Design of REACH: Phase 3 Randomized, Double-Blind, Placebo-Controlled, 48-Week Study of the Efficacy and Safety of Losmapimod in FSHD

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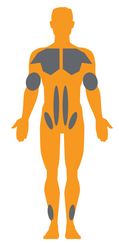
Introduction

- FSHD is a relentlessly progressive disease leading to significant disability that impacts quality of life
- FSHD initially affects facial and scapular muscles, eventually progressing to the arms, trunk and legs
- Muscle pathology leads to accumulation of disability
- Progression ultimately leads to significant impairment of upper extremity function and mobility, and many patients are unable to work or live independently

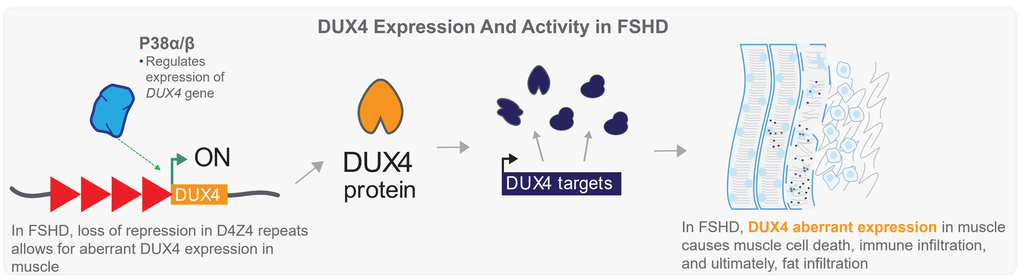


Fat infiltrates muscle

Currently, there are no treatment options for people living with FSHD that prevent and/or slow muscle wasting and weakness

Rationale

A treatment that reduces or prevents aberrant DUX4 activity in skeletal muscles may stop or prevent functional impairment and accumulation of disability and decrease/arrest replacement of muscle by fat.



- **Losmapimod** is an investigational small molecule inhibitor of p38α/β Mitogen Activated Protein Kinase (MAPK).
- Clinical studies in over 3,600 subjects across a diversity of diseases evidenced acceptable safety and tolerability for up to one year of treatment at relevant doses.
- Nonclinical studies have shown that losmapimod (a small molecule p38 α/β MAPK inhibitor) reduces the aberrant expression of DUX4, the underlying cause of FSHD.
- Two Phase 2 clinical studies, ReDUX4 (FIS-002-2019) and the open-label study (OLS, FIS-001-2019) demonstrated evidence of benefit of losmapimod on muscle structure and function, as well as FSHD-relevant clinical endpoints recognized by patients and favorable safety and tolerability.

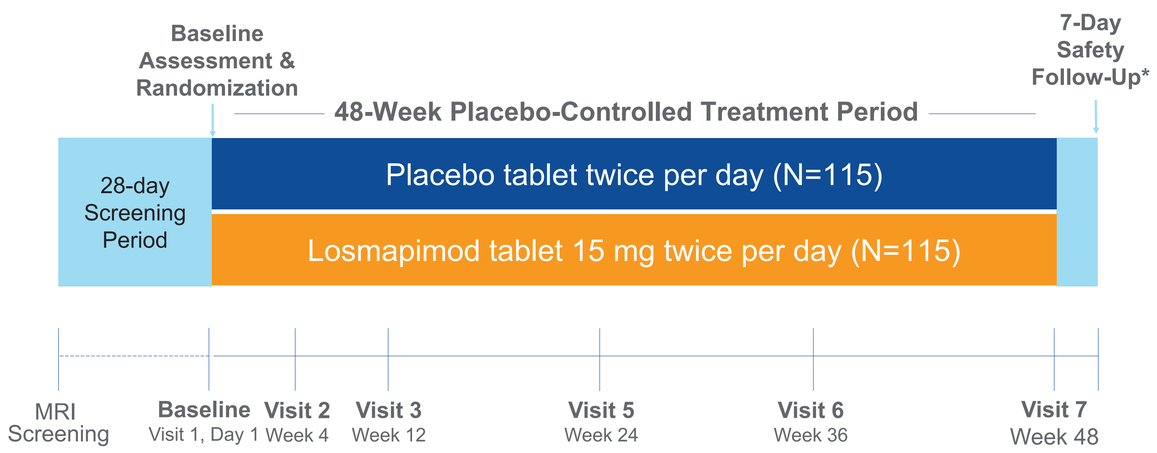
REACH Leverages Learnings from Prior Losmapimod Trials in FSHD

What we know from ReDUX4	REACH Phase 3 Trial Design
Losmapimod demonstrated measurable impact on disease progression at 48 weeks of treatment	48-week treatment duration
Reachable Workspace (RWS) is a reliable and quantifiable measure of function and disease progression	RWS is primary endpoint
Muscle Fat Infiltration (MFI) is a sensitive measure of muscle health most susceptible to disease pathology	MFI is secondary endpoint
Patient-reported outcomes are effective measure of disease progression in FSHD	Patient-reported outcomes (PGIC and Neuro-QoL) are secondary endpoints

