

INTRODUCTION

- While the underlying genetic causes of facioscapulohumeral muscular dystrophy (FSHD) differ from those of other muscular dystrophies, shared manifestations include muscle loss, weakness, and disability caused in large part by impaired muscle regeneration.
- Aberrant expression of the *DUX4* transcription factor and downstream repression of *PAX7* result in poor activation and differentiation of muscle stem cells¹⁻³. Chronic inflammation and oxidative stress may also contribute to a toxic milieu to further impair muscle stem cell function (**Figure 1**).
 - Together, these defects may reduce myogenic potential and regenerative capacity, thus limiting effective muscle repair following damage.
 - Ongoing muscle degeneration with impaired muscle stem cell activity likely exacerbates progressive loss of muscle mass⁴ and replacement with fat and fibrosis.

Figure 1: Aberrant *DUX4* expression, downstream *PAX7* repression, chronic inflammation, and oxidative stress may contribute to muscle stem cell dysfunction, impaired muscle regeneration, and progressive muscle weakness in FSHD¹⁻³.

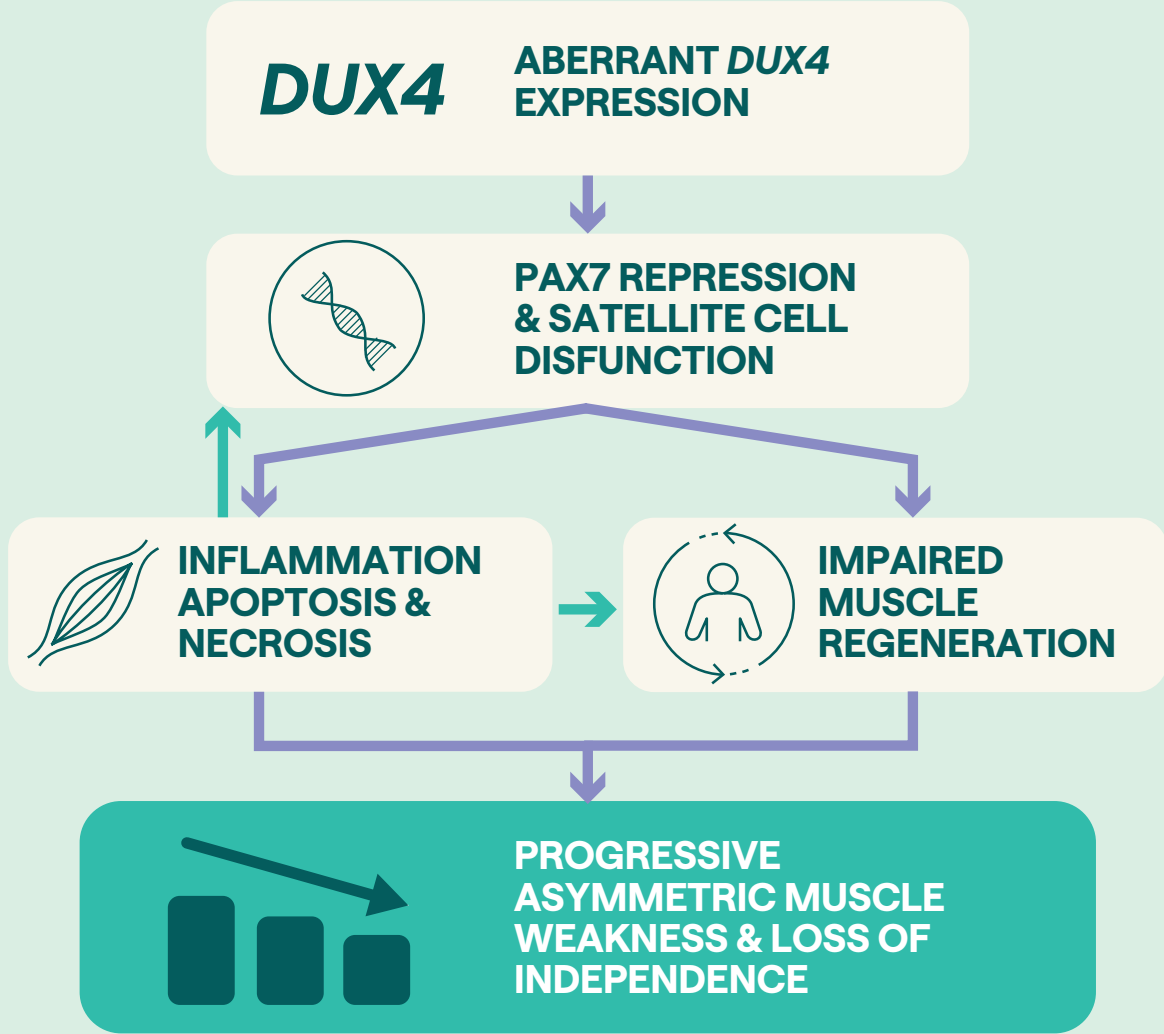
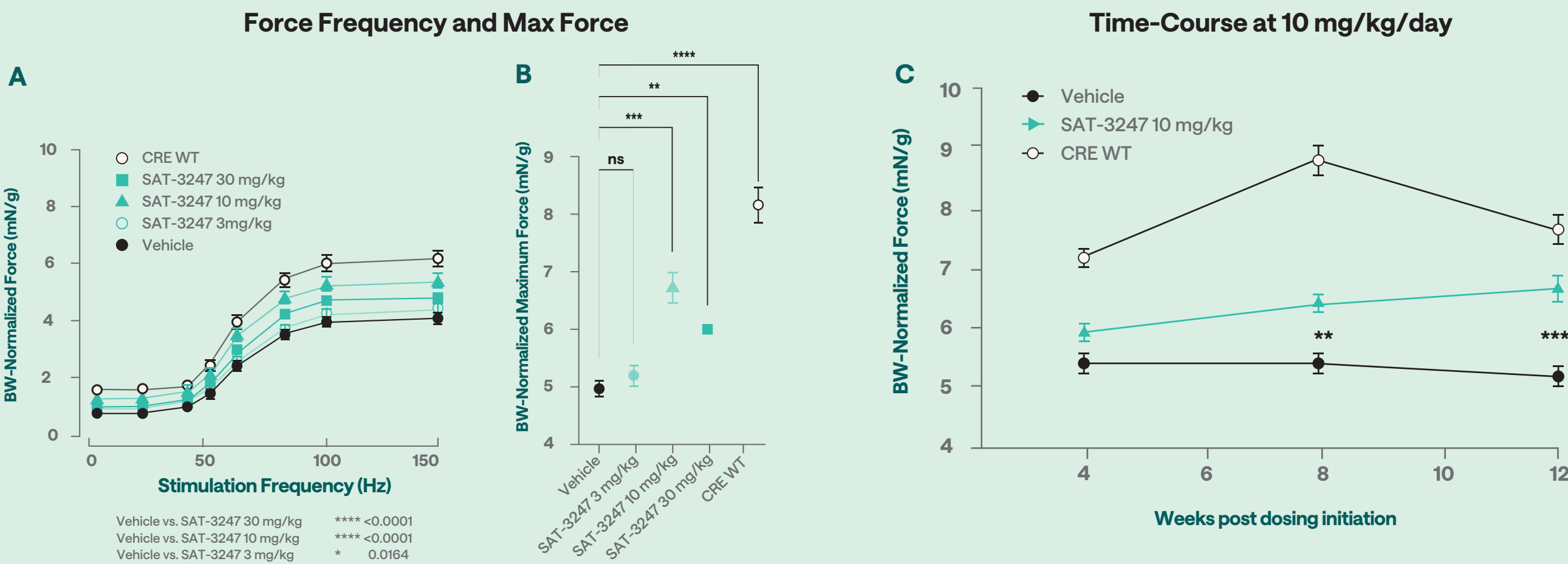


