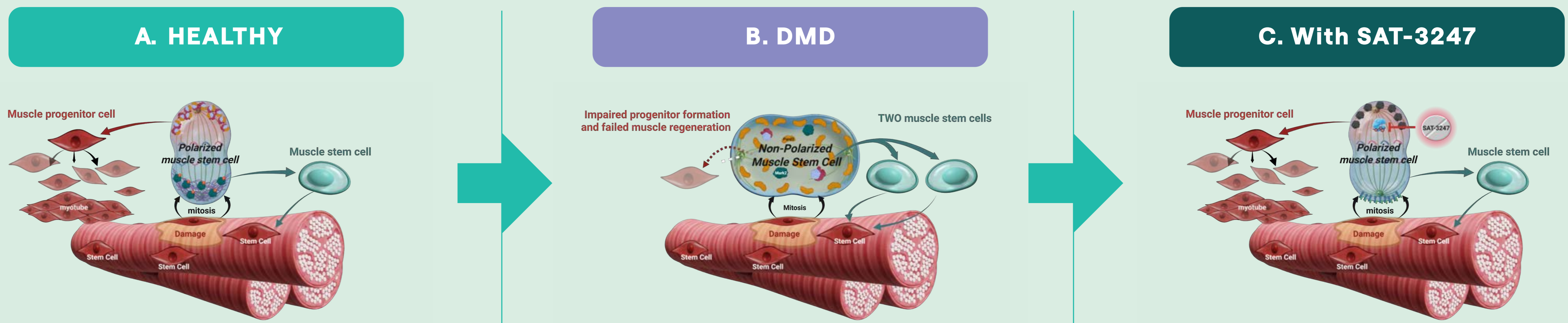


INTRODUCTION

- In Duchenne muscular dystrophy (DMD), muscle damage outpaces repair resulting in progressive muscle loss. This is due in part to variants in the *DMD* gene, absence (or near absence) of dystrophin protein, and impaired muscle stem cell division and muscle progenitor formation.
- Seminal research established dystrophin as a key signaling protein in muscle stem cells¹, in addition to its well-known role as a structural protein in muscle fibers. Since then, muscle stem cell dysfunction has become increasingly recognized as playing a key role in DMD and other muscular dystrophies²⁻⁴.
- SAT-3247 is an investigational, 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 disorders (Figure 1).
- Safety and efficacy data from a Phase 1a/b study of SAT-3247 (NCT06565208) have been described previously, as has early safety and efficacy data from the ongoing Phase 2 TRAILHEAD study (NCT06867107) in participants who continued from the Phase 1b study^{5,6}.
 - These early Phase 2 data continue to demonstrate an unremarkable safety profile for SAT-3247
 - Additionally, these data continue to show stability 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 and upper-limb strength and physical function after 5-months of total SAT-3247 exposure within the TRAILHEAD study.

Figure 1: Mechanism of SAT-3247 action on muscle stem cells, muscle repair, and regeneration. In damaged healthy muscle, stem cells become activated, polarized, and divide asymmetrically to form muscle progenitors for repair and regeneration and stem cells for self-renewal (A). In DMD, muscle stem cell polarity, division, progenitor formation and regeneration are impaired due to lack of dystrophin (B). Inhibition of adaptor-associated kinase-1 (AAK1) by SAT-3247 is designed to re-establish muscle stem cell polarity, progenitor formation, and regeneration in DMD muscle (C).



METHODS

- TRAILHEAD is an open-label, Phase 2 study evaluating the long-term safety, tolerability, and potential efficacy of orally-administered SAT-3247.
- 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 variant in the *DMD* gene.
- Participants 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 the Phase 1b study CL-101 (NCT06565208) who are receiving SAT-3247 for an additional 11 months.
 - Group B:** treatment naïve participants who will receive SAT-3247 for up to 12 months.
- Primary safety objective is to evaluate long-term safety and tolerability of SAT-3247 in participants with DMD.
- Primary efficacy objective is to determine the effect of SAT-3247 on MRI intramuscular fat-fraction following 12 months of treatment.

