Phase 1 Clinical Trial of Losmapimod in FSHD

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Abstract

Background: Fulcrum Therapeutics is developing losmapimod with the aim to treat FSHD at its root cause by inhibiting DUX4 expression. Fulcrum developed the losmapimod capsule for initial testing in FSHD; the losmapimod tablet formulation was previously tested, but not in FSHD. Phase 1 was conducted with the capsule formulation because it was available prior to the tablet formulation.

Objectives: The objective of this study is to investigate the initial safety, tolerability, pharmacokinetic (PK) profile, and target engagement (TE) in healthy volunteers (HV) and FSHD patients as well as drug concentrations and target engagement in muscle of FSHD patients.

Results: In part A 10 HV were randomized to losmapimod 7.5 mg in the first period (n=8) and 15 mg in the second period or to single oral dose placebo in both dosing periods (n=2). Part B is a parallel study design randomizing 15 FSHD patients to placebo (n=3), losmapimod 7.5 mg (n=6) or losmapimod 15 mg (n=6) po BID for 14 days. Part C is an open label design with 15 mg (n=5) po BID for 14 days.

Conclusions: In Part A of the study, the losmapimod capsule generally well tolerated and showed similar PK profile to published data of the losmapimod tablet. Part B and C of the study are ongoing.

1. Background

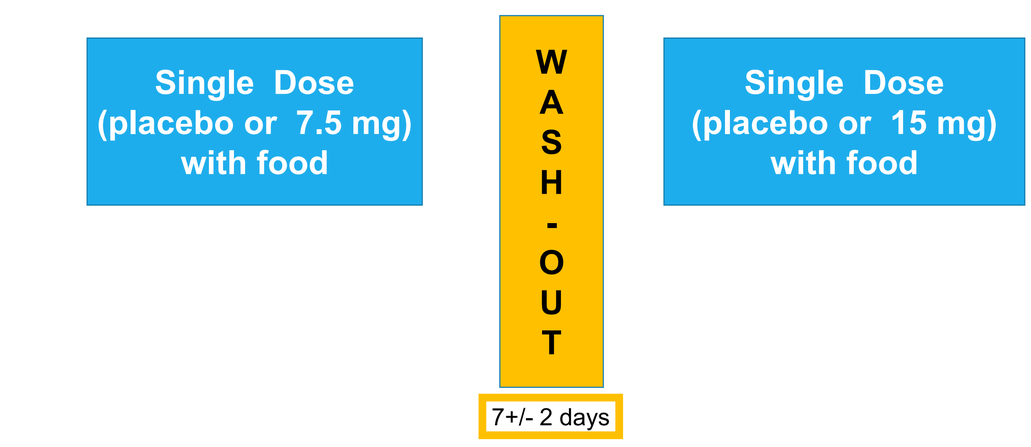
- Losmapimod is a selective p38 α/β MAP kinase inhibitor that has been shown to reduce DUX4 activation and expression of the DUX4 gene transcript pathway in preclinical studies
- The therapeutic hypothesis is that dosing FSHD patients with losmapimod may slow or arrest disease progression by reducing aberrant DUX4 activation via inhibition of p38 α/β MAP kinase.
- There is extensive exposure and safety data from previous clinical studies with over 3,500 human subjects (see poster by Cadavid D).

2. Objectives

- The objective of this study is to investigate the initial safety, tolerability, pharmacokinetic (PK) profile, and target engagement (TE) in healthy volunteers (HV) and FSHD patients as well as drug concentrations and target engagement in muscle of FSHD patients of losmapimod manufactured by Fulcrum Therapeutics as API in a capsule as compared with published data for the tablet formulation.

3. Study Design

Part A: Dose Escalation in 10 Healthy Volunteers
(2 placebo: 8 losmapimod single dose)



- **All Healthy volunteers were 18-65 years old**

Part B: Randomized, Double-Blind
Repeated Dose in 15 FSHD1 Patients
(3 placebo: 6 losmapimod 7.5 mg: 6 losmapimod 15 mg BID)
AND
Part C: Open-label Repeated Dose in 5 FSHD1 Patients
(15 mg BID)

