

TRAILHEAD: An Open-Label Study Evaluating Long-Term Safety and Efficacy of Forzapadin (SAT-3247) in Adults with Duchenne Muscular Dystrophy (DMD)

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INTRODUCTION

- In Duchenne muscular dystrophy (DMD), muscle damage outpaces repair, resulting in progressive muscle loss.
- Seminal research established dystrophin as a key signaling protein in muscle stem cells¹, in addition to its well-recognized structural role in muscle fibers. Variants in the *DMD* gene that result in the absence (or near absence) of dystrophin impair the ability of muscle stem cells to establish polarity in response to muscle damage, thereby reducing muscle progenitor formation and overall regenerative capacity.
- Forzapadin (formerly SAT-3247) is an investigational, orally administered small molecule inhibitor of adaptor-associated protein kinase (AAK1) that is designed to re-establish polarity and asymmetric division of muscle stem cells, muscle progenitor formation, and enhance muscle fiber regeneration in DMD and other muscle diseases. Detailed descriptions of muscle stem cell dysfunction in DMD and forzapadin mechanism of action are provided in **WMS Poster #2.74P**.
- Safety and efficacy data from a Phase 1a/b study of forzapadin (NCT06565208) have been previously reported, as has early safety and efficacy data from the ongoing Phase 2 TRAILHEAD study (NCT06867107) in participants who continued from the Phase 1b study^{2,3}.
 - These emerging Phase 2 data continue to demonstrate a favorable safety profile of forzapadin as well as stability or trends of improvement in assessments of muscle strength, function, and respiratory capacity.
- Here, we provide updated safety and tolerability data, as well as MRI evaluation of intramuscular fat, upper-limb strength, physical function, and Quality of Life after 140 days of total forzapadin exposure within the TRAILHEAD study.

METHODS

- TRAILHEAD is an open-label, Phase 2 study evaluating the long-term safety, tolerability, and potential efficacy of orally-administered forzapadin.
- TRAILHEAD will enroll up to 30 male participants aged ≥16 years in Australia and the United States with a definitive diagnosis of DMD and a confirmed variant in the *DMD* gene.
- Participants receive 60 mg forzapadin 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:** Four participants who completed 1 month of dosing in the Phase 1b study CL-101 (NCT06565208), receiving forzapadin for an additional 11 months.
 - Group B:** up to 25 treatment-naïve participants who will receive forzapadin for up to 12 months.
- The primary safety objective is to evaluate long-term safety and tolerability of forzapadin in participants with DMD.
- The primary efficacy objective is to determine the effect of forzapadin on MRI intramuscular fat fraction following 12 months of treatment.

RESULTS

- TRAILHEAD Group A baseline characteristics and demographics have been previously described^{5,6}.
- Overall, the safety and tolerability profile following 140 days of forzapadin dosing was favorable and consistent with what was previously reported (**Table 1**).
- Mean serum creatine kinase levels were 38% lower after 140 days of forzapadin dosing in TRAILHEAD than at baseline in the CL-101 Phase 1b study, despite a 7-11 month interval between studies (**Figure 1**).
- Absolute reductions of 3.7 percentage points in biceps brachii fat fraction and 1.8 milliseconds in T2 relaxation time, assessed by MRI, were observed from baseline to Day 140 of forzapadin dosing in TRAILHEAD (**Figure 2**).
- Consistent with previous observations^{2,3}, handgrip strength remained stable in Group A participants through Day 140 of TRAILHEAD (**Figure 3**). As previously reported³, elbow and shoulder strength also remained stable, with trends toward improvement among participants who entered CL-101 with greater baseline muscle mass (data not shown).

Table 1: Forzapadin Safety and Tolerability

Consistent with previously reported results^{5,6}, no new safety signals were observed with long-term administration of forzapadin (formerly SAT-3247). No serious treatment-emergent adverse events (TEAEs), no TEAEs leading to withdrawal or discontinuation, and 100% compliance over an average exposure of 186 days were observed.