RESULTS

- TRAILHEAD Group A baseline characteristics and demographics have been previously described^{5,6}.
- The safety and tolerability profile following 6-months of SAT-3247 dosing overall was unremarkable and consistent with what was previously reported in the CL-101 Phase 1b study (Table 1).
- Reductions in biceps brachii fat-fraction of 3.7% were observed from baseline through 5 months of SAT-3247 dosing in TRAILHEAD, assessed via MRI (Figure 2).
- A 5.47 J/kg improvement in total effort achieved during most physically intense (99th percentile) of daily movements was observed, as assessed via SYSNAV[™] wrist and ankle sensors (Figure 3).
- Consistent with previous observations^{5,6} handgrip (Figure 4), elbow, and shoulder strength (Figure 5) continue to remain stable in Group A participants through Day 104 in TRAILHEAD.
 - Trends of functional improvement in some measures were noted in those participants who entered CL-101 with higher baseline muscle mass⁵, despite a dosing pause of ~7-11 months that occurred between studies.
- Respiratory capacity remained generally stable from the CL-101 study baseline to TRAILHEAD month 6 (Figure 6).

Table 1: SAT-3247 Safety and Tolerability: Consistent with previously reported results^{5,6}, no new safety signals were observed with long-term administration of SAT-3247. 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.

| 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 |

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 4: Grip Strength: Consistent with and extending upon previous reports^{5,6} bilateral improvements in handgrip strength observed in the CL-101 study remained stable through Day 140 of TRAILHEAD, despite a treatment pause of 7-11 months between studies.

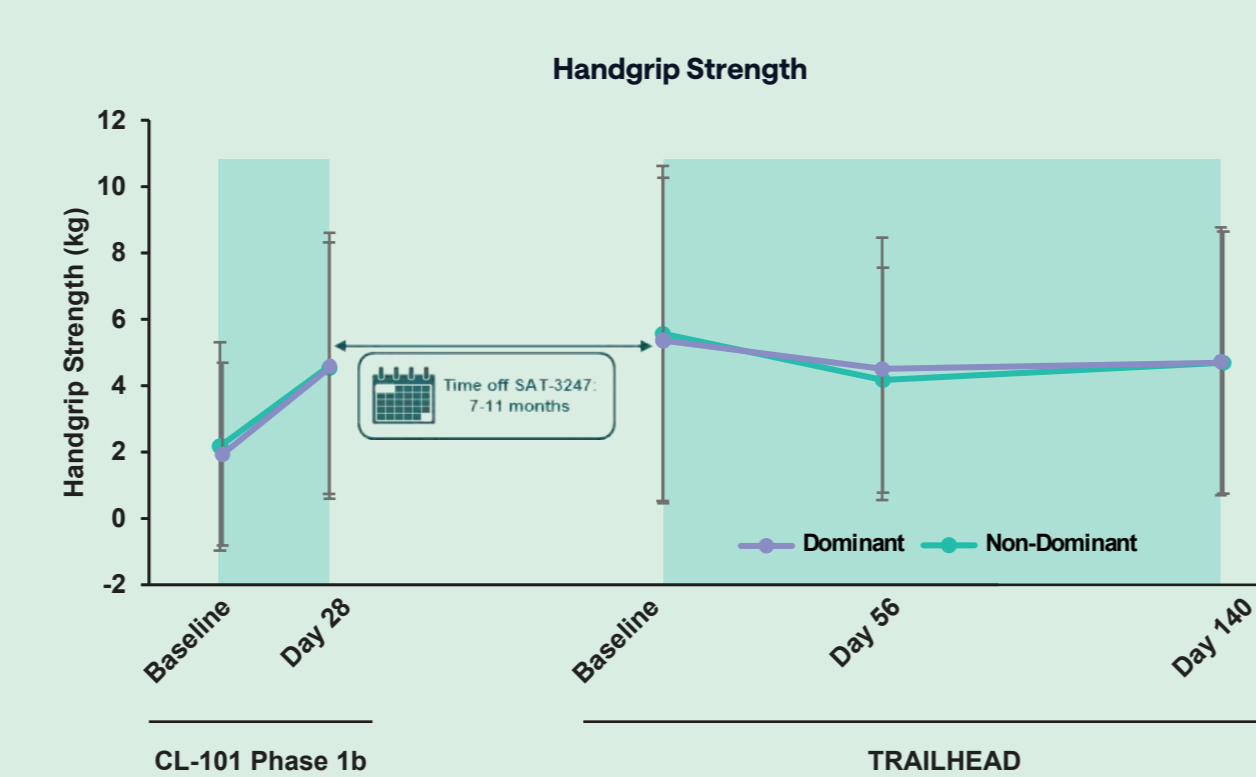


Figure 2: MRI: A 3.7% mean improvement in biceps brachii fat-fraction, assessed via MRI (Dixon chemical shift methodology) was observed during 5-months of SAT-3247 dosing in TRAILHEAD, with all 4 individual participants exhibiting reductions (diamonds and table inset). In contrast, fat-fraction increases of 5.9% per year are reported in elbow flexor muscles (which include biceps brachii) among non-ambulant boys⁷. SD = standard deviation.

