satellos

A Phase 1a/b study of SAT-3247 in healthy volunteers and adult participants with Duchenne muscular dystrophy

POSTER 394-0

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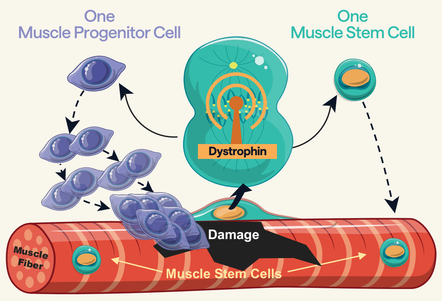
BACKGROUND

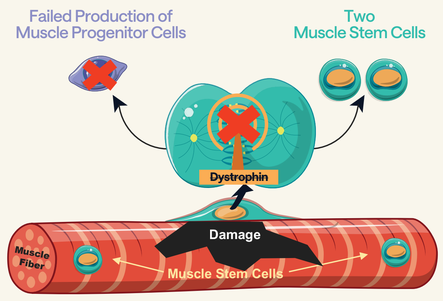
- Seminal research has established dystrophin as a key signaling protein in satellite cells (Dumont N, et al. *Nature Medicine*. (2015) 21:1455-1463), in addition to its well-known role as a structural protein in muscle fibers.
- In healthy skeletal muscle with normal dystrophin expression, stem cells 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 to increase asymmetric stem cell division, muscle progenitor formation, and muscle fiber regeneration which is impaired in DMD due to lack of dystrophin (**Figure 1c**).
- Safety and efficacy data from a Phase 1a/b study of SAT-3247 (NCT06565208) have been described previously. Here, we present new, preliminary analyses of plasma proteomic biomarkers in DMD participants who received SAT-3247 in the Phase 1b study.

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



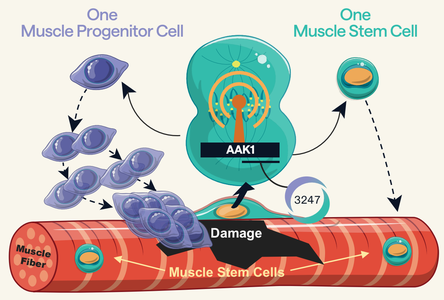
Asymmetric division with Dystrophin Signal
1 progenitor + 1 stem cell

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



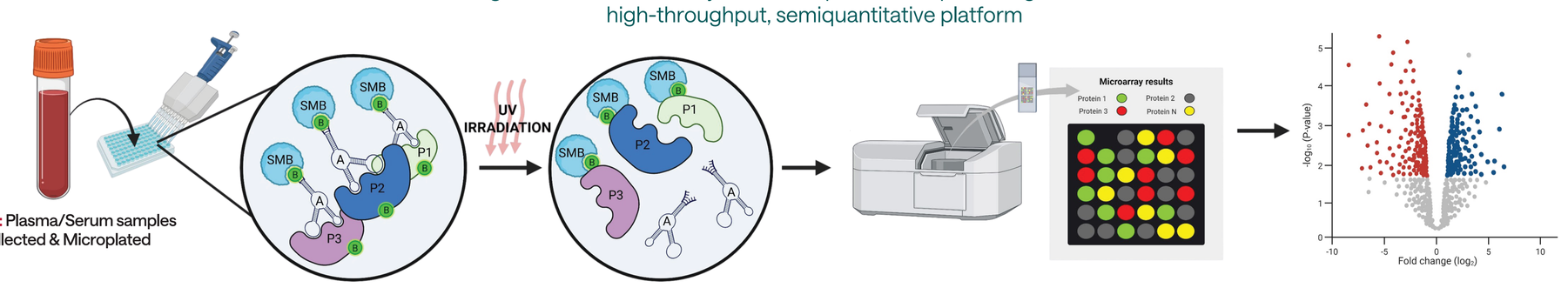
Asymmetric division with AAK1 inhibition
1 progenitor + 1 stem cell

SAT-3247-CL-101 (NCT06565208)

Methods

- SAT-3247-CL-101 was a first-in-human, combined Phase 1a study of orally administered SAT-3247 in healthy volunteers, and Phase 1b study, which examined 28-days of SAT-3247 dosing in five adults with DMD.
- While primary and secondary endpoints examined incidence and severity of treatment-emergent adverse events (TEAEs) and pharmacokinetics in all participants, exploratory endpoints were evaluated in DMD participants to assess muscle strength, respiratory function, and exploratory biomarkers of SAT-3247 mechanism of action and response.
- Plasma samples obtained from DMD participants at baseline (pre-dose) and after 15 days (post-dose) of SAT-3247 administration underwent proteomic analysis via SomaScan®. The Somascan® platform is a multiplexed, high-throughput, and semiquantitative proteomic tool that employs single-stranded DNA aptimers to capture and measure concentrations of ~11,000 proteins in biologic samples (**Figure 2**).