Safety	Group A (n=4)
Any TEAE; n (events)	4 (11)
Any related TEAE; n (events)	3 (4)
Any serious TEAE; n (events)	0
Any TEAE leading to withdrawal; n (events)	0
Any study withdrawals; n	0
Compliance = 100%	
Mean Adjusted exposure	186.3 days
Min, Max	162, 214

Data as of 18 May, 2026. Related TEAEs were 1) elevated neutrophils and mild, persistent elevation in white blood cells (consolidated into 1 adverse event), 2) decreased red blood cell count, and 3) tachycardia

Figure 1: Creatine Kinase

Serum creatine kinase (CK) concentrations were reduced by an average of 38% over 140 days of forzapadin dosing in TRAILHEAD compared with baseline in the Phase 1b CL-101 study. Mean serum CK levels (±SD, **bold purple**) are juxtaposed with individual participant values.

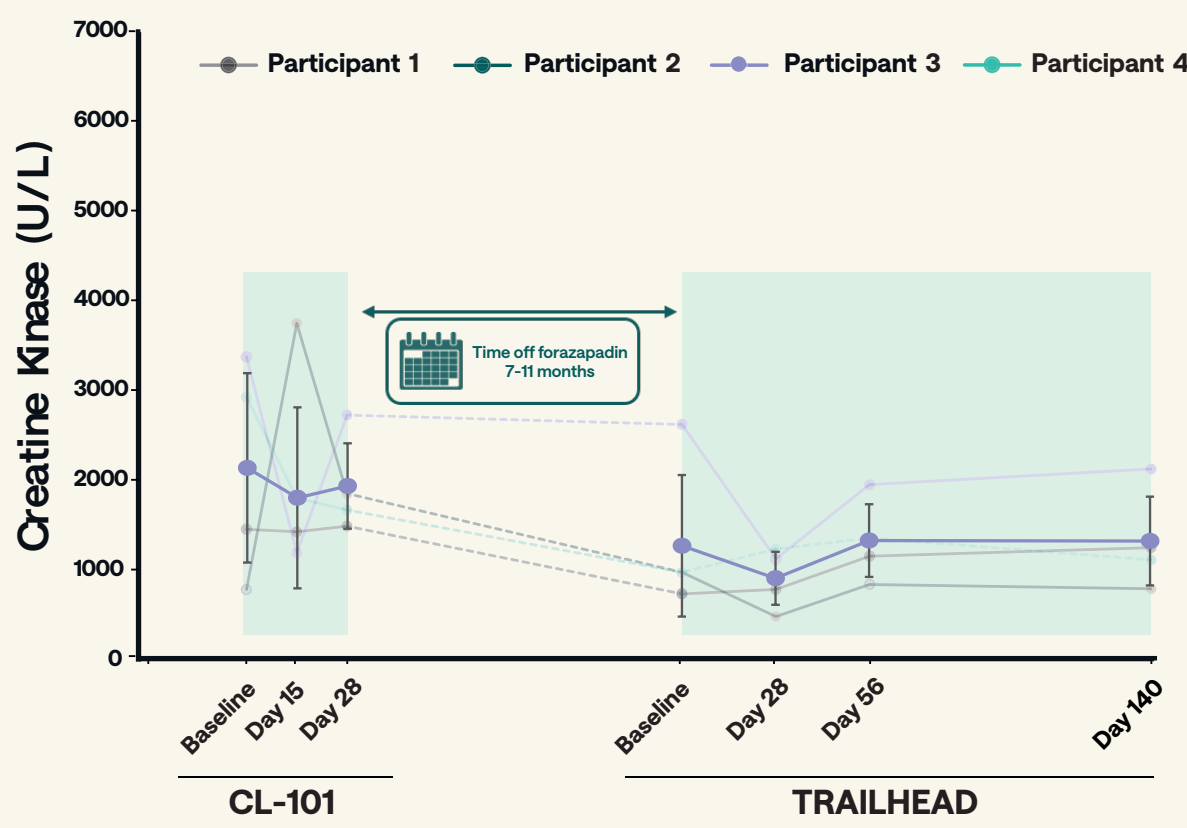


Figure 2: MRI

Biceps brachii fat fraction (A) and T2 relaxation time (B) were assessed by MRI at baseline and after 140 days of forzapadin dosing in TRAILHEAD. Mean reductions of 3.7 percentage points in fat fraction and 1.8 milliseconds (ms) in T2 relaxation time were observed, suggesting reduced active damage and edema. Notably, muscle fat fraction was reduced in all four participants (**Table 2**). Data presented as mean ± standard deviation.