Figure 3: Dose-responsiveness of forzapadin (3-30 mg/kg/day) on gastrocnemius isometric muscle force-stimulation frequency relationships (A), maximum force production (B), and time course of *in situ* muscle force during 12 weeks of 10 mg/kg/day forzapadin administration to FLExDUX4.CRE mice (C). Figures represent combined assessments of male and female mice (n = 14-18/group). ns= not significant, **p = <0.01, *** p = <0.001, **** p = <0.0001.



- Forzapadin (SAT-3247) is an investigational, orally administered small molecule inhibitor of adaptor-associated kinase 1 (AAK1) designed to re-establish polarity and enhance intrinsic regenerative capacity within muscle stem cells, independent of *DUX4* expression (**Figure 2**). Forzapadin improved muscle force production in a FLExDUX4.CRE mouse model of FSHD (**Figure 3**).
- Therapeutic strategies that target muscle stem cell signaling pathways and aim to enhance polarity and regeneration represent a promising approach for muscular dystrophies.
- Preclinical results described here along with emerging data in DMD demonstrating a favorable safety and tolerability profile, as well as reduced MRI muscle fat fraction (**Reference 5 and WMS poster 2.75.P**) support clinical evaluation of forzapadin as a potential *DUX4*-independent therapeutic approach in FSHD.
- Here, we describe the rationale and design of a global Phase 2 study of forzapadin in adult participants living with FSHD.

