TRAILHEAD: An open-label, Phase 2 study evaluating long-term safety and efficacy of SAT-3247 in adults with Duchenne muscular dystrophy

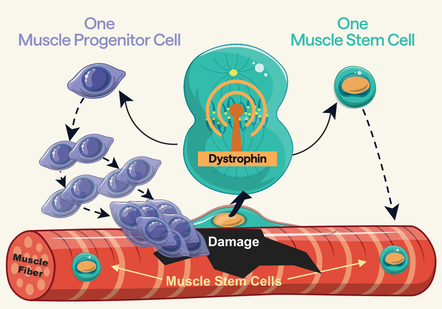
POSTER 487-LB

K. Salmon, W. Aschenbach, R. Mitchell, M. Rudnicki, F. Gleeson, W. Farwell

BACKGROUND

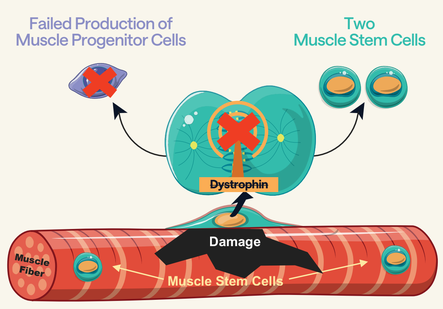
- Seminal research has established dystrophin as a key signaling protein in satellite cells (Dumont N, et al. Nature Medicine. (2015) 21:1455-1463), in addition to its well-known role as a structural protein in muscle fibers.
- In healthy skeletal muscle with normal dystrophin expression, stem cells respond to damage by dividing in a balanced way – some become new muscle progenitor cells to repair damaged tissue, while others remain as stem cells to support future repair (**Figure 1a**).
- In Duchenne muscular dystrophy (DMD), muscle damage outpaces repair resulting in progressive muscle loss. This is due to mutations in the dystrophin gene, absence (or near absence) of dystrophin protein, and impaired asymmetric stem cell division and muscle progenitor formation (**Figure 1b**).
- SAT-3247 is an investigational, small molecule inhibitor of adaptor-associated protein kinase (AAK1) that has been shown in preclinical models to increase asymmetric stem cell division, muscle progenitor formation, muscle fiber regeneration, and muscle strength that is impaired in DMD due to lack of dystrophin (**Figure 1c**).
- A recently completed Phase 1a/b study (NCT06565208) of SAT-3247 in healthy volunteers and five adults with DMD demonstrated a favorable safety profile with predictable, dose-proportional pharmacokinetics, and improved grip strength and forced vital capacity. Additionally, biomarkers that are elevated in DMD were reduced after 15-28 days of SAT-3247 administration (see Poster 394-O).
- Here, we describe the design, assessments, and provide baseline data from TRAILHEAD (NCT06867107), an ongoing Phase 2 study in adults with DMD.

Figure 1a: Asymmetric stem cell division and progenitor formation in healthy skeletal muscle



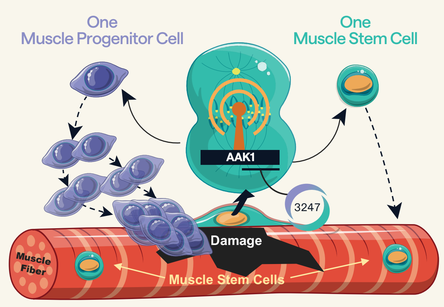
Asymmetric division with Dystrophin Signal
1 progenitor + 1 stem cell

Figure 1b: Symmetric division and impaired progenitor formation in DMD



Symmetric division without Dystrophin Signal
0 progenitors + 2 stem cells

Figure 1c: AAK1 inhibition via SAT-3247 increases muscle progenitor formation and muscle fiber regeneration

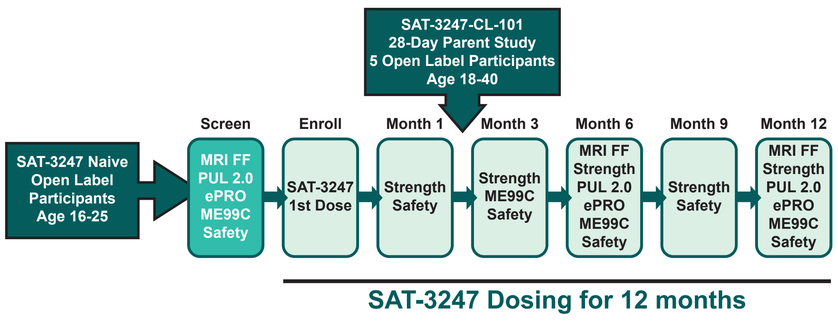


Asymmetric division with AAK1 inhibition
1 progenitor + 1 stem cell

TRAILHEAD (NCT06867107)

- TRAILHEAD is an open-label, Phase 2 study evaluating the long-term safety, tolerability, and potential efficacy of orally-administered SAT-3247 (**Figure 2**).
- TRAILHEAD will enroll up to 30 male participants in Australia and the United States aged ≥16 years with a definitive diagnosis of DMD and a confirmed mutation in the DMD gene.
- Participants will receive 60 mg SAT-3247 administered orally using a 5-days-on/2-days-off (weekday) dosing regimen for up to 12 months.
- The study includes two groups of participants:
  - Group A: up to 5 participants who completed 1 month of dosing in study CL-101 (NCT06565208), who will receive SAT-3247 for an additional 11 months.
  - Group B: treatment naïve participants who will receive SAT-3247 for up to 12 months.
- TRAILHEAD's primary safety objective is to evaluate the long-term safety and tolerability of SAT-3247 in participants with DMD.
- TRAILHEAD's primary efficacy objective is to determine the effect of SAT-3247 on intramuscular fat fraction following 12 months of treatment.