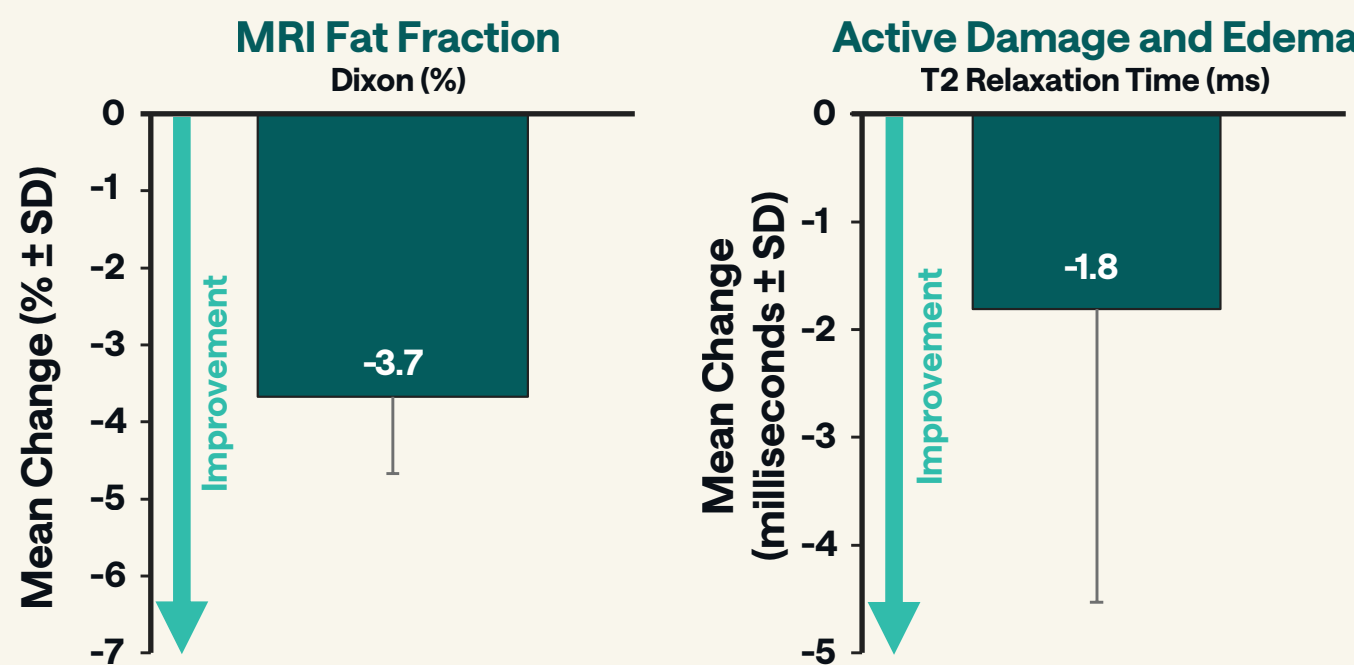


Figure 3: Grip Strength

Consistent with and extending upon previous reports²⁻⁴, bilateral improvements in handgrip strength observed in the CL-101 study remained stable through Day 140 of TRAILHEAD, despite a 7- to 11-month treatment pause between studies.