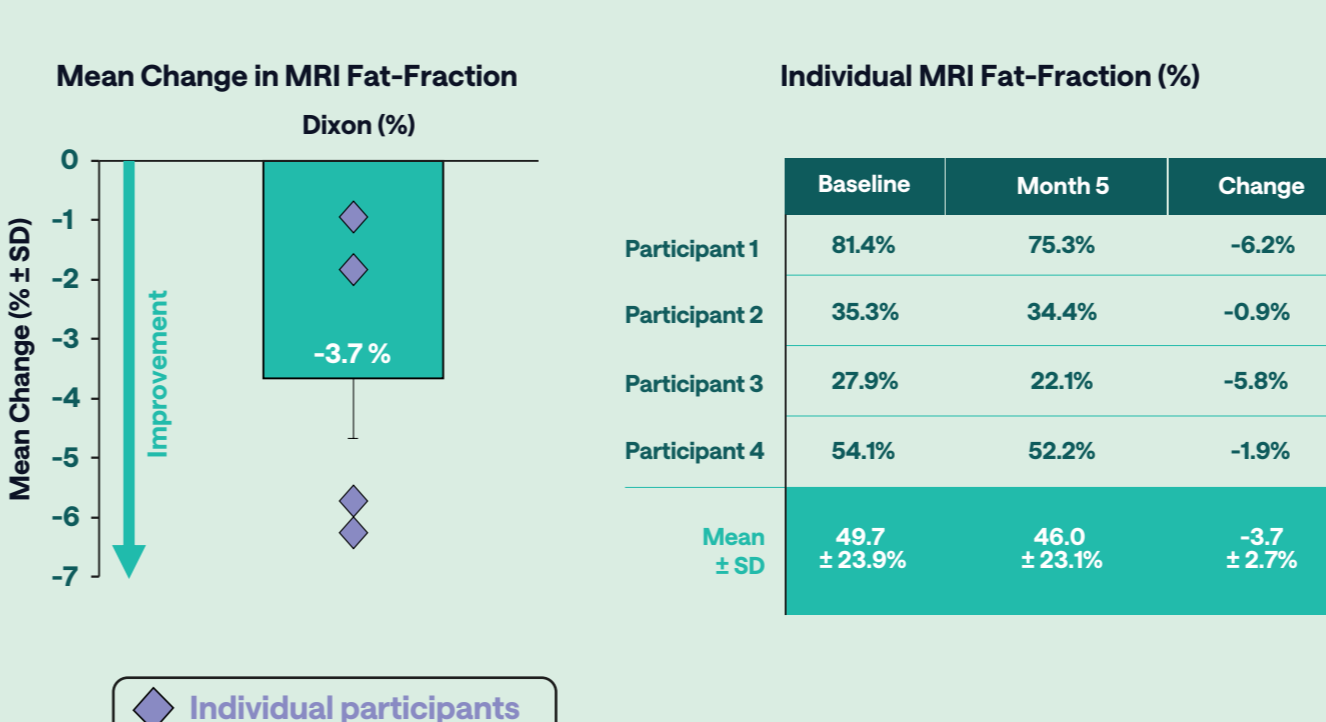


Figure 3: SYSNAV[™]: Daily activities of TRAILHEAD Group A participants were captured via SYSNAV[™] wrist and ankle sensors. Total combined effort (J/kg) of their 99th percentile of intense daily activities (TE99C) were summated and indexed against normative data. Group A participants exhibited a mean improvement of 5.47 J/kg (representing a 34% change) in total combined effort of captured activities. Individual total effort scores ¹ at CL-101 baseline and TRAILHEAD month 6 are provided below.

