Safety and tolerability of losmapimod, a selective p38α/β MAPK inhibitor, for treatment of FSHD at its root cause

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Abstract

- The root cause of FSHD is the loss of repression at the D4Z4 locus in chromosome 4 leading to aberrant expression of the transcription factor DUX4 in skeletal muscle that activates the DUX4-transcriptional program leading to death of skeletal muscle fibers.
- The loss of skeletal muscle fibers and their replacement by fat causes progressive loss of function and disability, affecting one or more of the face, shoulder and arms, trunk, and legs.
- Using optimized myotube culture conditions and FSHD1 and FSHD2 patient-derived myotubes, we identified p38α MAPK as a drug target that plays a critical role in aberrant DUX4 activation.
- We selected the small molecule p38α/β MAPK inhibitor **losmapimod** as a clinical development candidate for treatment of FSHD at its root cause.
- **Losmapimod** was previously studied in 25 clinical trials in over 3,500 subjects across 10 indications by GSK alone (N24) or in collaboration (N=1) but never in FSHD or muscle disease.
- Although **losmapimod** was never filed for approval, it showed favorable safety, tolerability, PK, and target engagement including during chronic administration.
- Fulcrum acquired an exclusive license for **losmapimod,** has initiated a phase 1 clinical trial in FSHD, and expect to initiate additional clinical trials in FSHD in 2019.
- Here we present an overview of the safety and tolerability of **losmapimod** in previous trials.