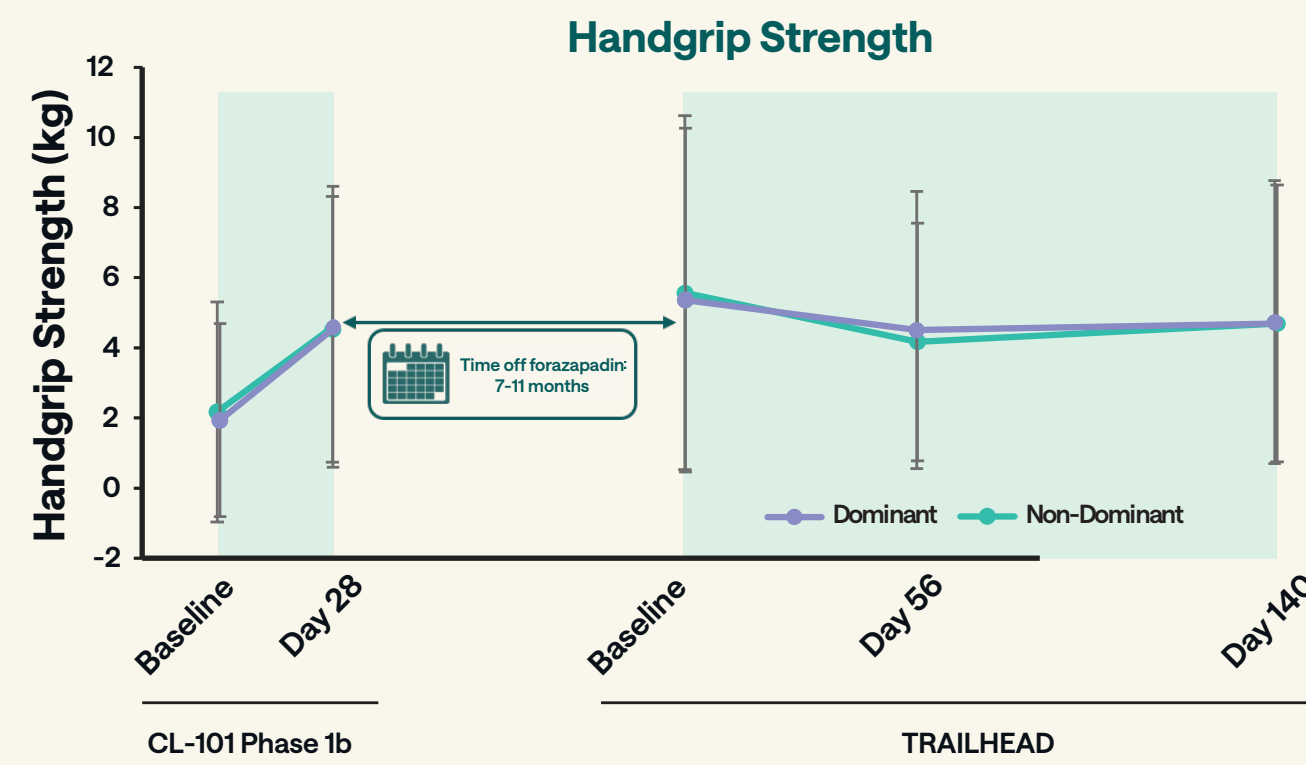


Figure 4: SYSNAV

Daily activities of TRAILHEAD Group A participants were assessed via SYSNAV™ wrist and ankle sensors. Total combined effort (J/kg) of their 99th percentile of intense daily activities (TE99C) were calculated and indexed to normative data. Group A participants demonstrated a mean improvement of 5.47 J/kg (+34%) in total combined effort of captured activities. Participants who entered the CL-101 study with greater muscle mass (assessed by serum creatinine) achieved a greater total effort and demonstrated the greatest improvements (**Table 2**).