Figure 2: Mechanism of forzapadin (SAT-3247) action to inhibit adaptor-associated protein kinase 1 (AAK1) and re-establish polarity via Numb/Notch orientation in muscle stem cells. This is designed to enable muscle repair, enhance regeneration, and maintain the muscle stem cell pool for future repair and regeneration.

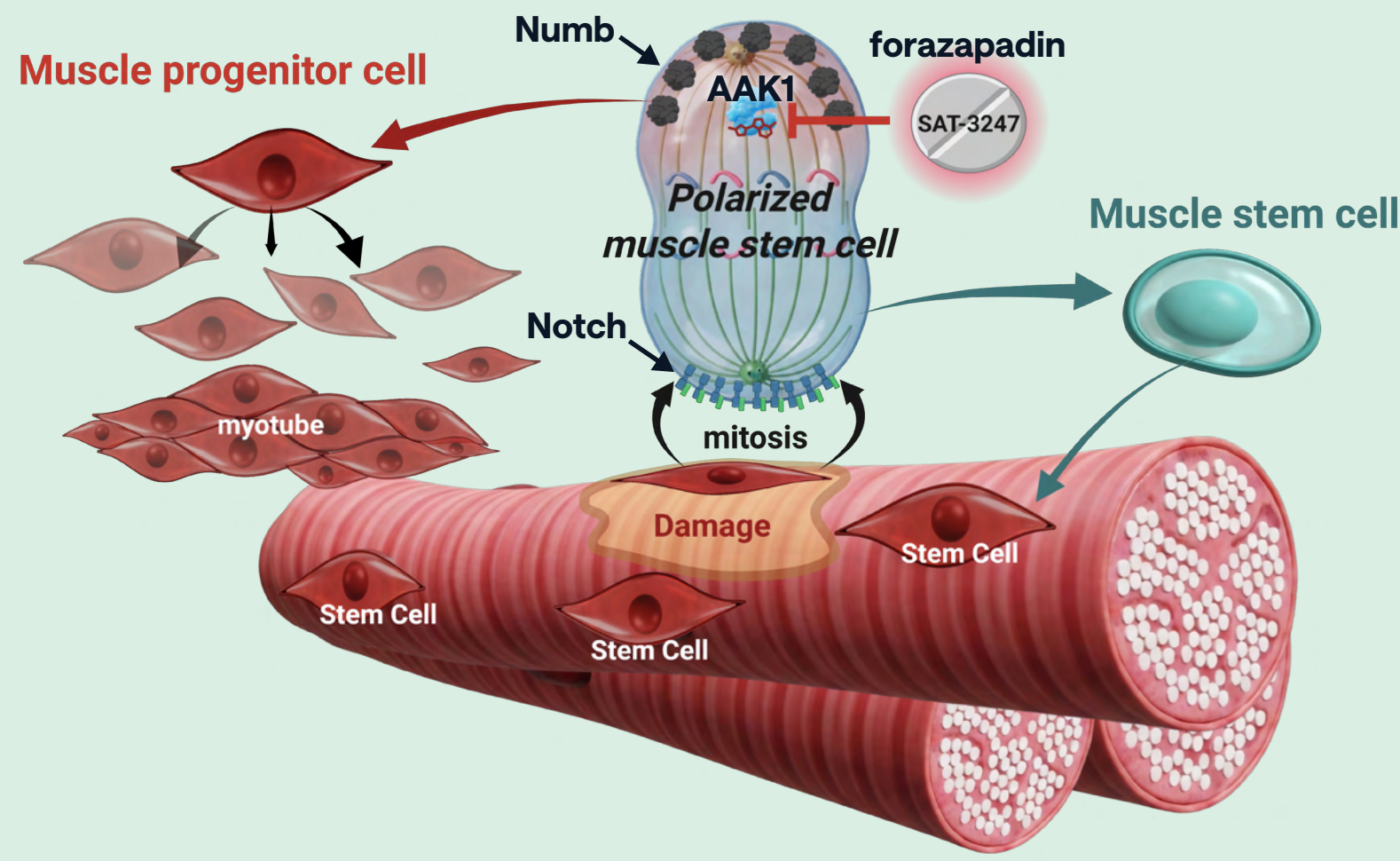
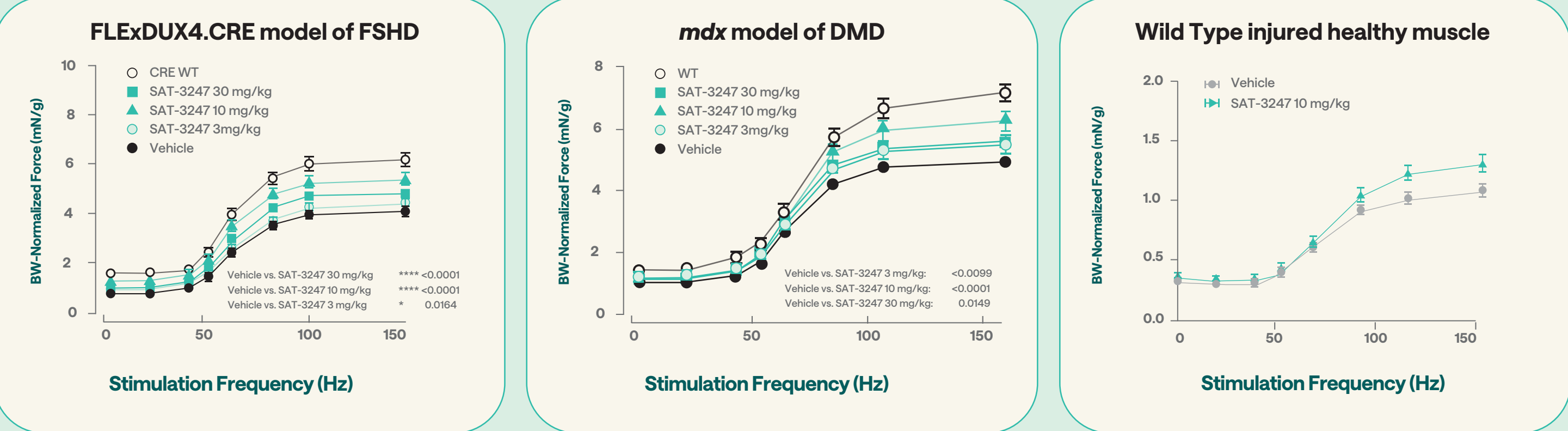


