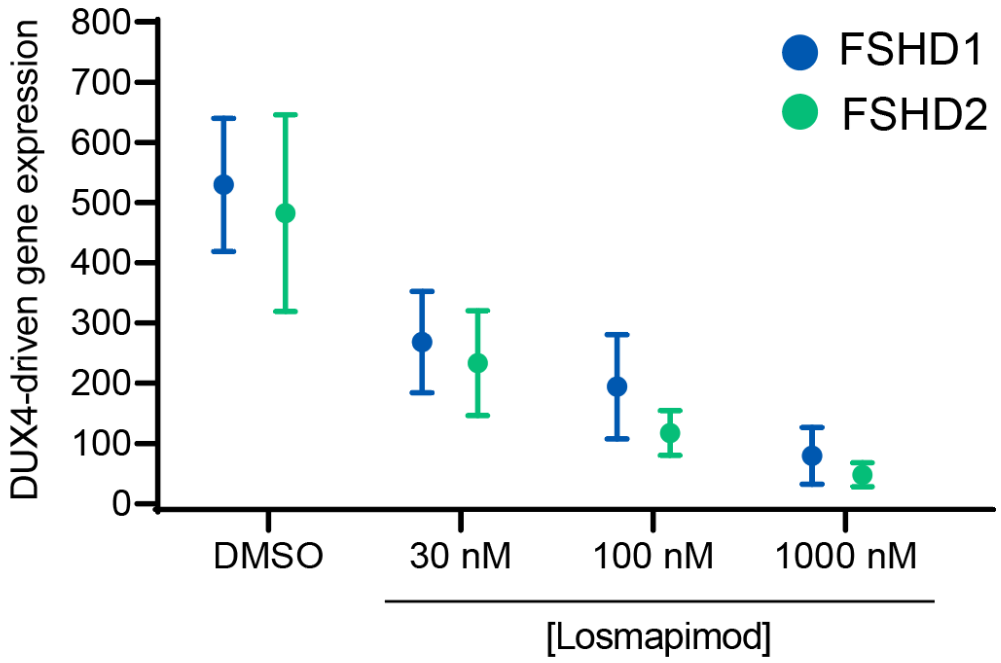
8 FSHD1 with different n of repeats

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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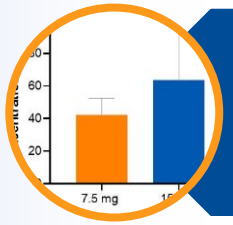
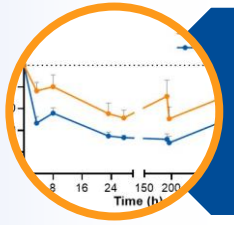
Phase 1 Key Questions

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?

