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# Clinical Development of SRK-015, a Fully Human Anti-proMyostatin Monoclonal Antibody, for the Treatment of Later-Onset Spinal Muscular Atrophy

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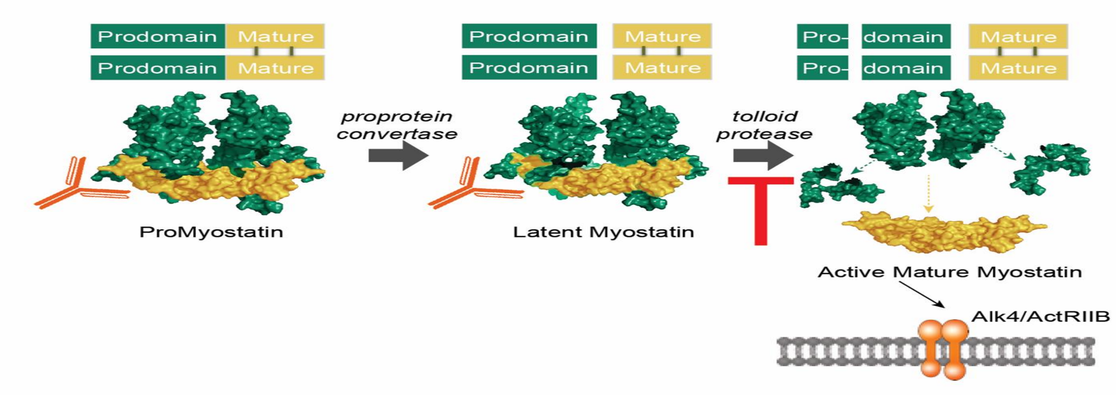
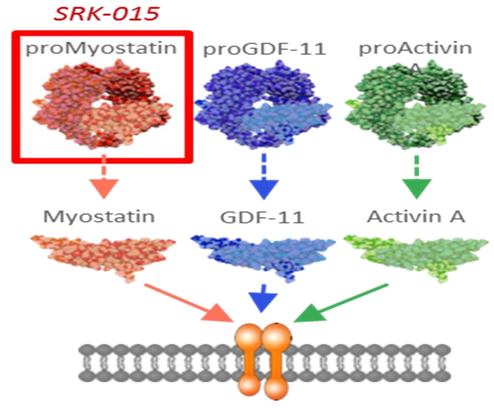
## Abstract

SRK-015 is a fully human anti-proMyostatin monoclonal antibody (mAb) that selectively binds to pro-/latent myostatin with high affinity, inhibiting the proteolytic activation of the growth factor. SRK-015 is being developed for the treatment of spinal muscular atrophy (SMA) by targeting muscle atrophy and improving muscle strength with the aim of offering clinically meaningful improvements in motor function. Nonclinical studies have demonstrated that specific inhibition of myostatin activation with muSRK-015P, the parental clone of SRK-015, effectively increases muscle mass and function in a mouse SMA model; no toxicologically significant findings were observed for SRK-015 in chronic exposure studies in rats and non-human primates. A Phase 1, single and multiple ascending dose study in healthy subjects, demonstrated no significant safety issues of SRK-015 administered intravenously (IV) at all doses tested (1-30 mg/kg single doses; 10-30 mg/kg multiple doses, every 2 weeks for a total of 3 doses). Serum drug exposure was dose-proportional with low variation and a half-life of 23-33 days across doses. SRK-015 at doses of ≥3 mg/kg robustly increased latent myostatin concentrations, indicating successful target engagement in humans that was saturable and durable. The ongoing Phase 2 proof-of-concept trial (TOPAZ) evaluates the safety and efficacy of SRK-015 dosed IV every four weeks over a 12-month treatment period. Fifty-eight patients in the U.S. and Europe, across three distinct and parallel cohorts have been enrolled. Cohort 1 (open-label, single-arm design) has enrolled 23 patients (5-21 years old) with ambulatory Type 3 SMA. Patients are treated with 20 mg/kg of SRK-015 as monotherapy or in conjunction with an approved SMN therapy. The primary objectives are to assess safety and the mean change from baseline in Revised Hammersmith Scale (RHS) over 12 months. Cohort 2 (open-label, single-arm design) has enrolled 15 patients (5-21 years old) with Type 2 or non-ambulatory Type 3 SMA, who are already treated with an approved SMN therapy. Patients are treated with 20 mg/kg of SRK-015 in conjunction with an approved SMN therapy. The primary objectives are to assess safety and the mean change from baseline in Hammersmith Functional Motor Scale Expanded (HFMSE) over 12 months. Cohort 3 (randomized, double-blind, parallel arm design) has enrolled 20 patients with Type 2 SMA, who are at least two years old and initiated treatment with an approved SMN therapy before five years of age. Patients are randomized 1:1 to be treated with either 2 or 20 mg/kg of SRK-015. The primary objectives are to assess safety and the mean change from baseline in HFMSE over 12 months. The first subject in the TOPAZ study was enrolled in April 2019. Enrollment is completed. Top-line results for the full 12-months of treatment period are expected starting in Q4 2020/Q1 2021. The study design and status will be presented.