Figure 2: Proteomic analysis of DMD plasma samples using SomaScan® high-throughput, semiquantitative platform



Results // Demographics, safety and tolerability of the overall SAT-3247-CL-101 study have been previously described.

Safety and Pharmacokinetics

- SAT-3247 demonstrated a favorable safety profile with predictable, dose-proportional pharmacokinetics in healthy volunteers and adults with DMD.
- SAT-3247 exposure levels were similar between healthy volunteers and adults with DMD and met desired criteria for translation from preclinical data.

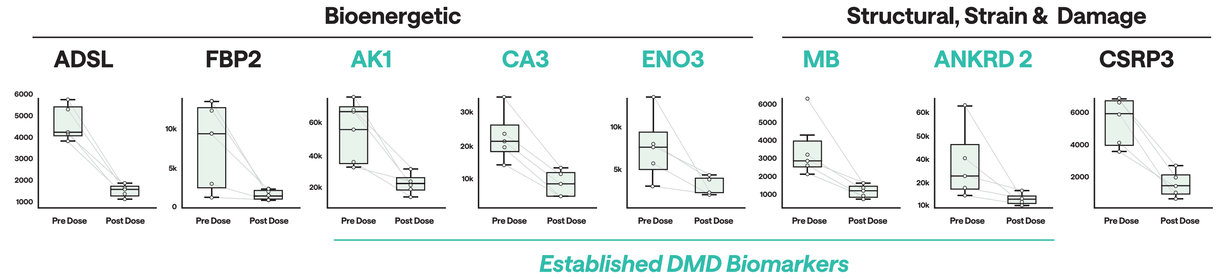
Functional Changes in DMD Participants after 28 days of SAT-3247 Administration

- A 5.8% mean increase in predicted forced vital capacity (FVC) was observed.
- Mean increases in grip strength of 118.6% and 97.9% in dominant and non-dominant hands, respectively, were observed.
- Improvements (in 3 out of 5 DMD participants) exceeded those observed in natural history cohorts of ambulatory and non-ambulatory patients treated with glucocorticoids.
- Improvements in grip strength correlated with Day 1 C_{max} of SAT-3247 and baseline serum creatinine, a surrogate marker of muscle mass.

Plasma Proteomics in DMD Participants

- Analysis of the full ~11,000 protein panel is ongoing. Numerous proteins were either increased or decreased by a biologically meaningful magnitude following 15 days of SAT-3247 administration
- Proteins related to muscle bioenergetics and markers of muscle structure, strain and damage were observed after 15 days of SAT-3247 administration (**Figure 3**).
- Of note, reductions in five established biomarkers of DMD (AK1, CA3, ENO3, MB, and ANKRD2) were observed in all five DMD participants evaluated, with the magnitude of changes being remarkably consistent

Figure 3: Plasma protein biomarkers of DMD decreased following 15 days of SAT-3247 administration



Abbreviations: ADSL=andenylosucinate lyase; AK1= adenylate kinase isoenzyme 1; ANKRD2= ankryn repeat domain-containing protein 2; ENO3=beta-enolase; CA3=carbonic anhydrase 3; CSRP3=cysteine and glycine-rich protein 3; FBP2=fructose-1,6-bisphosphatase isonezyme 2; MB=myoglobin

CONCLUSIONS AND NEXT STEPS

- SAT-3247 demonstrated a favorable safety and tolerability profile with predictable, dose-proportional pharmacokinetics in healthy volunteers and adults with DMD.
- Approximately two-fold improvements in both dominant and non-dominant hand grip strength were observed after 28 days of SAT-3247 administration in adults with DMD. This exceeds changes observed with glucocorticoid therapy in natural history cohorts.
- Improvements in grip strength were correlated with peak SAT-3247 concentrations in plasma and baseline creatinine (a surrogate marker for muscle mass).
- The 5.8% increase in predicted FVC appears to be in contrast to a 5% annual decrease in FVC observed in similarly-aged people with DMD from natural history cohorts.
- Preliminary plasma proteomic analysis demonstrated consistent reductions in well-recognized DMD biomarkers related to bioenergetics, mechanical stress, and muscle damage after only two weeks of SAT-3247 administration: mean levels were reduced in a consistent manner across all five DMD biomarkers, and levels of all biomarkers were reduced in all five DMD participants evaluated. The relationship of these (and other) changes to functional and clinical benefit is an area for future evaluation.
- Together, the observed reduction in biomarkers of DMD at 15 days, as well as improvements in grip strength and respiratory function at 28 days, support further development in DMD (NCT0687107, NCT07287189) and potentially other disorders characterized by muscle wasting.