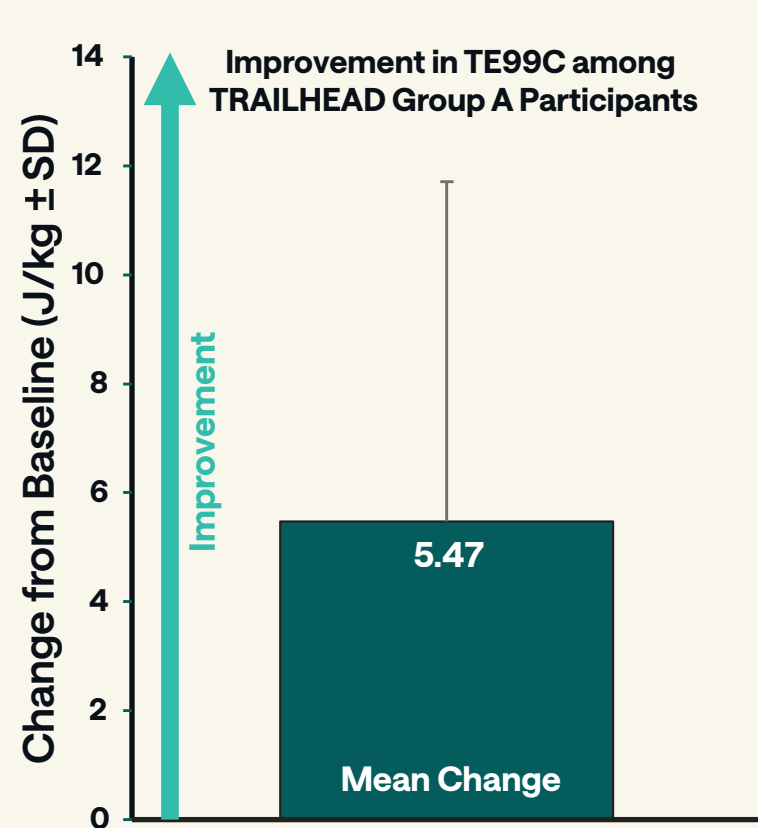


Figure 5: PUL2.0

Upper limb function was assessed using the Performance of the Upper Limb (PUL 2.0). Mean PUL 2.0 scores remained stable through Day 140, with two participants demonstrating 1-point improvements and two maintaining stable scores (**Table 2**).

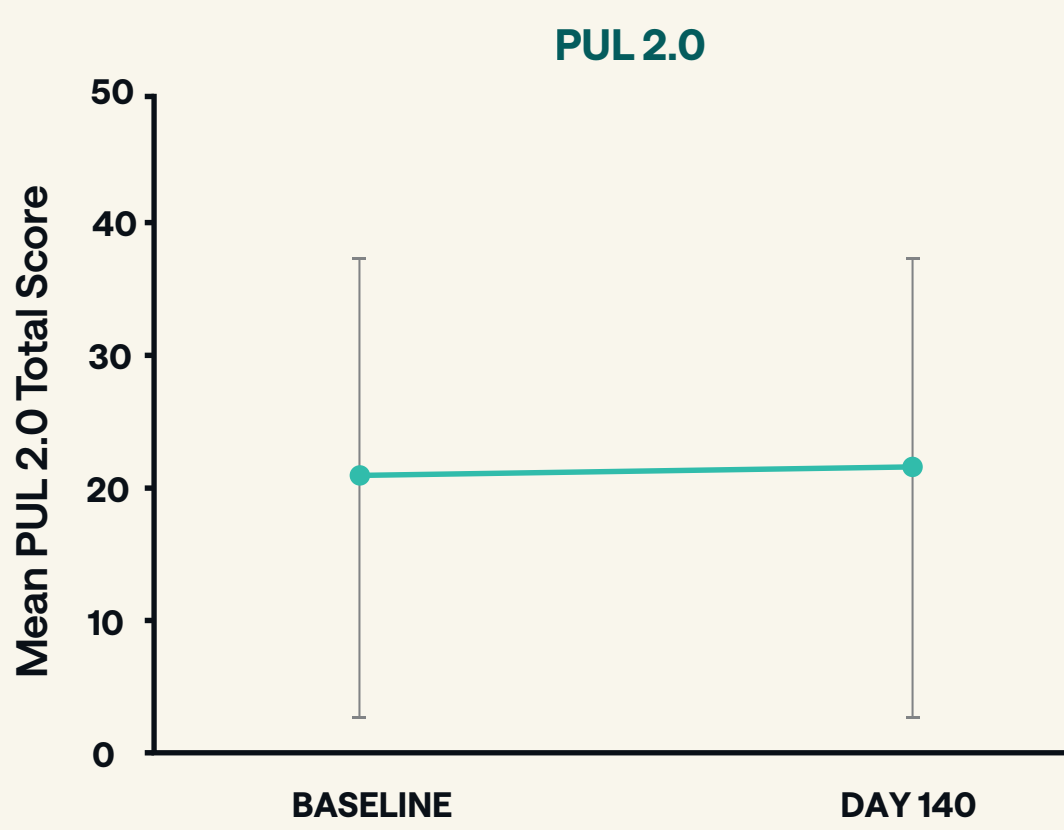


Figure 6: Fatigue-Related Quality of Life

Participant-reported fatigue was assessed via the adapted Pediatric Quality of Life Multidimensional Fatigue Scale (PedsQL-MFS). Mean PedsQL-MFS scores increased by 6.94 points from CL-101 baseline to Day 140 of TRAILHEAD, indicating reduced fatigue following forzapadin treatment.

