**Introduction**

- FSHD is a rare, progressive, and disabling disease, with no approved disease modifying therapies.
- DUX4 activates a downstream transcriptional program that causes myofiber death and replacement of muscle with fat resulting in progressive motor disability.
- Factors that alter muscle mass and composition, including muscle biopsies, are emphasized.
- Assessment of treatment efficacy is challenging because of the heterogeneity of muscle involvement within and between patients.
- Assessments show limited sensitivity in detecting slowing or arrest of disease progression in FSHD.

**MRI can potentially detect pathologic changes in muscle prior to changes in clinical outcome assessments (COAs) and correlates with COAs.**

**Rationale**

A treatment that reduces or prevents aberrant DUX4 activity in skeletal muscles has the potential to stop or slow disease progression.

- Losmapimod is a small molecule inhibitor of GBP1/MAPK activator protein (MAPK).
- Preclinical studies demonstrated treatment with losmapimod and other p38 inhibitors resulted in dose-dependent reduction of DUX4 protein.
- DUX4 transcriptional program and skeletal muscle cell death in FSHD mice across many genotypes tested.
- Clinical studies with losmapimod 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**

- Assess the efficacy of losmapimod with whole-body MRI using quantitative muscle and composite analyses.
- Quantitative muscle analyses include muscle fat infiltration (MFI), muscle fat fraction (MFF), and lean muscle volume (LMV).

**Methods**

- **Muscles Studied:** 18 muscles bilaterally, 36 total.
- **High-Resolution MRI:** Low fat replacement in almost all studies.
- **Whole Body MRI:** Not affected in all studies.
- **Controlled Treatment Period:** 24 weeks.
- **Amendment:** 48 weeks.

**Results – WB-MSK MRI Analysis**

- Losmapimod treated participants showed significantly less muscle fat infiltration (MFI) vs. placebo in intermediate muscles.
- Moderate and strong cross-sectional correlations of regional composites with COA at week 48 regardless of treatment arm.

**Conclusions**

- The reduction in skeletal muscle mass demonstrated decreases in a decrease of skeletal muscle mass at high risk of progression and normal appearing muscles, suggesting that losmapimod is a potential treatment for FSHD.
- After 48 weeks, reduction in the proportion of fat infiltrated muscle in patients treated with losmapimod suggests losmapimod has an impact on fat accumulation in muscles that have not yet reached an end-stage which has been previously reported to have little remaining functional capacity.
- Dose-finding studies suggest that improved efficacy is achieved with higher dosing regimens, indicating a potential reduction in muscle fat infiltration, which have not yet reached an end-stage.

**References / Acknowledgements**

- **Thank our collaborators and supporting patient organizations for their support.**
- **Acknowledgements:**
  - Losmapimod: F. Hoffmann-La Roche Ltd and Genfit Inc.
  - Study Design:**
  - p38α Regulates Expression of DUX4 in a Model of Facioscapulohumeral Muscular Dystrophy. 2019. doi:https://doi.org/10.1101/700195
  - Moxham et al. 2015. doi:https://doi.org/10.1002/mus.24500
  - Moxham et al. 2018. doi:https://doi.org/10.1016/j.muscle.2017.09.001
  - Moxham et al. 2020. doi:https://doi.org/10.1002/mus.25082

**Keywords:** FSHD, Losmapimod, Muscle Mass, Muscle Fat, Lean Muscle, MRI, Whole Body MRI, Muscle Fat Infiltration (MFI), Muscle Fat Fraction (MFF), Lean Muscle Volume (LMV), Cross-Sectional Correlations, Whole Body Magnetic Resonance Imaging (WB-MSK).