SRK-015 Builds Muscle Mass and Strength in Combination with Dystrophin Upregulation in a Mouse Model of DMD

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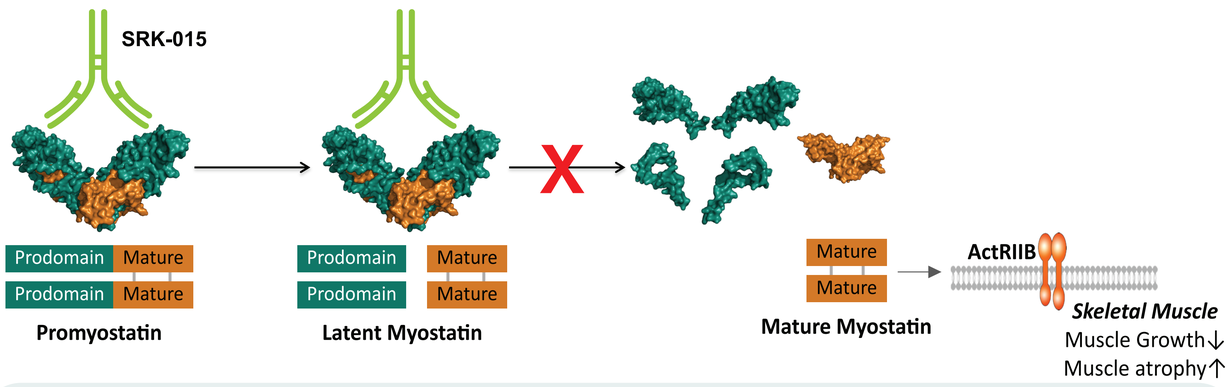
Background

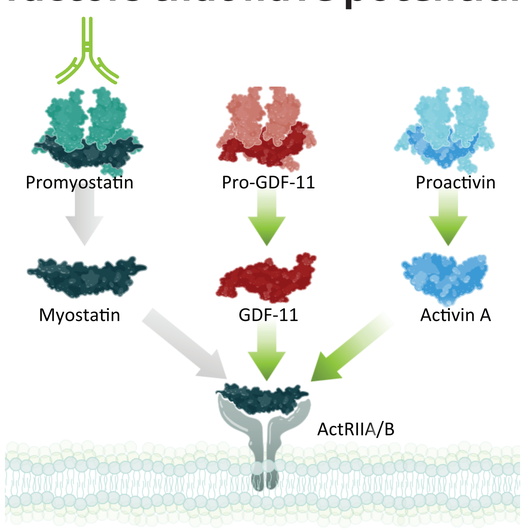
Selective inhibition of myostatin activation with apitegromab (SRK-015) is a promising approach for safely building skeletal muscle and strength in neuromuscular disorders. Apitegromab enhances strength in preclinical models of SMA in combination with SMN upregulator, and this result is now supported by data from multiple clinical trials. We here tested the capacity of apitegromab to build strength in dystrophic muscle with partial dystrophin restoration to model the potential of apitegromab in DMD and/or BMD.

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



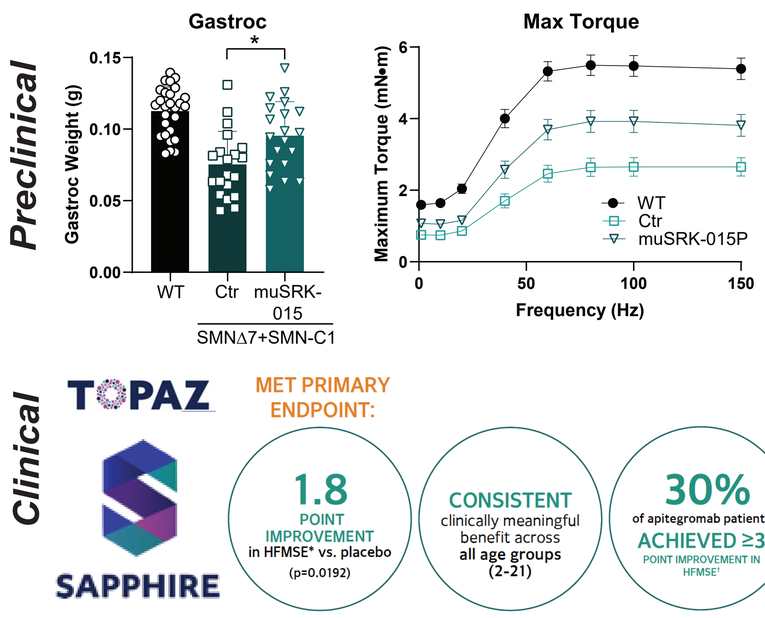
- SRK-015 binds to pro- and latent myostatin and blocks the conversion of the latent form to mature myostatin
- By inhibiting the release of mature myostatin, SRK-015 blocks the activity of mature myostatin and promotes muscle growth

