muSRK-015 Improves Muscle Function and Biomarkers in the FLExDUX4 Mouse Model of FSHD

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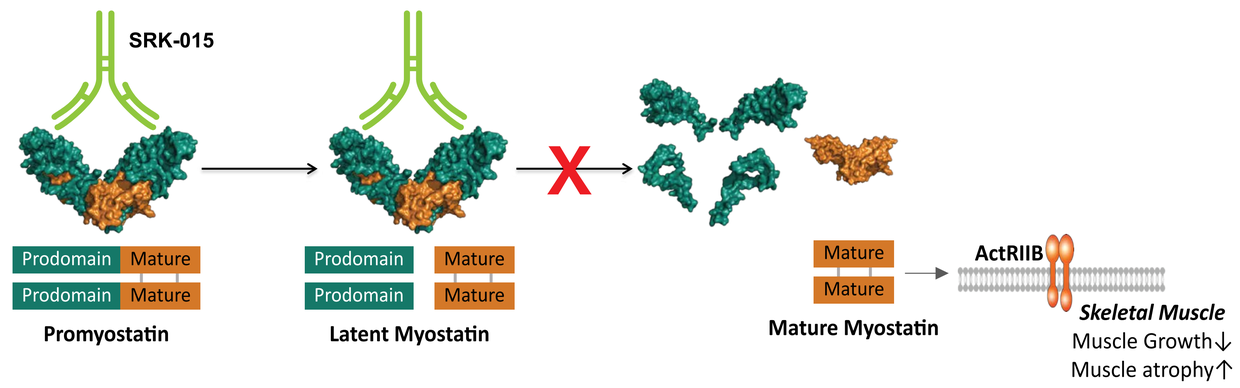
Background

Selective inhibition of myostatin activation with apitegromab (SRK-015) is a promising approach for building muscle and strength in neuromuscular disorders. Apitegromab has demonstrated positive results in a placebo-controlled phase III clinical trial in Spinal Muscular Atrophy (SMA) patients. We present data on two preclinical studies of muSRK-015 in a mouse model of facioscapulohumeral muscular dystrophy (FSHD). These data support a rationale to extend selective myostatin inhibition beyond SMA into additional neuromuscular disorders characterized by progressive muscle weakness, including FSHD.

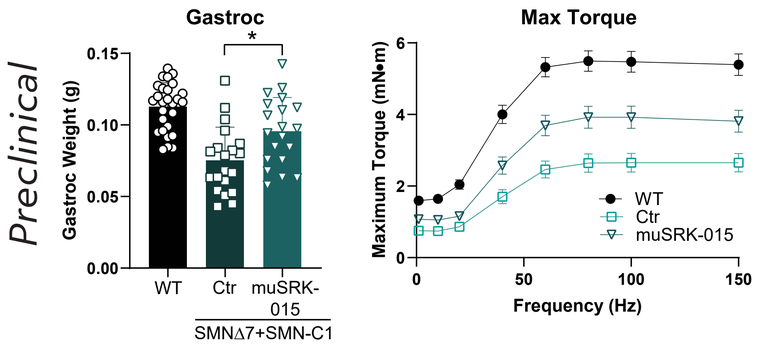
SRK-015 binds to pro- and latent myostatin to prevent activation and enable muscle growth



- SRK-015 binds to pro- and latent myostatin and blocks the conversion of the latent form to mature myostatin
- By inhibiting the release of mature myostatin, SRK-015 blocks the activity of mature myostatin and promotes muscle growth

SRK-015 enhances muscle strength and function in combination with SMN therapy in Spinal Muscular Atrophy

Preclinical



- In the SMNΔ7 mouse model, significant increases in muscle mass and strength were observed with muSRK-015 (a preclinical version of apitegromab) in combination with the SMN upregulator SMN-C1 over SMN-C1 alone treated animals
- These results translated to clinical efficacy as assessed with the HFMSE (Hammersmith Functional Motor Scale) in the phase II PoC clinical trial TOPAZ, and more recently in the phase III SAPPHIRE clinical trial

Clinical

TOPAZ

SAPPHIRE

MET PRIMARY ENDPOINT:

1.8 POINT IMPROVEMENT in HFMSE* vs. placebo (p=0.0192)

CONSISTENT clinically meaningful benefit across all age groups (2-21)

