Results from 96 Weeks of Dosing from the Open-Label Extension of a Phase 2 Trial of Losmapimod in Subjects with FSHD: ReDUX4

ReDUX4 — Assessing losmapimod in FSHD

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Introduction

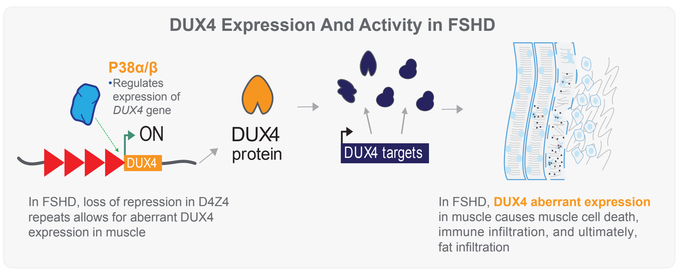
- FSHD is a progressive disease leading to accumulation of muscle and functional loss
- FSHD initially affects facial and scapular muscles, eventually progressing to the arms, trunk and legs
- Muscle pathology leads to accumulation of disability
- Progression ultimately leads to significant impairment 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

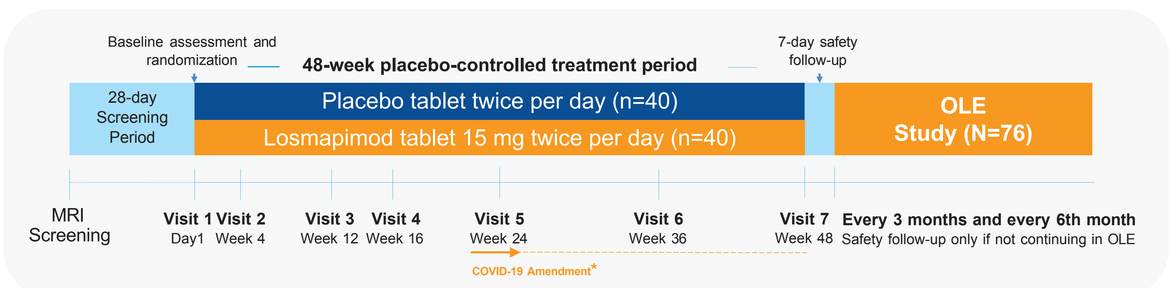
Rationale

- **Losmapimod** is a highly selective p38α/β MAPK inhibitor
- Losmapimod was generally well-tolerated in clinical studies with >3600 people across 11 indications
- In preclinical studies, losmapimod reduced DUX4 expression
- Aberrant expression of *DUX4* gene is the known root cause of FSHD



Methods

Open Label Extension (OLE) from ReDUX4: Phase 2 Randomized Placebo-Controlled, 48-Week, Multicenter Study



- *Protocol was amended due to COVID-19 to allow collection of data to inform study endpoints. Sixteen patients completed the week 24 visit and had already rolled over to the OLE at the time of amendment approval
- Three participants discontinued the study during the randomized placebo-controlled treatment period due to reasons unrelated to safety
- Patients with FSHD who completed the randomized placebo-controlled treatment period were eligible to enroll in the OLE study
  - Key inclusion randomized placebo-controlled period: Genetically confirmed FSHD1, Age 18-65, Ricci Score 2-4 (scale 0-5), STIR+ muscle identified by MRI

Primary Objective of OLE: evaluate the safety and tolerability of long-term dosing of losmapimod in FSHD1 subjects

- Results presented here represent a preliminary analysis of the OLE data as of 20 Jan 2022, after all participants had completed the Week 96 visit

Participant Disposition and Exposure

>97% Retention Rate at Study Week 96

- 76 of 77 (99%) participants enrolled in the OLE and had at least 1 dose of study drug
- 2 participants (2.6%) withdrew from the OLE for reasons unrelated to safety

n (%)	Losmapimod / Losmapimod (LOS/LOS) (N=39)	Placebo / Losmapimod (PBO/LOS) (N=37)	Total N=76
Treatment / Study Status			
Discontinued	1 (2.6%)	1 (2.7%)	2 (2.6%)
Ongoing	38 (97.4%)	36 (97.3%)	74 (97.4%)