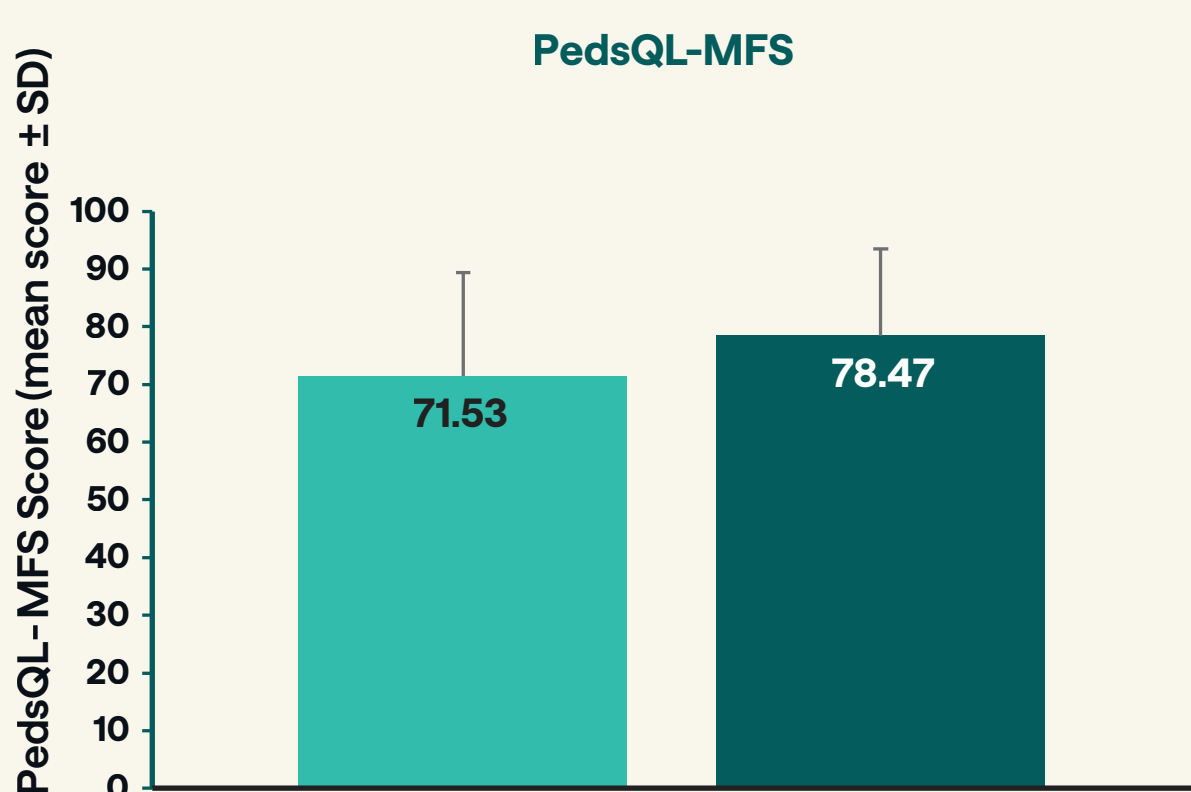


Table 2: Individual TRAILHEAD Participant Responses

Individual participant age, baseline serum creatinine (an estimation of muscle mass), MRI, strength and physical function assessments are summarized. Overall, a pattern of stability or improvement was observed across participants. Those who entered the Phase 1b CL-101 study with greater baseline muscle mass demonstrated greater reductions in muscle fat fraction, greater physical effort, and greater upper limb function during TRAILHEAD.

	Participant Age (years)	CL-101 Baseline Creatinine (μmol/L)	Magnetic Resonance Imaging				Muscle Strength (Handgrip)				Physical Function			
			Fat Fraction (%)	T2 Relaxation (milliseconds)	Dominant (kg)	Non-Dominant (kg)	SYSNAV Total Effort 99 th Percentile (J/kg)	PUL 2.0 Total Score	TH Baseline	CH Baseline	TH Baseline	CH Baseline	TH Baseline	CH Baseline
Participant 1	24	10.5	81.4	-6.2	N.A.	N.C.	0.25	1.07	0.47	0.48	3.43	+0.02	10	0
Participant 2	26	9.0	35.3	-0.9	37.5	-3.7	1.43	-0.14	1.23	0.39	8.05	+1.07	10	+1
Participant 3	21	31.5	27.9	-5.8	33.2	1.3	5.97	4.33	6.83	1.02	21.95	+13.50	41	+1
Participant 4	28	24.0	54.1	-1.9	45.9	-3.1	0.10	7.13	0.16	8.19	30.98	+7.47	26	0
Mean ± SD	24.8± 2.6	18.8± 9.4	49.7± 23.9	-3.7± 2.7	38.9± 6.4	-1.8± 2.7	1.94± 2.38	3.10± 2.84	2.17± 2.72	2.52± 3.28	16.10± 12.66	5.47± 6.24	22 ± 15	0.5± 0.5