30% of apitegromab patients ACHIEVED ≥3 POINT IMPROVEMENT IN HFMSE†

Hypothesis

- Facioscapulohumeral muscular dystrophy (FSHD) results from aberrant and sporadic expression of DUX4 in myonuclei, ultimately leading to muscle fiber cell death
- The pattern of muscle fiber death is mosaic and poorly understood
- We hypothesized that muscle enhancement with SRK-015 may provide compensatory strength benefit by building the remaining, DUX4 negative, healthly muscle fibers

Study Design: Treatment with muSRK-015 in the FLExDUX4 model of FSHD

Study #1

Sex	Genotype	Treatment
Male	Wild Type	IgG Control
Male	FLExDUX4	IgG Control
Male	FLExDUX4	muSRK-015
Female	Wild Type	IgG Control
Female	FLExDUX4	IgG Control
Female	FLExDUX4	muSRK-015

Male and Female mice
8-10 weeks of age

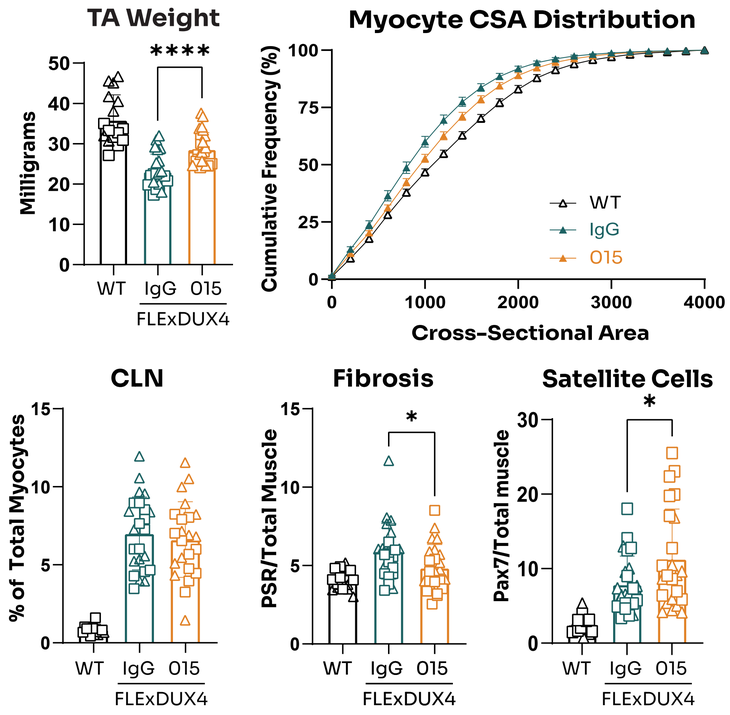
Study #2

Sex	Genotype	Treatment
Female	Wild Type	IgG Control
Female	FLExDUX4	IgG Control
Female	FLExDUX4	muSRK-015

Female mice aged
~8 months

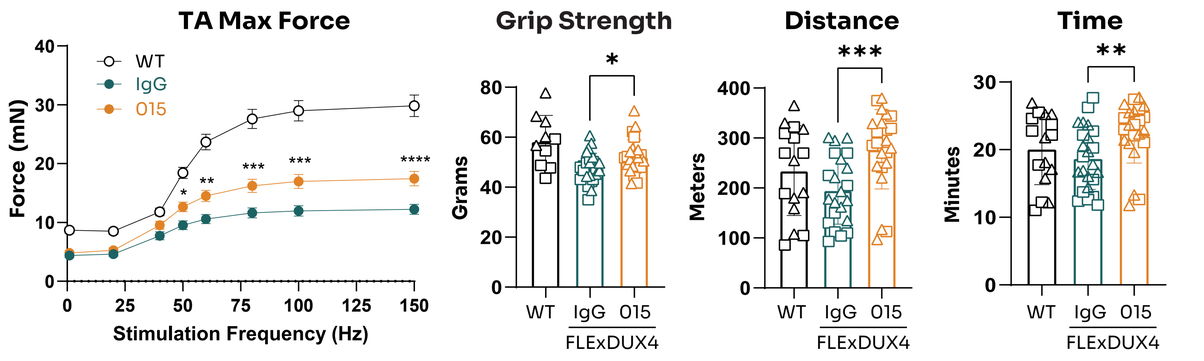
Multiple studies were run with muSRK-015 (015) in the FLExDUX4 mice. In study #1, younger mice with balanced M/F were dosed QW for 4 weeks before functional evaluation. In study #2, the same dosing regimen was used to study aged female FLExDUX4 mice. Pharmacokinetics of muSRK-015 and target engagement (not shown) were consistent with previous studies in mice.