Study Design

Study Population:

- ~230 participants aged 18-65 with FSHD1 and FSHD2
- Population characteristics similar to those in Phase 2 ReDUX4, including disease severity
- Clinical sites in the US, Canada, UK and Europe

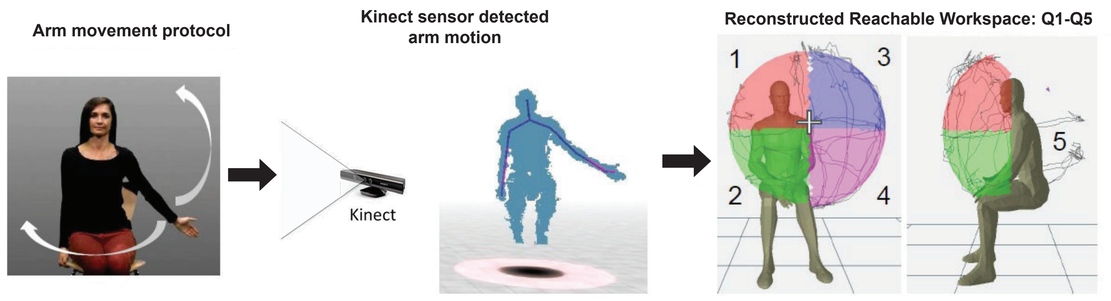


**Open label extension will be added in a forthcoming amendment*

Study Objectives

Primary Objective

To evaluate the efficacy of losmapimod for the treatment of FSHD on disease progression assessed by Reachable Workspace (RWS) quantification of Relative Surface Area (RSA) Q1-Q5 with 500 g wrist weight in the dominant arm

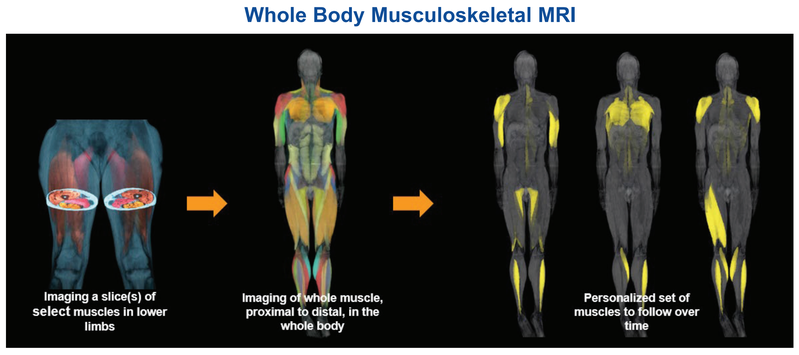


- Reachable Workspace (RWS) is a centrally read evaluation of individual global upper extremity function, including shoulder and proximal arm, which tracks 3D upper limb trajectory using the Microsoft Kinect device
- Divided into 5 regions; shoulder as origin (each quintant = 0.25, total scale 0-1.25)

Secondary Objectives

1. To evaluate the change in Neuro-QoL Upper Extremity (UE) relative to placebo
2. To evaluate Patient Global Impression of Change (PGIC) relative to placebo
3. To evaluate efficacy of losmapimod to slow accumulation of fat in muscle by muscle fat infiltration (MFI) with whole body musculoskeletal MRI relative to placebo
4. To assess safety and tolerability of losmapimod in patients with FSHD

Whole Body Musculoskeletal MRI



Patients' Global Impression of Change (PGIC)

"Since the start of the study, my overall status is…"

7: Very much worse
6: Much worse
5: Minimally worse
4: No Change
3: Minimally improved
2: Much improved
1: Very much improved

Exploratory Objectives Include

- Additional Patient Reported Outcomes (PROs)
- Healthcare utilization questionnaires
- Muscle Strength through handheld dynamometry

Key Inclusion / Exclusion Criteria

Inclusion Criteria

- Age 18-65 years
- Genetically confirmed diagnosis of FSHD1 or FSHD2
- Ricci score 2-4 (range 0-5). Patients who are wheelchair-dependent or dependent on walker or wheelchair for activities are not permitted to enroll in the study
- Screening total RSA (Q1-Q4) without weight in the dominant arm assessed by RWS ≥0.2 and ≤0.7
- Agree to use protocol approved methods of contraception for the duration of the study

Exclusion Criteria

- Medical conditions that can confound results of the study
- Contraindication to MRI
- Acute or chronic liver or renal impairment
- If using drugs or supplements that affect muscle function, must be on stable dose and remain on that dose for the duration of the study