1. Listing of previous losmapimod phase 2 and phase 3 clinical trials

Study Identifier	Study Objectives	Study Design	Diagnosis of Patients	Treatment; Dosage Regimen; Route; Duration	Total No. of Subjects by Group Entered/Completed	Type of Report
Cardiovascular						
PM1108357	Phase 2 PoC Effect on endothelial function/vascular compliance	R, DB, PLC, PRL	Dyslipidemia	Losmapimod 7.5 mg BID Placebo Oral; repeat dose; 28 days	Losmapimod 7.5 mg BID: 27 randomized/26 completed Placebo: 29 randomized/28 completed	Completed (Full CSR)
PM1111138	Phase 2 In vivo macrophage activity assessed by FDG-PET/CT imaging	R, DB, PLC, PRL	Atherosclerosis	Losmapimod 7.5 mg BID Losmapimod 7.5 mg QD Placebo Oral, repeat dose; 12 weeks	Losmapimod 7.5 mg BID: 34 randomized/33 completed Losmapimod 7.5 mg QD: 33 randomized/32 completed Placebo: 32 randomized/27 completed	Completed (Full CSR)
PM1111810	Phase 2 Safety and effects on inflammatory markers, infarct size, and cardiac function	R, DB, PLC, PRL	Acute coronary syndrome (NSTEMI)	Losmapimod 15 mg loading dose then 7.5 mg BID Losmapimod 7.5 mg BID Placebo Oral, repeat dose; 12 weeks	Losmapimod 15 mg + 7.5 mg BID: 197 randomized/192 Safety Population/116 completed Losmapimod 7.5 mg BID: 198 randomized/199 Safety Population[a]/121 completed Placebo: 140 randomized/135 Safety Population/92 completed	Completed (Full CSR)
PM1116197	Phase 3 Clinical outcomes (major adverse cardiovascular events) and safety	R, DB, PLC, PRL Two parts planned: Part A: leading cohort of ~3500 subjects Part B: main cohort of ~22,000 subjects (this part was not conducted)	Acute coronary syndrome (NSTEMI and STEMI)	Losmapimod 7.5 mg BID Placebo BID Oral, repeat dose; 12 weeks treatment and 12 weeks follow-up (24 weeks total)	Part A: Losmapimod: 1731 randomized/ 1456 completed Placebo: 1758 randomized/ 1512 completed	Completed (Full CSR) – study was terminated
Chronic Obstructive Pulmonary Disease						
MKI102428	Phase 2 PoC Anti-inflammatory activity, efficacy, and safety	R, DB, PLC, AC, PRL	COPD	Losmapimod 7.5 mg BID SFC 50/500 (positive control) Placebo Oral, repeat dose; 12 weeks	Losmapimod: 101 randomized/86 completed SFC 50/500: 102 randomized/89 completed Placebo: 98 randomized/86 completed	Completed (Full CSR)
MKI113006	Phase 2 Efficacy and safety	R, DB, DR, PLC, PRL	COPD	Losmapimod 2.5 mg BID Losmapimod 7.5 mg BID Losmapimod 7.5 mg BID (first 4 weeks) 15 mg BID (remaining 20 weeks) Placebo Oral; repeat dose; 24 weeks	Losmapimod 2.5 mg BID: 149 randomized/127 completed Losmapimod 7.5 mg BID: 151 randomized/127 completed Losmapimod 15 mg BID: 150 randomized/114 completed Placebo: 154 randomized/129 completed	Completed (Full CSR)
CRT116192 (non-GSK-sponsored)	Phase 2 Effect on vascular structure and function	R, DB, PLC, PRL	COPD	Losmapimod 7.5 mg BID Placebo Oral, repeat dose, 16 weeks	Losmapimod: 36 randomized/25 completed Placebo: 37 randomized/32 completed	Completed (Fisk et al, 2018)
201496	Phase 2 Safety and efficacy in frequently exacerbating subjects	R, DB, PLC, PRL	COPD	Losmapimod 15 mg BID Placebo Oral, repeat dose, up to 52 weeks	Losmapimod: 90 randomized/10 completed Placebo: 94 randomized/14 completed	Completed (Full CSR)
Focal Segmental Glomerulosclerosis						
FSG117283	Phase 2 Reduce proteinuria	OL	FSGS (idiopathic)	Losmapimod 15 mg BID (7.5 mg BID for first 2 weeks) Oral, repeat dose, 24 weeks	Losmapimod: 17 randomized/13 completed	Completed (Full CSR)
Rheumatoid arthritis						
RA3103718	Phase 2 PoC Safety, tolerability, and clinical activity	R, DB, PLC	RA	Sequence 1: Losmapimod 7.5 mg BID for 28 days followed by placebo for 28 days Sequence 2: Placebo for 28 days followed by losmapimod 7.5 mg BID for 28 days Sequence 3: Placebo for 56 days Sequence 4: Losmapimod 7.5 mg BID for 56 days followed by losmapimod 10 mg BID for 28 days Sequence 5: Placebo for 28 days followed by losmapimod 7.5 mg BID for 28 days followed by losmapimod 10 mg BID for 28 days Sequence 6: Placebo for 84 days Oral; repeat dose; up to 84 days	Total: 57 randomized/53 completed/ 1 unknown Received losmapimod: 37 Received placebo: 48	Completed (Synopsis- only CSR)
Major Depression Disorder						
PKI108574	Phase 2 Clinical antidepressant effects and levels of circulating serum cytokines	R, DB, PLC, PRL	MDD	Losmapimod 7.5 mg BID Placebo Oral, repeat dose; 6 weeks	Losmapimod: 12 randomized/8 completed Placebo: 12 randomized/7 completed	Completed (Abbreviated CSR)
PKI113009	Phase 2 Clinical antidepressant effects	R, DB, PLC, PRL	MDD	Losmapimod 7.5 mg BID Placebo Oral; repeat dose; 6 weeks	Losmapimod: 64 randomized/51 completed Placebo: 64 randomized/50 completed	Completed (Abbreviated CSR)
Neuropathic Pain						
KIP112967	Phase 2 Safety and efficacy	R, DB, PLC, PRL	Neuropathic pain (peripheral nerve injury)	Losmapimod 7.5 mg BID Placebo Oral, repeat dose; 4 weeks	Losmapimod: 87 randomized/78 completed Placebo: 81 randomized/73 completed	Completed (Synopsis- only CSR)
KIP113049	Phase 2 Safety and efficacy	R, DB, PLC, PRL	Neuropathic pain (lumbosacral radiculopathy)	Losmapimod 7.5 mg BID Placebo Oral, repeat dose; 4 weeks	Losmapimod: 68 randomized/1 did not receive DB treatment/ 63 completed Placebo: 71 randomized/4 did not receive DB treatment/ 68 completed	Completed (Synopsis- only CSR)

Abbreviations: AC, active control; ADME, Absorption, distribution, metabolism, and excretion; BID, twice daily; COPD, chronic obstructive pulmonary disease; CSR, clinical study report; DB, double blind; DC, direct compression; DR, dose response; FDG-PET/CT, 18F-2-fluoro-2-deoxy-D-glucose positron emission tomography-computed tomography; FSGS, focal segmental glomerulosclerosis; FTIH, first time in human; IV, intravenous; MDD, major depressive disorder; NSTEMI, non-ST-segment elevation myocardial infarction; OL, open label; PD, pharmacodynamic(s); PK, pharmacokinetic(s); PLC, placebo control; PoC, proof of concept; PRL, parallel group; QD, once daily; R, randomized; RA, rheumatoid arthritis; RD, repeat dose; SB, single blind; SD, single dose; SFC, salmeterol plus fluticasone propionate; STEMI, ST-segment elevation myocardial infarction; WG, wet granulation; XO, crossover.