SRK-015 selectively binds to myostatin and not related growth factors that have potential health risks



- ActRIIB/Activin A/GDF11 KO mice have varying degrees of developmental defects in multiple organ systems
- Inhibition of ActRII or Activin A remain untested approaches with potential risk in pediatric populations
- GDF11 LOF variants are associated with severe craniofacial, neurological, and skeletal phenotypes in humans
- Apitegromab (selective targeting of myostatin) has been tested extensively in a pediatric population with Spinal Muscular Atrophy

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



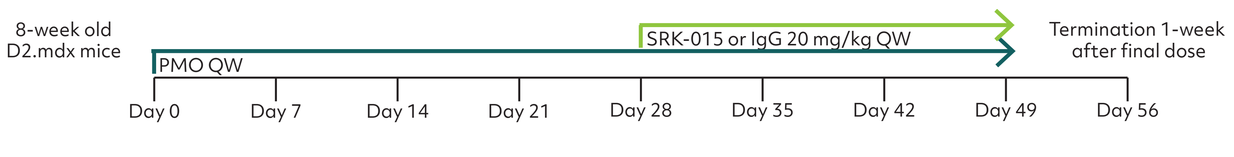
- In the SMNΔ7 mouse model, significant increases in muscle mass and strength were observed with muSRK-015 (a preclinical version of apitegromab) in combination with the SMN upregulator SMN-C1 over SMN-C1 alone treated animals
- These results translated to clinical efficacy as assessed with the HFMSE (Hammersmith Functional Motor Scale) in the phase II PoC trial TOPAZ, and more recently in the phase III SAPPHIRE trial (see poster O284)

Hypothesis

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) result from the full loss or partial reduction in the protein dystrophin, resulting in sarcolemma destabilization and muscle fiber death. It has been hypothesized that myostatin pathway inhibition may increase strength in the DMD population, but clinical trials to date have proven disappointing. An open question is whether selective myostatin inhibition in the presence of dystrophin upregulation or natural partial dystrophin levels (BMD) may result in functional benefit. We tested the effects of SRK-015 alone or in combination with a PMO which can partially restore dystrophin, in the D2.mdx mouse model of DMD.

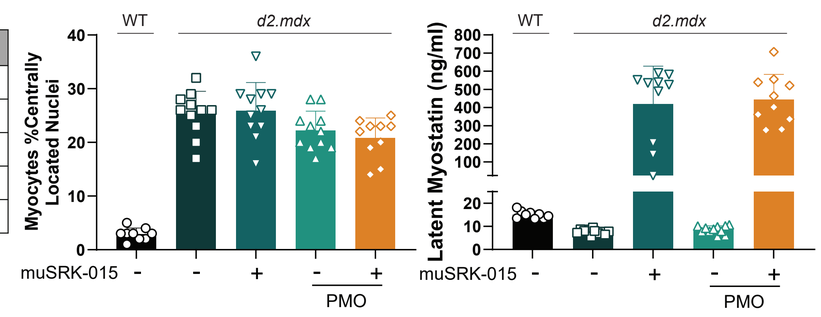
Study Design: Combination treatment of muSRK-015 and dystrophin upregulator in d2.mdx

- D2.mdx was preferred to B10 due to the atrophy phenotype in the limb muscles
- Moderate levels of dystrophin correction were modelled
- A lead-in period with dystrophin correction was chosen to model the scenario in which SRK-015 would be administered after muscle stabilization
- To reduce immunogenicity, a preclinical version of SRK-015, muSRK-015 was used