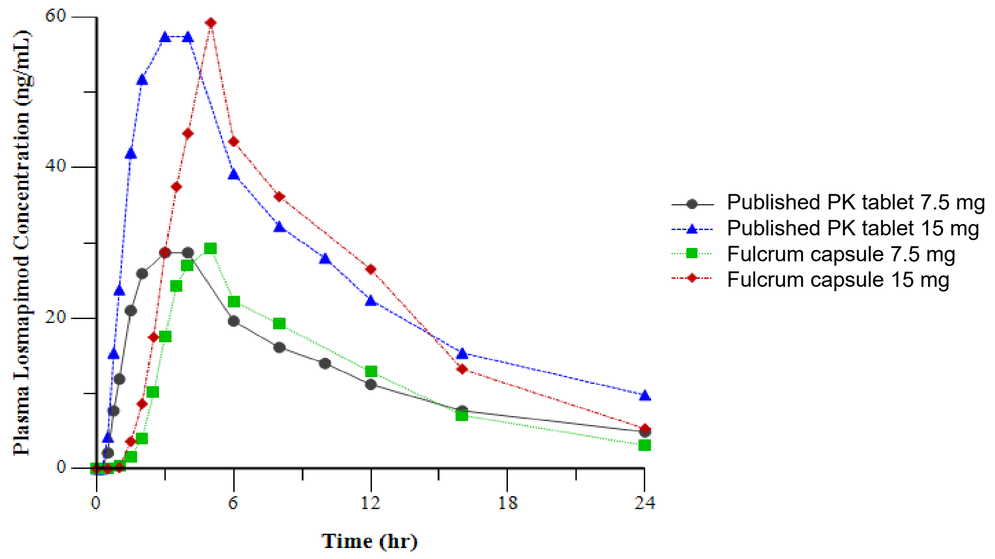
- **Patients were 18-65 years old**
- **All Patients genetically confirmed to have FSHD 1**
- **Ricci Clinical Severity Score 2.0-4.5 (range 0-5)**
- **Part B only: Normal appearing muscle eligible for biopsy**
- **Part C only: STIR+ muscle eligible for biopsy**

4. Demographics

	Gender	Average Age (range)
Part A Healthy Volunteers	4 Female 6 Male	31 (19-64) 31 (22-63)
Part B and Part C	Ongoing in FSHD1 Patients	

5. Results

Mean Pharmacokinetics in Healthy Volunteers



- 15 mg tablet data referenced from Barbour et al., 2012.
- 7.5 mg tablet data extrapolated from 15 mg tablet data.
- Reference tablet data adjusted for food effect:
  - AUC increase by 10% of reported value
  - C_{max} increase 40% of reported value

	C_{max} ng/mL (Fasted)*	C_{max} ng/mL Expected (Fed)	C_{max} ng/mL Observed (Fed)	AUC ng*hr/mL (Fasted)*	AUC ng*hr/mL Expected (Fed)	AUC ng*hr/mL Observed (Fed)
7.5 mg	23.0	32.1	37	264	290	304
15 mg	45.9	64.3	75	528	581	547

*Based on Barbour, et al. 2012 for 15 mg. Results from Barbour extrapolated to 7.5 mg.

- The losmapimod capsule demonstrated similar PK to published PK for the losmapimod GSK tablet after correction for the known difference between fed and fasted conditions
- For the Barbour observed and Phase 1 data the %CV ranged from approximately 25-50% for both C_{max} and AUC
- T_{max} was delayed by ~1 hour likely due to slowed gastric emptying

Safety

- The losmapimod capsule has been well tolerated in healthy volunteers
- Most common side effects include:
  - Headache
  - Somnolence
- Observed side effects are consistent with prior clinical studies

6. Conclusion

- The losmapimod capsule demonstrates similar PK to published PK for the tablet and is well tolerated in healthy volunteers.
- Evaluation of safety, tolerability, PK and target engagement in blood and muscle in genetically confirmed patients with FSHD 1 is ongoing. Results will be reported at a later date.

References

- Barbour AM et al. Safety, tolerability, pharamacokinetics and pharmacodynamics of losmapimod following a single intravenous or oral dose in healthy volunteers. BJCP 2012; 76(1): 99-106.
- Fisk M, Cheriyan J, Mohan D, McEniery CM, Forman J, Cockcroft JR, et al. The p38 mitogen activated protein kinase inhibitor losmapimod in chronic obstructive pulmonary disease patients with systemic inflammation, stratified by fibrinogen: A randomized double-blind placebo-controlled trial. PLoS One. 2018;13(3):e0194197.