2. Summary of Data Safety Integration in Previous losmapimod trials

Summary Type Study Number	Indication
Phase 2 Repeat Dose Integration: 11 Studies	
MKI102428	COPD
MKI106209	COPD
MKI113006	COPD
RA3103718	RA
PKI108574	MDD
PKI113009	MDD
PM1108357	Dyslipidemia
PM1111138	Atherosclerosis
PM1111810	NSTEMI
KIP112967	Peripheral nerve injury
KIP113049	Lumbosacral radiculopathy

3. AES and SAEs (Fatal and Non-Fatal) during Treatment Across 11 Integrated GSK-Sponsored Repeat Dose Studies in Patient Populations

Adverse Events by Treatment Group

Indication	Study	Placebo N=735 n/n (%)	Losmapimod N=1327 n/n (%)
	Total	**406/735 (55)**	**815/1327 (61)**
COPD	MKI102428	55/98 (56)	67/101 (66)
	MKI106209	8/12 (67)	12/24 (50)
	MKI113006	93/153 (61)	270/449 (60)
RA	RA3103718	7/48 (15)	10/37 (27)
MDD	PKI108574	3/12 (25)	5/12 (42)
	PKI113009	27/64 (42)	25/64 (39)
Dyslipidemia	PM1108357	17/29 (59)	22/27 (81)
Atherosclerosis	PM1111138	31/32 (97)	56/67 (84)
NSTEMI	PM1111810	88/135 (65)	246/391 (63)
Peripheral nerve injury	KIP112967	52/81 (64)	64/87 (74)
Lumbosacral radiculopathy	KIP113049	25/71 (35)	38/68 (56)

COPD=chronic obstructive pulmonary disease; MDD=major depressive disorder; n/n=number of subjects experiencing an adverse event/total number of subjects assessed per study (% total); NSTEM= non-ST-segment elevation myocardial infarction; RA=rheumatoid arthritis.

Most Frequent (≥5%) Adverse Events

Preferred term	Placebo N=735	Losmapimod N=1327	Relative risk (95% CI)
Headache	13%	12%	0.94 (0.74, 1.19)
Nasopharyngitis	6%	5%	0.93 (0.64, 1.36)
Chronic obstructive pulmonary disease	7%	6%	0.90 (0.65, 1.23)

Serious Adverse Events by Treatment Group

	Placebo N=735 n (%)	Losmapimod N=1327 n (%)
Any SAE	**47 (6)**	**120 (9)**
Cardiac Disorders	17 (2)	41 (3)
Respiratory, Thoracic and Mediastinal Disorders	11 (1)	26 (2)
Infections and Infestations	7 (<1)	14 (1)
General Disorders and Administration Site Conditions	7 (<1)	13 (<1)
Nervous System Disorders	5 (<1)	10 (<1)
Injury, Poisoning and Procedural Complications	1 (<1)	11 (<1)
Gastrointestinal Disorders	1 (<1)	7 (<1)
Vascular Disorders	1 (<1)	5 (<1)
Renal and Urinary Disorders	2 (<1)	4 (<1)
Musculoskeletal and Connective Tissue Disorders	2 (<1)	4 (<1)
Skin and Subcutaneous Tissue Disorders	2 (<1)	4 (<1)
Hepatobiliary Disorders	0	4 (<1)
Psychiatric Disorders	2 (<1)	3 (<1)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	1 (<1)	3 (<1)
Blood and Lymphatic System Disorders	0	1 (<1)
Immune System Disorders	0	1 (<1)
Metabolism and Nutrition Disorders	0	1 (<1)

Incl=including; SAE=serious adverse event.
Studies included: MKI102428, MKI106209, MKI113006, RA3103718, PKI108574, PKI113009, PM1108357, PM1111138, PM1111810, KIP112967, and KIP113049.