TH = TRAILHEAD; N.A. = not assessed; N.C. = not calculated; mean T2 at TRAILHEAD Day 140 for Participants 2-4 who completed both Baseline and Day 140 assessments = 37.1 ± 5.0 milliseconds

CONCLUSIONS & NEXT STEPS

- Safety & Tolerability:** Consistent with previous reports^{2,3} no new safety signals were observed with long-term administration of forzapadin (SAT-3247). As of May 18, 2026, no serious treatment-emergent adverse events (TEAEs), no TEAEs leading to withdrawal or discontinuation, and 100% compliance over an average of 186 days of exposure were noted.
- Biomarkers of Muscle Damage:** A 38% reduction in mean serum creatine kinase levels during 140 days of forzapadin dosing was observed in TRAILHEAD, compared to baseline levels in the CL-101 Phase 1b study. Given the putative mechanism of forzapadin action to enhance muscle regeneration, the significance of creatine kinase levels requires further investigation. Nevertheless, the reductions observed here are consistent with prior observations that serum proteomic biomarkers of muscle damage were reduced during 15 days of forzapadin dosing in the CL-101 Phase 1b study².
- MR Imaging:** Biceps brachii fat fraction declined over 140 days of forzapadin dosing in all four participants with a mean reduction of 3.7 percentage points, suggesting improved muscle composition. In contrast, annual fat fraction increases of 5.9% are reported in elbow flexor muscles among non-ambulant boys⁹. Additionally, the mean reduction in T2 relaxation time of -1.8 milliseconds suggests reduced active damage and edema during forzapadin dosing.
- Muscle Strength:** Overall, participants continued to maintain hand grip strength improvements as well as elbow and shoulder strength through 140 days of forzapadin dosing. In CL-101, signs of improvement were observed in participants who entered with greater muscle mass^{2,3}.
- Physical Function:** TE99C, a measure of total effort at the 99th percentile of the most intense real-world daily physical activities, increased 34% between baseline of the CL-101 study to TRAILHEAD day 140, with all four participants demonstrating greater total effort. On average, PUL 2.0 scores were stable over 5-months of forzapadin dosing in TRAILHEAD, with 2 of 4 participants demonstrating 1-point improvements. Natural history studies report that PUL 2.0 scores decline over time⁶.
- Participant-Reported Fatigue:** Higher PedsQL-MFS scores were also observed after 5-months of forzapadin dosing, indicating that participants experienced lower levels of fatigue.
- Taken Together:** While participant numbers are limited (N=4), these results collectively demonstrate an overall pattern of stability and improvement in a variety of biomarker, strength, function, and Quality of Life assessments in young men with advanced DMD progression. Participants who entered the CL-101 Phase 1b study with greater muscle mass tended to exhibit the best performances and responses. These observations provide continued support for development of forzapadin in DMD and other severe muscle diseases.

REFERENCES

- Dumont N, et al. *Nature Medicine* 2015. 21:1455-1463
- Farwell W et al. A Phase 1a/b study of SAT-3247 in healthy volunteers and adult participants with Duchenne muscular dystrophy. MDA Clinical & Scientific Conference (Orlando, FL), March 8-11. Presentation 394-O.
- Farwell W et al. A Phase 1a/b study of SAT-3247 in healthy volunteers and adult participants with Duchenne muscular dystrophy. AAN Annual Scientific Sessions (Chicago, IL), April 18-22. Presentation 19-003.
- Farwell W et al. LT-001 a long-term follow-up study for the participants that completed the SAT-3247-CL-101 study: 6-month update. International Congress on Neuromuscular Disorders (Florence, Italy), July 7-11, 2026.
- Naarding KJ, et al. *Neurology* 2021. 97:e1737-e1742.
- Pane M et al. *J Neuromuscular Disorders* 2023. 10: 567-574.