## SRK-015: A fully human antibody that blocks cleavage of the Myostatin prodomain



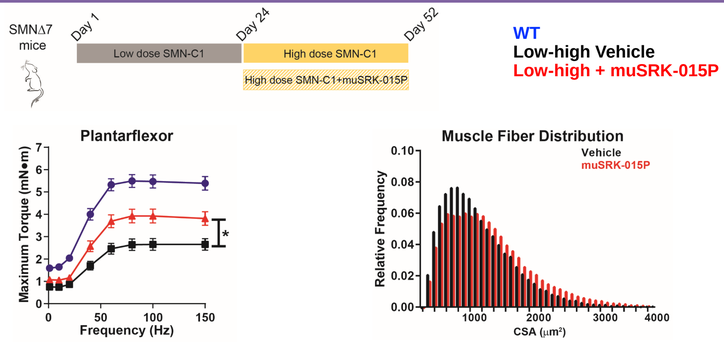

## Selective targeting of proMyostatin over other growth factors




| Analyte | SRK-015 Binding Affinity (nM) |
|---|---|
| **ProMyostatin** | **2.9** |
| **Latent Myostatin** | **2.4** |
| Myostatin | NB |
| ProGDF11 | NB |
| GDF11 | NB |
| ProActivin A | NB |
| Activin A | NB |
| BMP9 | NB |
| BMP10 | NB |
| TGFβ1 | NB |

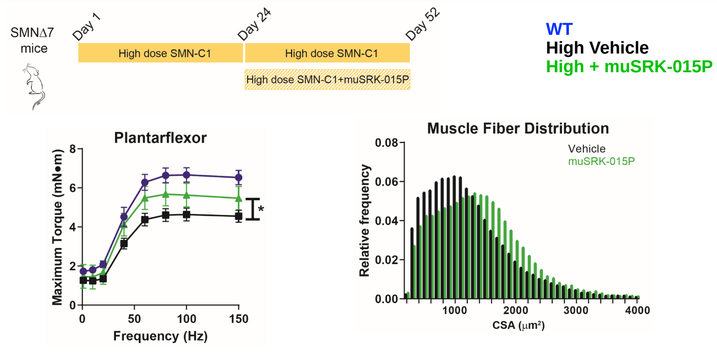
NB: no binding detected at 200nM of antibody

## muSRK-015P treatment improved muscle strength in a mouse model of late SMN restoration



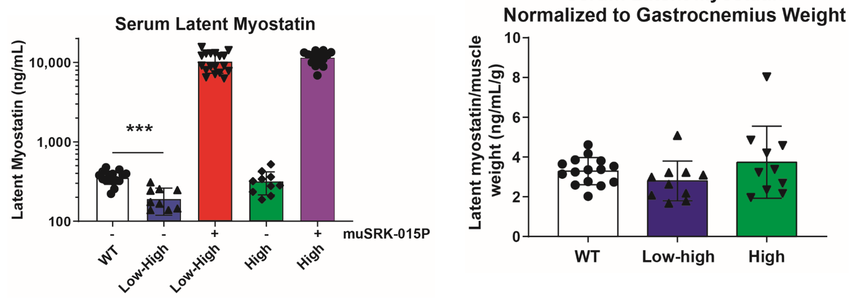

- 44%-51% increase in maximal torque (at ≥ 40Hz) of the plantarflexor muscle group
- Greater percentage of large muscle fibers