muSRK-015 drives increases in muscle mass and myofiber size



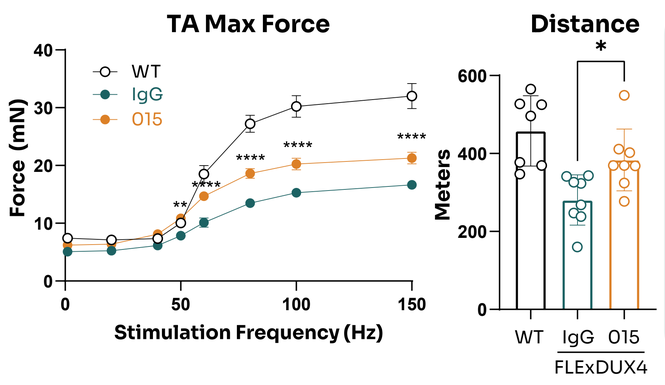
Study #1: Treatment with muSRK-015 significantly increased the size of the tibialis anterior muscle (TA), and cross-sectional area (CSA) of the myocytes, consistent with the mechanism of action of a myostatin inhibitor. No changes in centrally located myonuclei (CLN) were observed, and a mild reduction in muscle fibrosis (measured with picrosirius read, PSR) and increase in Pax7+ satellite cells were observed with muSRK-015 treatment. Data are mean ± SEM. *<p0.05, ****p<0.0001 by Tukey's T-test.

muSRK-015 treatment increases muscle strength and endurance



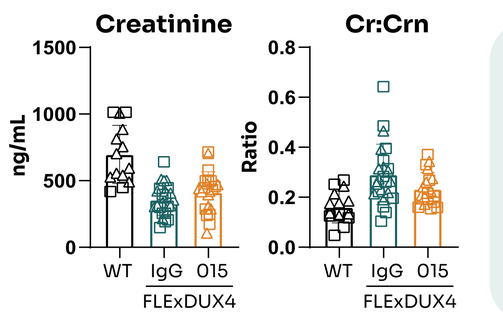
Study #1: Treatment with muSRK-015 resulted in increased in situ force in the tibialis anterior muscle (TA), forelimb grip strength, and distance run and time on treadmill in a forced treadmill test. Data are mean ± SEM. *<p0.05,**p<0.01, ***p<0.001, ****p<0.0001 by Tukey's T-test. Force frequency comparisons are by Two-Way ANOVA.

muSRK-015 increases strength and endurance in aged FSHD mice



Study #2: In 8-month old FLExDUX4 mice, treatment with muSRK-015 increased in situ force, and distance run and time on treadmill in a forced treadmill test. This study was previously presented at the FSHD IRC in 2025. Data are mean ± SEM. *<p0.05,**p<0.01, ****p<0.0001 by Tukey's T-test. Force frequency comparisons are by Two-Way ANOVA.

muSRK-015 increases exploratory biomarkers of muscle mass



Study #1: Creatinine (Crn) and creatine (Cr) are muscle metabolites which interconvert non-enzymatically. Creatinine correlates with muscle mass in related muscle disorders such as DMD. Creatinine is reduced in FLExDUX4 mice, and increases with muSRK-015 treatment. The ratio of Cr:Crn also tracks inversely with muscle and responds to muSRK-015.

Summary and Conclusions

- muSRK-015 treatment yielded increases in muscle mass and muscle fiber cross-sectional area
- These changes correlated with increased muscle force, forelimb grip strength, and treadmill endurance, which were consistent in male and female mice, and in aged mice
- Circulating biomarkers of skeletal muscle mass correlate with muSRK-015 treatment effect
- These data demonstrate that inhibition of myostatin activation with muSRK-015 increases muscle mass, strength and endurance in FLExDUX4 model, strengthening the bridge to clinical benefit in FSHD and supporting advancement of SRK-015 into the planned phase II FORGE clinical trial

FORGE

- Clinical Trial with apitegromab in FSHD patients (NCT07435129)
- Please Visit Poster #308T for more information

References and Acknowledgements

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