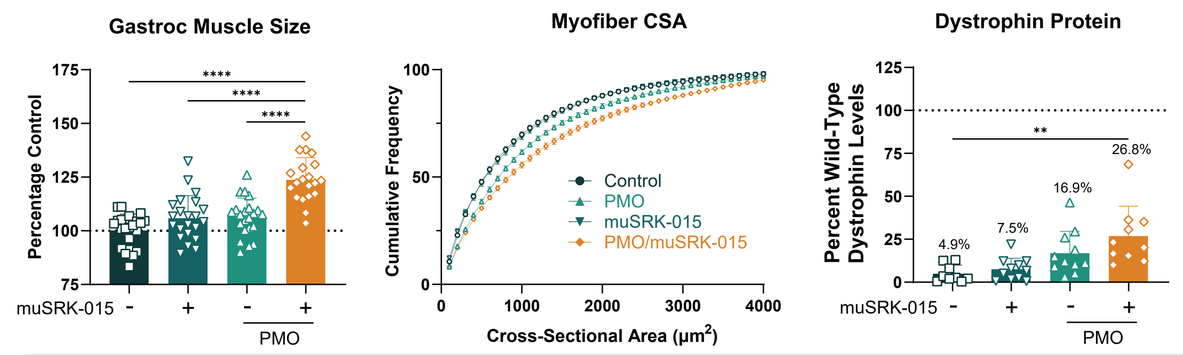
Genotyp	Treatment #1	Treatment #2
Wild-Type	Vehicle	IgG Control
D2.mdx	Vehicle	IgG Control
D2.mdx	Vehicle	muSRK-015
D2.mdx	M23D PMO	IgG Control
D2.mdx	M23D PMO	muSRK-015

Mice were randomized by BW and baseline force



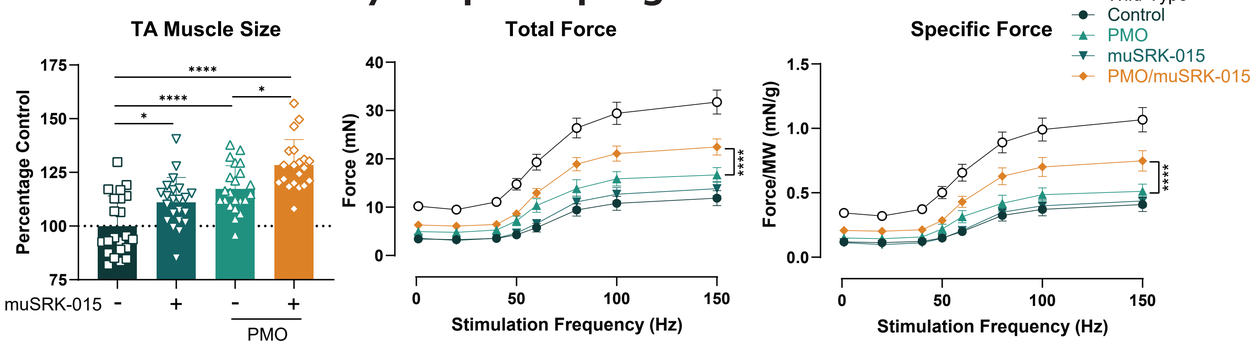
D2.mdx mice were dosed for 5 weeks with the m23d in vivo morpholino (PMO) or vehicle, after which 4-weeks dosing of muSRK-015 or IgG control was initiated. Data at study termination on centrally localized nuclei (slightly reduced with PMO treatment) or circulating latent myostatin (highly elevated with muSRK-015) indicate both treatments had effects consistent with their mechanisms of action.

muSRK-015 drives muscle mass and dystrophin increases in gastroc muscle in combination with PMO



Treatment with PMO and muSRK-015 resulted in synergistic increases in muscle size and modest improvements in myofiber cross-sectional area in the gastroc of D2.mdx mice. While PMO alone enhanced dystrophin protein levels as assessed by western blot analysis, the addition of muSRK-015 further boosted dystrophin protein levels.

muSRK-015 treatment results in synergistic strength increases in combination with dystrophin upregulation



Treatment with PMO alone resulted in a moderate increase in the size and strength of the TA. Combination with muSRK-015 resulted in synergistic improvements in both total force and force normalized to muscle size (specific force).

Summary and Conclusion

- muSRK-015 treatment resulted in additive/synergistic increases in muscle size and dystrophin levels in combination with dystrophin corrector
- Combination treatment also resulted in synergistic effects on both total force and specific force
- These results support the potential of apitegromab to safely provide strength benefit in DMD treated with dystrophin upregulator or in BMD

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