Figure 2: TRAILHEAD study schema



Abbreviations: Strength=grip & pinch, elbow extension/flexion, shoulder abduction/flexion via dynamometry; ePRO=electronic Patient Reported Outcomes; ME99C=maximum effort 99th centile; MRI FF=Magnetic Resonance Imaging fat fraction; PUL 2.0=Performance Upper Limb 2.0

TRAILHEAD GROUP A BASELINE CHARACTERISTICS

Table 1: TRAILHEAD Group A Participants – Adults with DMD who completed CL-101

Participant	Age at DMD diagnosis	Ambulatory status	Age at loss of ambulation (years)	Steroid use	TRAILHEAD Baseline PUL2.0	Time between last dose in CL-101 & 1st dose TRAILHEAD (days)*
A	7	Non-ambulatory	12	YES	10	265
B	9	Non-ambulatory	18	YES	10	224
C	5	Ambulatory	N/A	YES	41	205
D	19	Ambulatory	N/A	YES	26	328

*Number of days in between last dose in CL-101 and first dose in LT-001, not including days of last or first doses.

Table 2

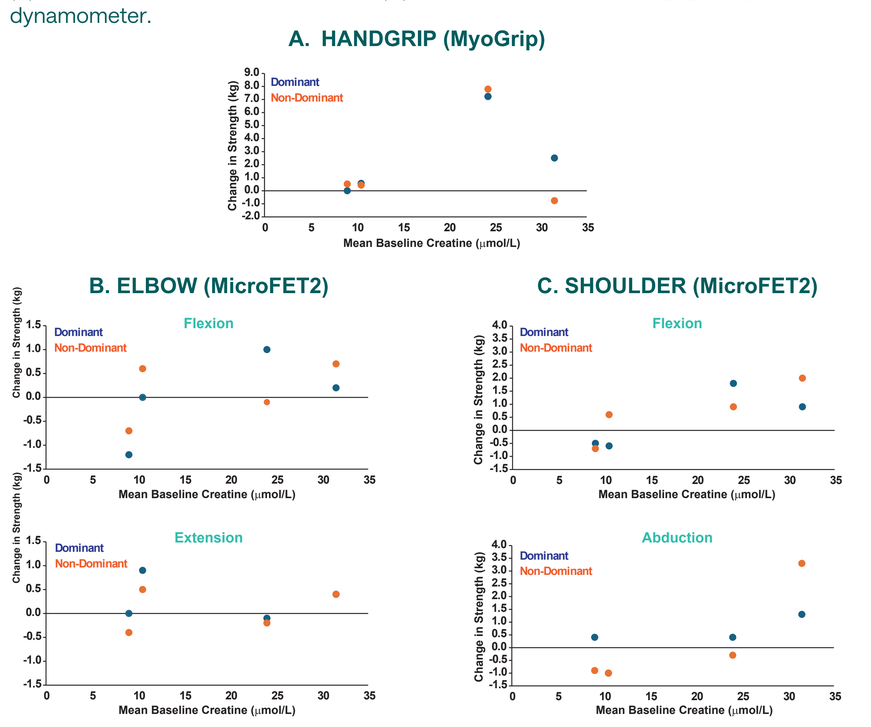
Participant Baseline Demographics	Group A n = 4
Age (years) Mean (SD) Min, Max	24.8 (2.99 21, 28
Weight (kg) Mean (SD) Min, Max	55.10 (14.597) 33.4, 67.6
Height (cm) Mean (SD) Min, Max	140.88 (8.290) 130.0, 150.0
Time from DMD diagnosis to SAT-3247 treatment initiation in TRAILHEAD (years) Mean (SD) Min, Max	20.671 (4.8127) 16.07, 26.94

Table 3

Baseline Clinical Outcomes	Group A n = 4	
% Predicted FVC Mean (SD) Min, Max	47.18 (15.400) 27.2, 59.6	
	Dominant Side	Non-Dominant Side
Grip Strength (kg) Mean (SD) Min, Max	5.363 (4.9057) 1.05, 11.20	5.573 (5.0477) 0.79, 10.18
Pinch Strength (kg) Mean (SD) Min, Max	1.3460 (1.04517) 0.365, 2.290	1.4293 (1.20228) 0.337, 2.676
Dynamometry (kg) Mean (SD) Min, Max	Elbow Extension	
	1.38 (1.318) 0.0, 2.9	1.48 (1.360) 0.0, 3.1
	Elbow Flexion	
	1.38 (1.533) 0.0, 3.4	1.23 (1.676) 0.0, 3.7
	Shoulder Abduction	
	2.45 (2.374) 0.5, 5.9	2.00 (0.987) 0.9, 3.1
	Shoulder Flexion	
	2.20 (2.348) 0.8, 5.7	1.75 (1.827) 0.0, 4.3
CK (U/L) Mean (SD) Min, Max	1263.00 (909.588) 729.0, 2617.0	

% Predicted FVC, Grip Strength, Pinch Strength, and Dynamometry data all represent maximum effort

Figure 3: Participants with higher baseline creatinine, a surrogate marker of muscle mass, generally demonstrated greater muscle strength as assessed by dynamometry. Handgrip strength assessed with the MyoGrip device (A), elbow flexion and extension (B) and shoulder flexion and abduction (C) assessed with the MictroFET2 handheld dynamometer.



CONCLUSIONS and NEXT STEPS

- TRAILHEAD is an ongoing, open-label study enrolling adult participants living with DMD in Australia and soon in the United States.
- TRAILHEAD will allow long-term evaluation of the safety and tolerability of SAT-3247 along with efficacy measures relevant to adults.
- Biomarker sample collection throughout the study will allow exploratory analyses of markers relevant to SAT-3247 mechanism of action and DMD.

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