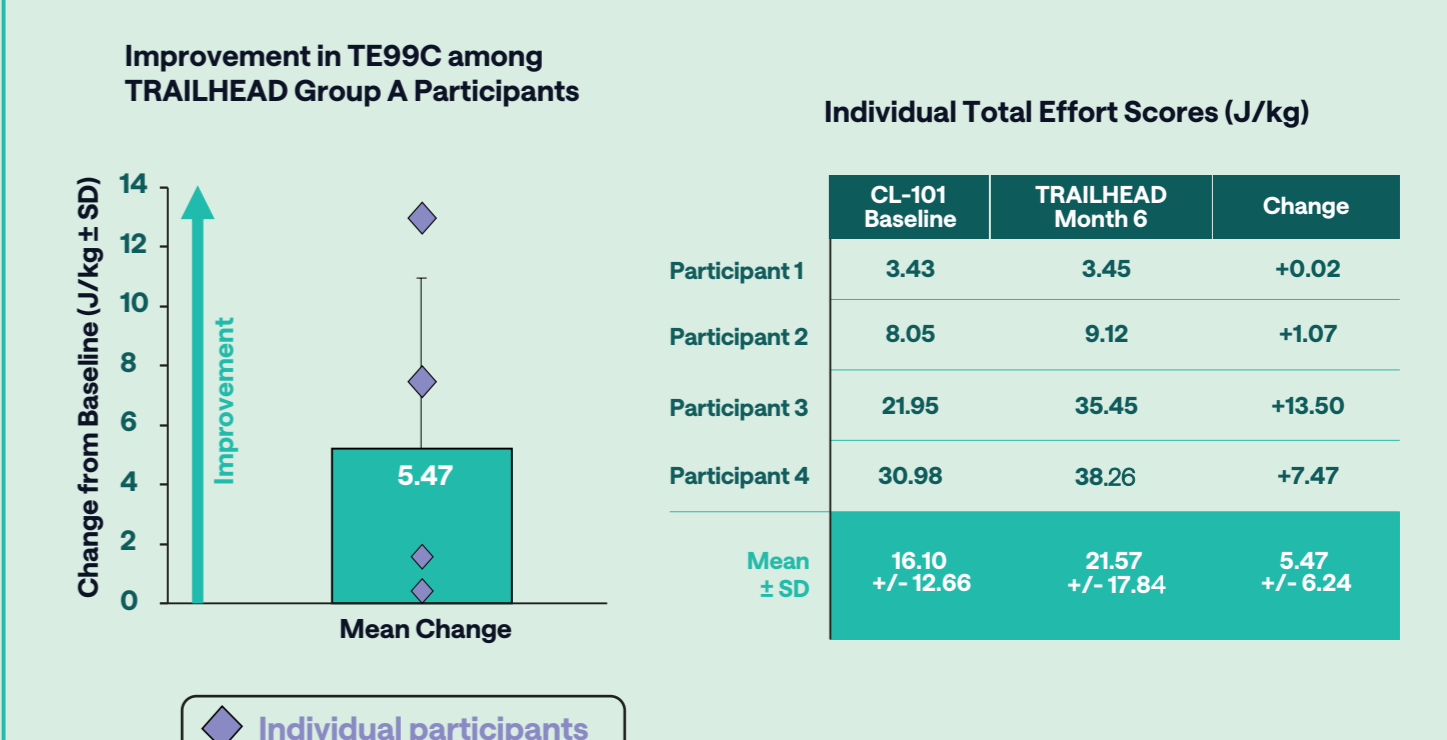


Figure 5: Elbow and Shoulder Strength: Extending upon previous reports^{5,6} elbow (left) and shoulder (right) strength continued to remain stable over 5-months of SAT-3247 dosing in TRAILHEAD, with trends of improvement observed among participants with greater muscle mass⁵.