Figure 4: Increased muscle force observed in the FLExDUX4.CRE mouse model of FSHD (left) mirrored increases observed in the Satellos preclinical DMD program (center) with forzapadin (SAT-3247), as well as an injured muscle model in healthy wild-type mice (right).



METHODS

- SAT-3247-CL-211 is a planned Phase 2, randomized, double-blind, placebo-controlled study designed to evaluate safety, tolerability, pharmacokinetics and potential efficacy of orally administered forzapadin (SAT-3247) in adult participants with FSHD.
- SAT-3247-CL-211 will enroll up to 51 male and female participants aged ≥18 years with a definitive diagnosis of FSHD type 1 or type 2, confirmed by clinical findings and prior genetic testing. Key inclusion and exclusion criteria are provided in **Table 1**.

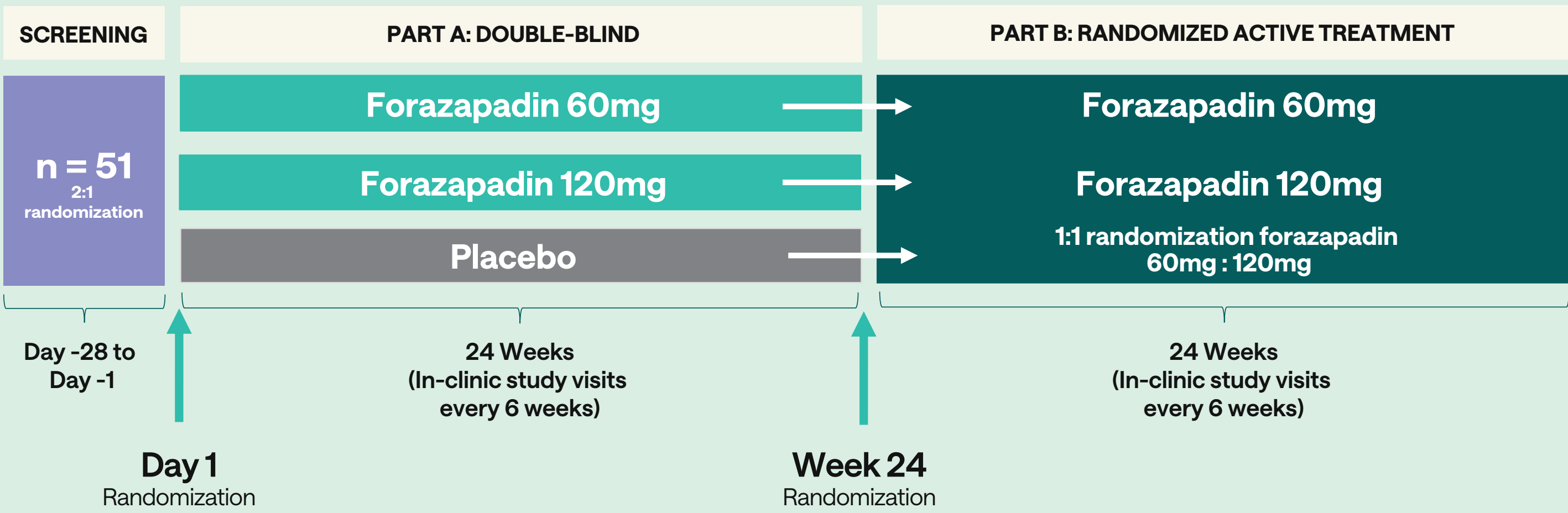
- This study is being conducted in two parts:**
 - Part A:** Participants will be randomized to receive placebo or forzapadin at doses of 60 or 120 mg once daily using a 5 days on/2 days off (weekday) dosing regimen through Week 24.
 - Part B:** Participants who received forzapadin in Part A will continue at their assigned dose for an additional 24 weeks. Participants who received placebo in Part A will be re-randomized to receive forzapadin at either 60 or 120 mg once daily through Week 48, using the same dosing regimen as in Part A.
- The primary safety objective is to evaluate safety and tolerability as incidence, temporal profile, and severity of treatment-emergent adverse events (TEAEs).
- The primary efficacy objective is to evaluate the effect of forzapadin on muscle force at the end of Parts A (Week 24) and B (Week 48). A study schematic is provided in **Figure 5**.