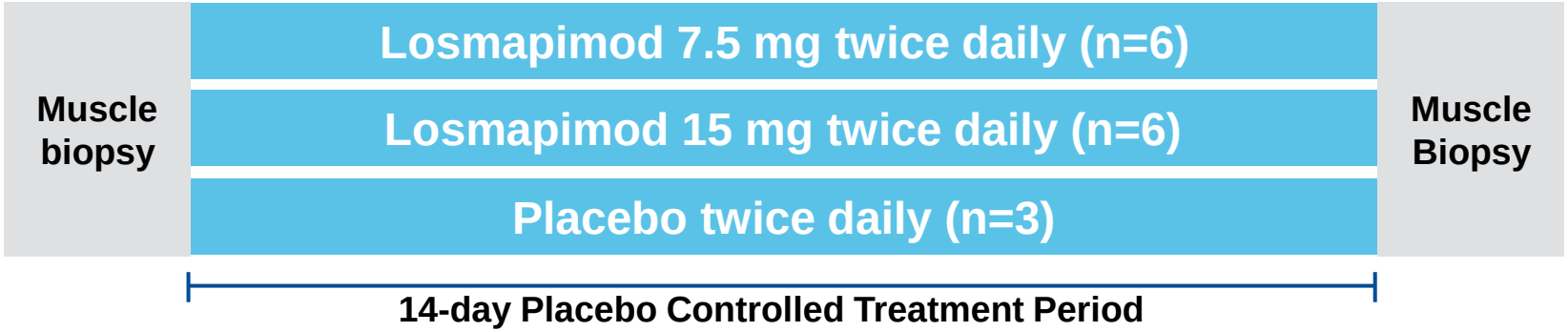
Phase 1 study: Study design

PART A

Cross Over Design

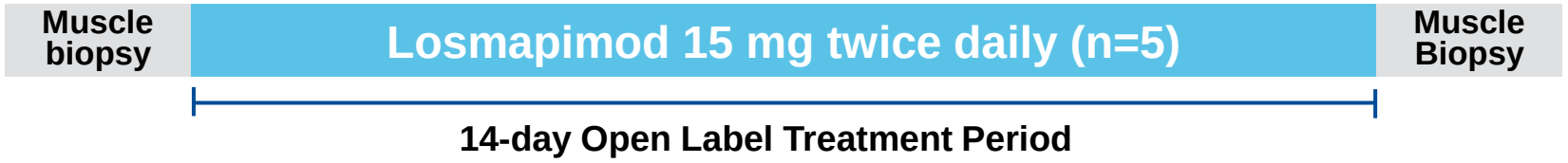
PART B

Randomized Controlled Design



PART C

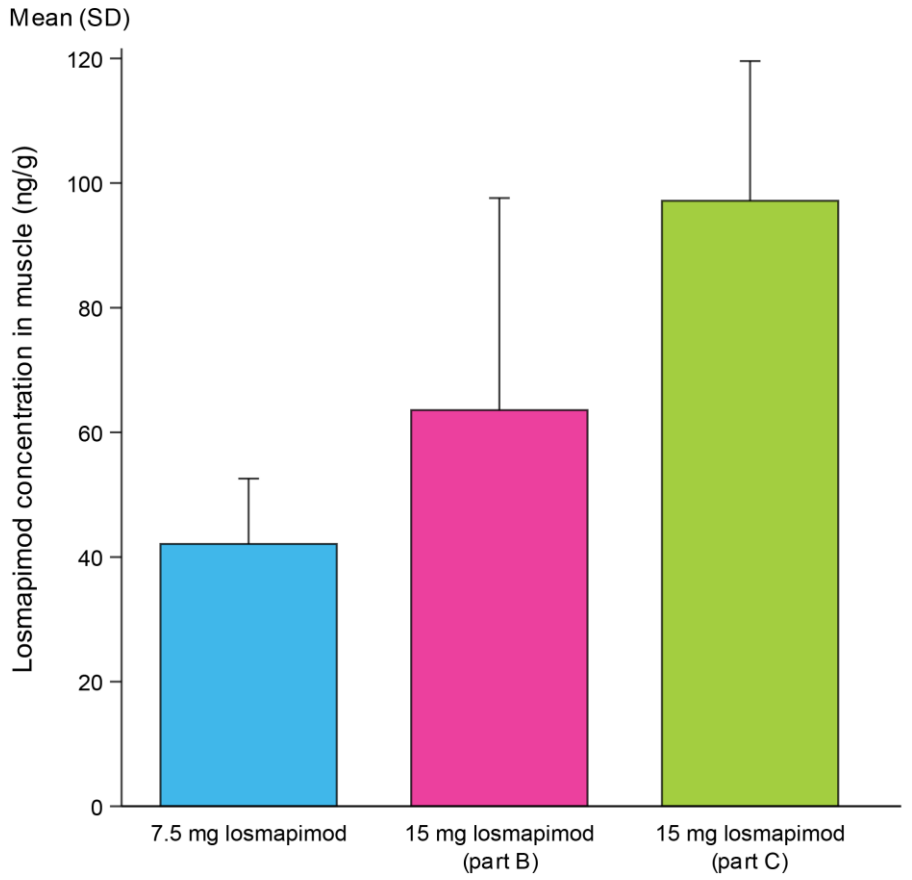
Open Label Design



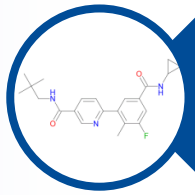
Adverse Events Summary

- **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

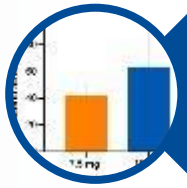
Drug Levels in Muscle



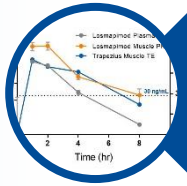
Phase 1 Confirmed Safety and Selection of 15 mg Dose