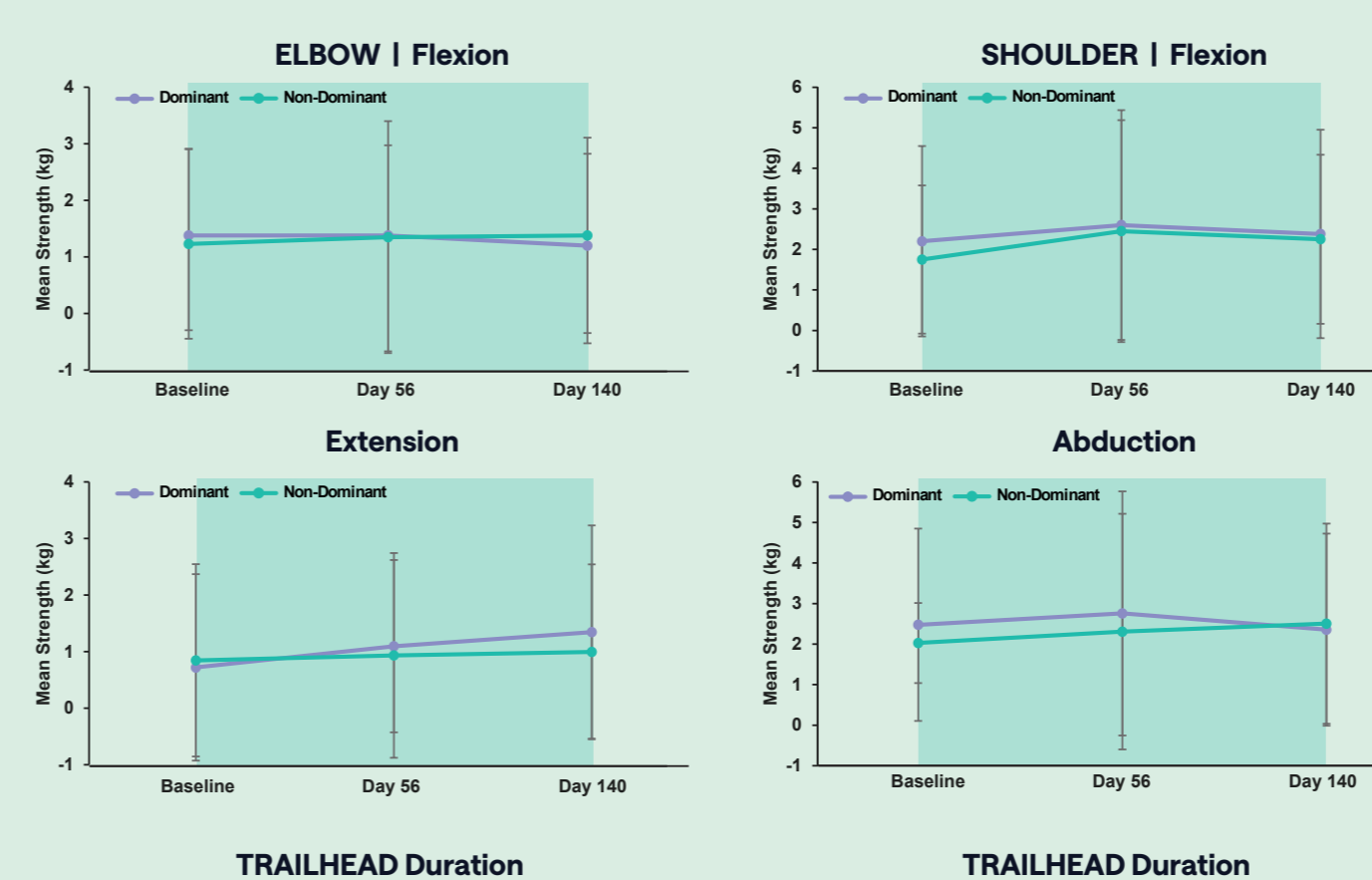
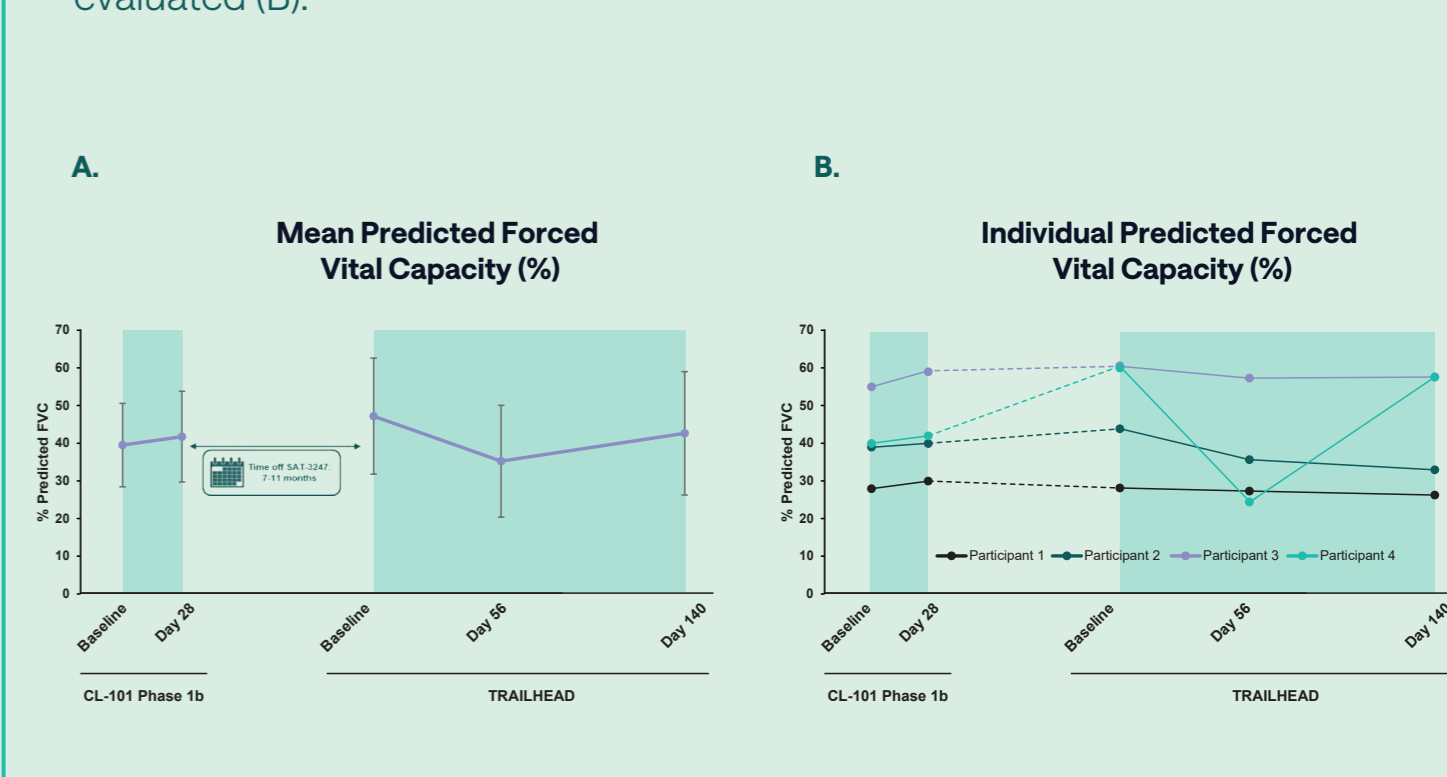