Tables 1: Key inclusion and exclusion criteria

Key* Inclusion Criteria	Key* Exclusion Criteria
- Definitive diagnosis of FSHD1 or FSHD2, confirmed by clinical findings and prior genetic testing - Age ≥18 years - Presence of upper limb weakness - Presence of weakness in at least one lower limb muscle - Ambulatory at screening (≥10m without assistance) - Stable doses of supplements and herbal remedies that may impact muscle strength - Stable doses of prescription medications	- Expected loss of ambulation within ≤12 months - Medical conditions (other than FSHD) impacting ambulation or functional assessments - Medical conditions that adversely affect participant safety, reduce likelihood treatment course or follow-up would be completed, or impair study results - Recent history of drug and/or alcohol abuse - Participants for whom MRI is contraindicated - Surgeries that might affect absorption of medicines - Treatment with another investigational drug or biological agent within 30 days or 5 half-lives (whichever is longer) of screening - Treatment with glucagon-like peptide-1 (GLP-1) or dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor antagonists within 3 months prior to screening or, anticipated use during the study - Received forzapadin (SAT-3247) in another study

*Non-exhaustive list of criteria; MRI = magnetic resonance imaging

Figure 5: SAT-3247-CL-211 Study Design



CONCLUSIONS & NEXT STEPS

- While the underlying genetic causes of FSHD differ from those of other muscular dystrophies, shared manifestations include muscle loss and replacement by fat and fibrosis, weakness, and physical disability caused in large part by impaired muscle regeneration.
- Forzapadin (SAT-3247) is an investigational, orally administered small molecule inhibitor of adaptor-associated kinase 1 (AAK1) designed to re-establish polarity and enhance intrinsic regenerative capacity of muscle stem cells, independent of *DUX4* expression and downstream effects on *PAX7*.
 - Preclinical studies in a rodent model of FSHD demonstrated that forzapadin improved muscle force production, consistent with observations of forzapadin effects in preclinical models of DMD and injured healthy muscle in wild-type mice.
 - Emerging clinical trial data in participants with DMD demonstrate a favorable safety and tolerability profile for forzapadin along with improvements relevant to FSHD, including reduced MRI muscle fat fraction and stabilization of muscle strength and physical function.

- AAK1 inhibition by forzapadin may enhance an alternative regenerative pathway, thereby increasing the percentage of activated muscle stem cells undergoing asymmetric division and, ultimately, promoting effective muscle regeneration.
- SAT-3247-CL-211 is a planned Phase 2, randomized, double-blind, placebo-controlled study to evaluate safety, tolerability, pharmacokinetics and potential efficacy of orally administered forzapadin in adult male and female participants with FSHD types 1 and 2.
- There is considerable unmet medical need in FSHD, with no disease-modifying therapies currently approved. In addition to genetic approaches, novel therapeutic strategies such as targeting muscle regeneration have the potential to provide meaningful clinical impact for those living with FSHD

REFERENCES

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