Participants Exposed for up to 96 weeks of Losmapimod 15 mg Twice Daily Dosing

- Those originally randomized to losmapimod during the randomized placebo-controlled period (LOS/LOS), have been exposed to losmapimod 15mg BID for an average of **96 weeks**
- Those originally randomized to placebo who converted to losmapimod 15 mg BID during the OLE (PBO/LOS) have been exposed for an average of **47 to 72 weeks**, depending on when they entered the OLE due to implementation of the COVID-19 protocol amendment

Results

No additional safety signals observed with up to 96 weeks of losmapimod 15 mg BID dosing

- No Drug-related SAEs or TEAEs leading to study discontinuation or death
- Most adverse events were mild in severity

n (%)	LOS / LOS (N=39)	PBO / LOS (N=37)
Any TEAE	31 (79.5)	30 (81.1)
Any Study Drug-related TEAE	10 (25.6)	5 (13.5)
Any Serious TEAE	3 (7.7)	1 (2.7)
Any Study drug related SAE	0	0

Data from both placebo-controlled treatment period and Open-label Extension period are included.

Most Common TEAEs (n>5 across groups)

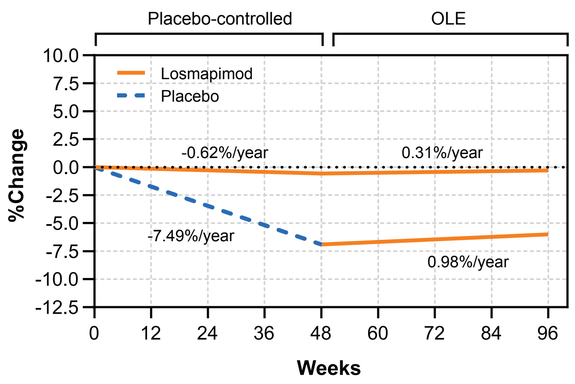
- Fall (22.4%)
- headache (14.5%)
- arthralgia (7.9%)
- back pain (7.9%)
- pain in extremities (6.6%)
- nasopharyngitis (6.6%)
- pyrexia (6.6%)

Reachable Workspace (RWS)

- Durability of treatment response in RWS was observed at 96 weeks in the LOS/LOS group
- Placebo participants who converted to losmapimod (PBO/LOS) at Week 48 demonstrated trends of slowing or stopping disease progression
- Similar trends were observed in change in Total Relative Surface Area (RSA) without weight
- Mean (SE) change in dominant RSA from Week 48 to Week 96 was 0.00 (0.01) for LOS/LOS demonstrating stability of treatment effect and 0.00 (0.01) for PBO/LOS

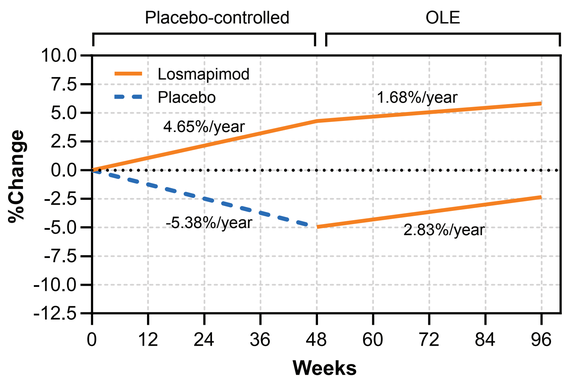
Annualized RWS

Dominant Total (Q1-Q5) RSA + Weight



Slope (SE)	LOS (n=30)	PBO (n=30)
RCT	-0.003 (0.02)	-0.037 (0.01)
OLE	0.001 (0.01)	0.005 (0.01)

Non-Dominant Total (Q1-Q5) RSA + Weight



Slope (SE)	LOS (n=30)	PBO (n=30)
RCT	0.022 (0.02)	-0.026 (0.01)
OLE	0.008 (0.01)	0.013 (0.01)

RSA = Relative surface area; RCT = randomized placebo-controlled period; Q = quintant; SE = standard error
Data includes just those who rolled over into OLE at Week 48

Conclusion

- Losmapimod was generally well tolerated with no additional safety signals observed
- Losmapimod slowed disease progression and demonstrated maintenance of effect through a 96-week period as measured by reachable workspace RSA mean change from baseline

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