Figure 6: Respiratory Capacity: Mean respiratory capacity (predicted forced-vital capacity (FVC)) after 28 days of SAT-3247 dosing in CL-101 remained generally stable over 5 months of dosing in TRAILHEAD (A). Transient variability was observed in one of the four participants evaluated (B).



CONCLUSIONS & NEXT STEPS

- Safety & Tolerability:** Consistent with previous reports^{5,6}, no new safety signals were observed with long-term administration of SAT-3247. 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.
- MR Imaging:** Biceps brachii fat-fraction declined over 5 months of SAT-3247 dosing in all four participants with a mean reduction of 3.7%, suggesting improved muscle composition. In contrast, annual fat-fraction increases of 5.9% are reported in elbow flexor muscles among non-ambulant boys⁷.
- Physical Function:** TE99C, a measure of total effort at the 99th percentile of the most intense real-world daily physical activities, increased 34% from baseline to month 6 with increases observed in all four participants.
- Muscle Strength:** Overall, participants continued to maintain hand, elbow, and shoulder strength through 5 months of SAT-3247 dosing and for up to 17 months overall duration. In CL-101, signs of improvement were observed in participants who entered with greater muscle mass^{5,6} and the initial improvement in bilateral grip strength was maintained in TRAILHEAD. Importantly, all participants entered the CL-101 study receiving corticosteroid therapy and maintained this regimen throughout TRAILHEAD.
- Respiratory Capacity:** Mean predicted %FVC continues to be maintained in TRAILHEAD. Typically, DMD patients in this age range experience a ~5% annual decline.
- Taken Together:** These results and others to be discussed on **8 July at 4:05pm (ST01)** provide continued support for development of SAT-3247 in DMD and potentially other severe muscle disorders.

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