## muSRK-015P treatment improved muscle strength in a model of early SMN restoration



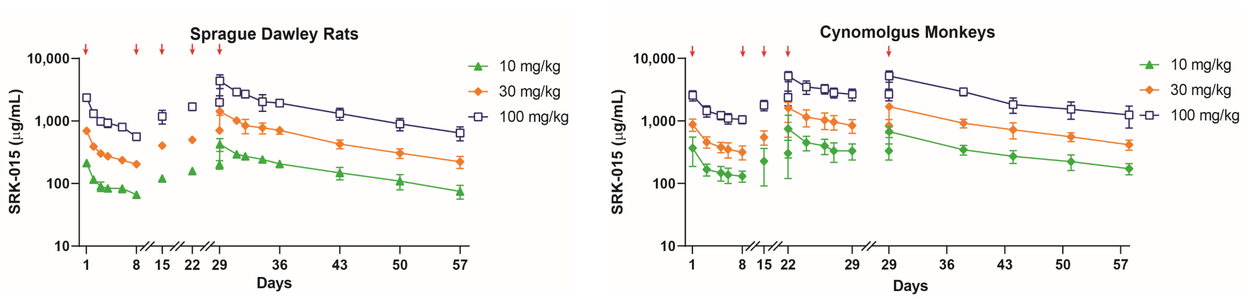

- 20%-30% increase in maximal torque (at ≥ 40Hz) of the plantarflexor muscle group
- Greater percentage of large muscle fibers

## muSRK-015P engages latent Myostatin to an equal extent across both early and late SMN restoration models



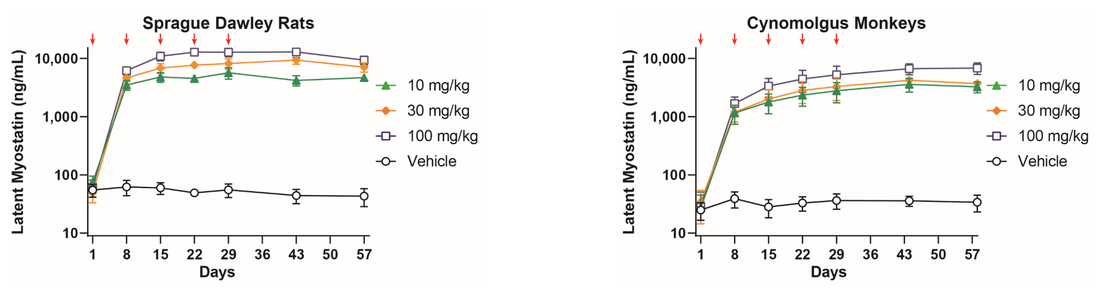

- Achieved multifold increase in serum latent myostatin levels
- Confirms presence of target in disease setting
- Lower latent myostatin levels in the SMA group may be attributable to reduced overall muscle mass

## SRK-015 displays well-behaved Pharmacokinetic (PK) profile across animal species




- SRK-015 PK profile following repeat dose IV administration (in adult rats and monkeys)
- Maximum serum concentration achieved 1-hour post-dose
- Relative dose-proportional accumulation of SRK-015

## Pharmacodynamic (PD) data demonstrate target engagement across animal species




- Latent myostatin accumulation following repeat dose IV administration of SRK-015
- Latent myostatin levels appear to plateau at all doses suggesting target saturation
- No meaningful change observed with placebo (vehicle)

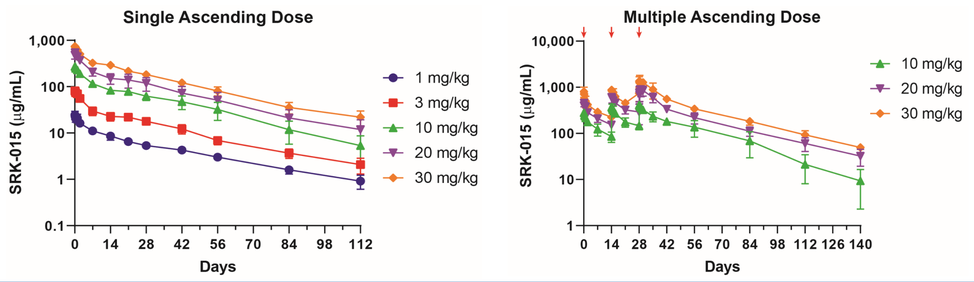
## Phase 1, Single and Multiple Ascending-Dose Study to Assess Safety, Tolerability, Pharmacokinetics (PK) and Pharmacodynamics (PD) of SRK-015 IV in Healthy Volunteers