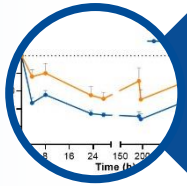
Losmapimod was generally safe well tolerated in FSHD patients



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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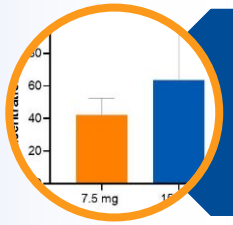
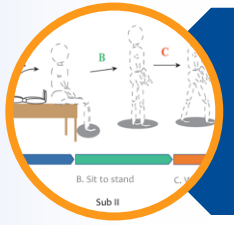
Phase 2 Key Questions

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



Is there evidence of safety and tolerability during chronic dosing?



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

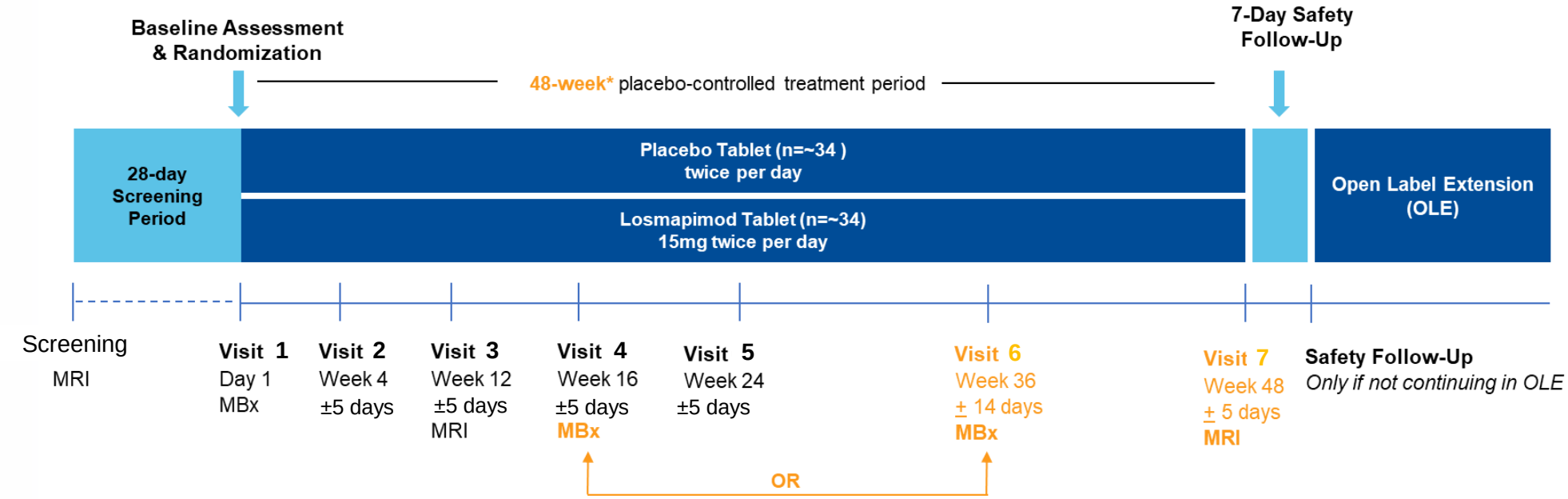
Reduction of aberrant DUX4-driven gene expression in affected skeletal muscle cells (the target tissue) primary endpoint

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

ReDUX4
Assessing losmapimod in FSHD

ReDUX4 Study Schematic



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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- 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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Silvere van der Maarel, PhD
Stephen Tapscott, MD, PhD
Leslie Leinwand, PhD
Lee Sweeney, PhD

Other collaborators

Jay Han, MD, UC Irvine and his team

UCI Health

Patient groups

FSHD SOCIETY

friends of FSH research

MDA Muscular Dystrophy Association

NORD National Organization for Rare Disorders

Collaborating organizations

CHDR Centre for Human Drug Research

AMRA PRECISION FOR DECISION

Radboudumc university medical center

Cambridge BIOMEDICAL Over 20 years of Science and Service

LUMC Leiden University Medical Center

IMMUNOLOGIX LABORATORIES

PPD

Q² Solutions a Quintiles Quest Joint Venture

VIRTUALSCOPICS Imaging for Clinical Trials

BIONIKS GIVING THE WORLD A HELPING HAND

Thank you

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