4. Summary of Data Safety Integration from COPD losmapimod trials

Phase 2 Focused COPD Integration: 3 Studies	
MKI102428	COPD
MKI106209	COPD
MKI113006	COPD

Most Frequent (≥5%) AEs	Placebo N=263	Losmapimod N=574	Relative risk (95% CI)
Chronic obstructive pulmonary disease	18%	16%	0.90 (0.65, 1.23)
Nasopharyngitis	8%	7%	0.85 (0.51, 1.40)
Back pain	6%	4%	0.65 (0.34, 1.23)
Headache	11%	7%	0.64 (0.39, 1.05)

COPD=chronic obstructive pulmonary disease; CI=confidence interval; CMH= Cochrane-Mantel-Haenszel.
Studies included: MKI106209, MKI102428, and MKI113006.

Across 3 integrated GSK-sponsored repeat dose studies in subjects with COPD, on-treatment SAEs (fatal and non-fatal) were reported by a similar percentage of subjects in the placebo group (21/263, 8%) and the losmapimod group (43/574, 7%). On-treatment SAEs were most frequently reported within the SOC of Respiratory, Thoracic and Mediastinal Disorders.

5. Summary of Data Safety from losmapimod Phase 3 Study in Acute Coronary Syndrome (Study PM1116197)

Most Common (at Least 2%) On-treatment AEs Excluding Adjudicated Cardiovascular Events

Preferred term	Placebo N=1752 n (%)	Losmapimod 7.5 mg BID N=1724 n (%)
Any AE	972 (55.5)	972 (56.4)
Atrial fibrillation	61 (3.5)	76 (4.4)
Dyspnoea	54 (3.1)	41 (2.4)
Non-cardiac chest pain	37 (2.1)	46 (2.7)
Diarrhoea	38 (2.2)	41 (2.4)
Troponin increased	48 (2.7)	31 (1.8)
Hypertension	48 (2.7)	30 (1.7)
Angina pectoris	29 (1.7)	48 (2.8)
Cough	31 (1.8)	40 (2.3)

- This is the largest clinical trial ever performed with losmapimod.
- AEs considered by the investigator to be related to investigational product were reported for 91 (5.2%) subjects in the placebo group and 104 (6.0%) subjects in the losmapimod group.
- A total of 125 subjects died (all-cause mortality) through Week 24 (Day 182). Of these 125 deaths, 57 (3.3%) were in the losmapimod group (47 were adjudicated positively as CV deaths) and 68 (3.9%) were in the placebo group (59 were adjudicated positively as CV deaths).

Fatal and Non-Fatal SAEs by System Organ Class and Preferred Term Reported by >0.5%

System organ class Preferred term	Placebo N=1752 n (%)	Losmapimod 7.5 mg BID N=1724 n (%)
Any SAE	**323 (18.4)**	**363 (21.1)**
Cardiac disorders		
Any event	114 (6.5)	138 (8.0)
Angina unstable	24 (1.4)	26 (1.5)
Angina pectoris	14 (0.8)	19 (1.1)
Atrial fibrillation	14 (0.8)	13 (0.8)
Acute myocardial infarction	7 (0.4)	13 (0.8)
Cardiac failure	6 (0.3)	10 (0.6)
Infections and infestations		
Any event	54 (3.1)	55 (3.2)
Pneumonia	12 (0.7)	16 (0.9)
Respiratory, thoracic and mediastinal disorders		
Any event	24 (1.4)	41 (2.4)
Pleural effusion	6 (0.3)	9 (0.5)
General disorders and administration site conditions		
Any event	35 (2.0)	26 (1.5)
Non-cardiac chest pain	19 (1.1)	15 (0.9)
Renal and urinary disorders		
Any event	18 (1.0)	31 (1.8)
Acute kidney injury	9 (0.5)	13 (0.8)
Investigations		
Any event	28 (1.6)	18 (1.0)
Troponin increased	11 (0.6)	9 (0.5)
Musculoskeletal and connective tissue disorders		
Any event	14 (0.8)	25 (1.5)
Musculoskeletal chest pain	4 (0.2)	14 (0.8)

6. Conclusion

- There has been extensive investigation of the safety and tolerability of losmapimod in humans.
- Data from over 3,500 healthy and diseased subjects generally shows no clinically significant differences in safety and tolerability comparing losmapimod to placebo.
- There have been no clinically relevant differences between placebo and losmapimod with regard to ECG abnormalities, rash, immune compromise, liver or renal toxicity.
- No safety information exists in human pregnancy.
- Assessment of safety, tolerability, ECG, and laboratory abnormalities in FSHD patients is ongoing.