| | Single Ascending Dose (SAD) | Multiple Ascending Dose (MAD) |
|---|---|---|
| Design | Double-blind, placebo-controlled 3:1 randomization | Double-blind, placebo-controlled 3:1 randomization |
| Subjects | 40 Adult healthy volunteers (Ages 18-55) | 26 Adult healthy volunteers (Ages 18-55) |
| Dosing | Single doses at: 1, 3, 10, 20, or 30 mg/kg | Q2W dosing for 3 doses at: 10, 20, or 30 mg/kg |

Key Results:

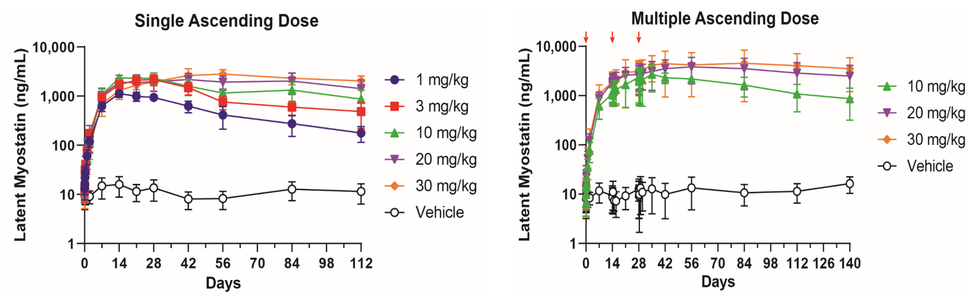
- SRK-015 was well-tolerated with no apparent safety signals
- No dose-limiting toxicities identified up to highest evaluated dose of 30 mg/kg in both SAD & MAD
- No discontinuations due to treatment-related adverse events (AEs)
- No treatment-related serious adverse events (SAEs) or deaths
- No hypersensitivity reactions
- PK/PD results informed Phase 2 dosing regimen

### PK Data Support IV Dosing Every 4 Weeks




- SRK-015 displayed well-behaved PK profile
- Half-life supports infrequent dosing

### PD Data Demonstrate Target Engagement




- Robust target engagement observed
- Evidence supports durable target saturation

## TOPAZ: Phase 2 Active Treatment Study to Evaluate the Efficacy and Safety of SRK-015 in Patients with Later-Onset Spinal Muscular Atrophy

| | Cohort 1 | Cohort 2 | Cohort 3 |
|---|---|---|---|
| Design | • N= 20; ages 5-21<br>• Open-label, single-arm<br>• 20 mg/kg SRK-015 IV Q4W<br>• 12-month treatment period | • N= 15; ages 5-21<br>• Open-label, single-arm<br>• 20 mg/kg SRK-015 IV Q4W<br>• 12-month treatment period | • N= 20; ages ≥2<br>• Double-blind, randomized (1:1) to 2 mg/kg or 20 mg/kg SRK-015 IV Q4W<br>• 12-month treatment period |
| Patients | • Ambulatory Type 3 SMA<br>• Patients receive SRK-015 in combination with approved SMN up-regulator or as monotherapy | • Type 2 or non-ambulatory Type 3 SMA<br>• Receiving treatment with approved SMN up-regulator | • Type 2 SMA<br>• Initiated treatment with approved SMN up-regulator before age 5 |
| Primary Objectives | • Safety<br>• Mean change from baseline in RHS | • Safety<br>• Mean change from baseline in HFMSE | • Safety<br>• Mean change from baseline in HFMSE |
| Trial Status | • Enrolled, treatment on-going | • Enrolled, treatment on-going | • Enrolled, treatment on-going |

**Primary efficacy endpoints will measure motor function through clinically meaningfully outcome measures validated in SMA over a 12-month period**

- For Cohort 1: Revised Hammersmith Scale (RHS) in ambulatory SMA
- For Cohorts 2 and 3: Hammersmith Functional Motor Scale Expanded (HFMSE) in non-ambulatory SMA

**Secondary efficacy endpoints include**

- For Cohort 1: 6-minute Walk Test (6MWT)
- For Cohorts 2 and 3: Revised Upper Limb Module (RULM)

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**References:**

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