Introduction
- FSHD is a serious, rare, progressive and disabling disease, caused by the aberrant expression of DUOX in skeletal muscle
- Stochastic DUOX expression contributes to disease heterogeneity, asymmetry, and variability in disease phenotype
- Pathological activity and maladaptive remodeling lead to muscle fiber death and immune and fat infiltration
- Progressive muscle loss and fatty replacement causes heterogeneous, progressive descending weakness and loss of function
- Muscle pathology leads to accumulation of disability
- Currently, there are no approved disease modifying therapies for people living with FSHD that prevent and/or slow muscle wasting and weakness

Rationale
- A treatment that reduces or prevents aberrant DUOX activity in skeletal muscles may stop or prevent functional impairment and accumulation and decrease/replace replacement of muscle by fat
- Losmapimod is an investigational small molecule inhibitor of p38α/β Mitogen Activated Protein Kinase (MAPK).
- Pre-clinical studies demonstrated in vivo efficacy
- Other p38 inhibitors resulted in dose-dependent reduction of DUOX protein, DUOX transcriptional program and skeletal muscle cell death in FSHD myoblasts across all genotypes tested
- 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

Objective
- Evaluate the long-term safety and tolerability of losmapimod in participants with FSHD
- Evaluate on-treatment change from baseline in selected clinical outcome assessments and imaging modalities

Open-Label Study Design
- This is an open-label, single-site study of losmapimod to evaluate the safety, tolerability, and changes in biomarker and clinical outcome assessments in subjects with facioscapulohumeral muscular dystrophy 1 (FSHD1)

Results
- Baseline muscle concentrations were within the expected range based on pre-clinical data
- Target engagement in blood was within the expected range (50% to 70% change from baseline at CMAX)
- All subjects completed the study
- 2 subjects declined participation in the extension study for reasons unrelated to study drug/events
- Pharmacodynamics and Pharmacokinetics
- Baseline muscle concentrations were within the expected range based on pre-clinical data
- Target engagement in blood was within the expected range (50% to 70% change from baseline at CMAX)
- Pharmacodynamics of losmapimod was dose-proportional

Safety and Tolerability
- Changes from baseline were not observed
- DUOX alpha gene expression was highly variable

Conclusions
- Losmapimod was generally well-tolerated in FSHD study participants for approximately 52 weeks of treatment in an open-label, single-site study
- Losmapimod demonstrated expected PK and PD improvement or minimal changes were observed in structural (MRI and ultrasound) and FSHD-relevant functional measures (RWS, HHD, and QMT)
- Patients recognized benefit of treatment based on reported improvement on PGIC
- The results of this open-label, single site study seem to confirm and extend in an independent cohort the results of the RedUX study, supporting the benefit-risk of losmapimod as a disease-modifying therapy and continued development of losmapimod in FSHD

Acknowledgements
We thank the patients and their families for their participation in this study; the staff at our study site for their contributions to the care of the patients. We also thank our collaborators and supporting patient organizations for their support.

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