SRK-015, a Fully Human Monoclonal Antibody Inhibiting Myostatin Activation, Offers Sustained Target Engagement Across Multiple Species, Including Humans

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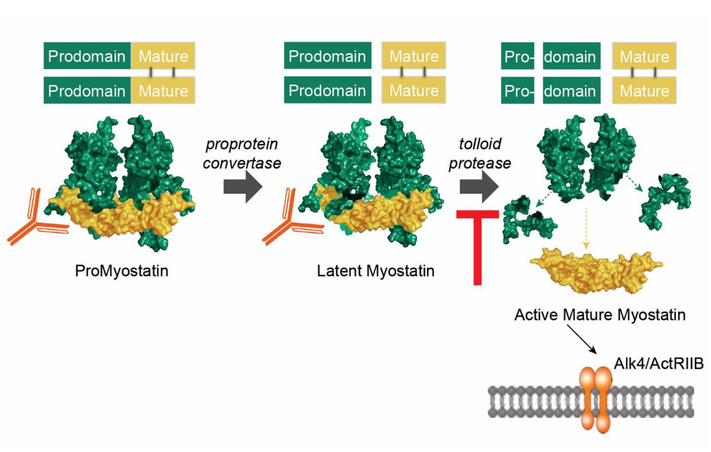
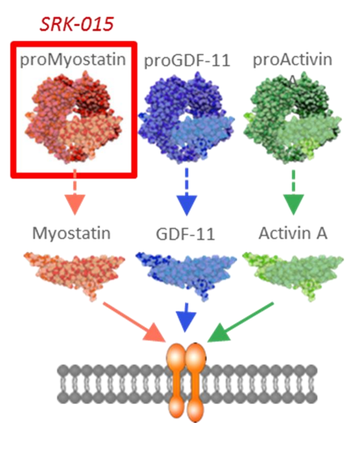
Abstract

SRK-015 is currently being evaluated in a Phase 2 clinical trial for the treatment of a rare pediatric disease, spinal muscular atrophy (SMA) with the aim of offering clinically meaningful improvements in motor function. We previously demonstrated that specific inhibition of myostatin activation effectively increases muscle mass and function in mouse models of SMA. Here, we present pharmacokinetic (PK) and pharmacodynamic (PD) data of SRK-015 from preclinical studies and a first-in-human phase 1 study in healthy adult subjects. In rodent and nonhuman primate studies, SRK-015 was administered as intravenous (IV) weekly doses (10 to 300 mg/kg). In the single dose part of the phase 1 study, 40 subjects received SRK-015 IV at 1, 3, 10, 20, or 30 mg/kg, or placebo. SRK-015 displayed a well-behaved PK profile across multiple species. In the phase 1 study, serum drug exposure was dose-proportional, with a half-life of 23-33 days across doses. PD was evaluated by measuring latent myostatin concentrations in serum. Serum latent myostatin levels in animals were low (<50 ng/ml) at baseline and increased substantially following SRK-015 treatment, indicating target engagement with SRK-015. Similarly, in humans, the levels were low (< 20 ng/ml) at baseline and across the study in placebo-treated subjects. Treatment with a single dose of SRK-015 of 3 mg/kg or greater led to increases in latent myostatin levels to approximately 2000 ng/ml, confirming target engagement with SRK-015 in humans. This effect was durable, with levels sustained for at least 84 days following single doses of 20 or 30 mg/kg. The phase 1 PD results demonstrate robust target engagement which saturates and is durable. PK data show the potential for infrequent dosing. A comparable pharmacologic profile was observed in rodents and non-human primates. Moreover, the low baseline serum levels of latent myostatin as compared to high levels following treatment indicate that most of the drug target resides within skeletal muscle, not circulating systemically. Collectively, this preclinical and Phase 1 data support the ongoing investigation of SRK-015 in a Phase 2 trial in patients with SMA.

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



Selective targeting of proMyostatin over other growth factors



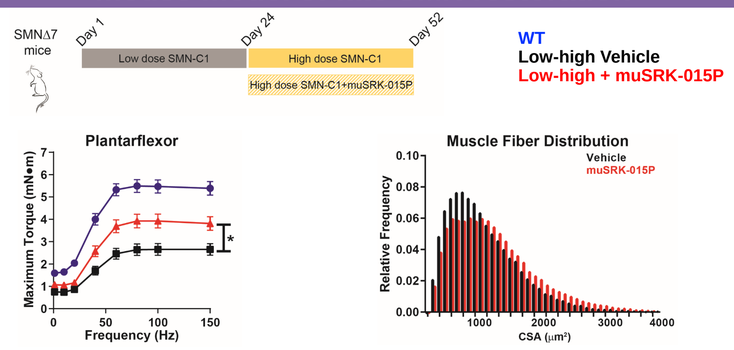
Analyte	SRK-015 Binding Affinity (nM)
ProMyostatin	**2.9**
Latent Myostatin	**2.4**
Myostatin	NB
ProGDF11	NB
GDF11	NB
ProActivin A	NB
Activin A	NB
BMP9	NB
BMP10	NB
TGFβ1	NB

NB: no binding detected at 200nM of antibody

Rationale for Investigating Myostatin as drug target for building motor function in SMA

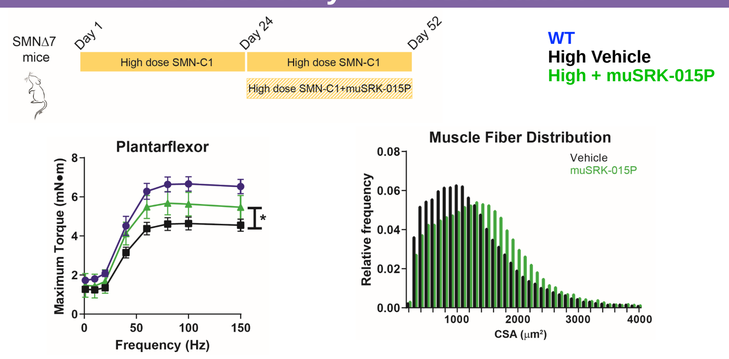
Potential Clinical Settings	Key Characteristics of Spinal Muscular Atrophy (SMA)
Younger Population	Genetic disorder with onset in childhood
Muscle disease with generally intact structure	Muscle structure appears generally intact
Need for increase in fast-twitch muscle fibers	Substantial deficit in fast-twitch fibers
Clinical trial endpoint driven by fast-twitch fiber function	Fast-twitch fiber function; prominent role in SMA outcome measures

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



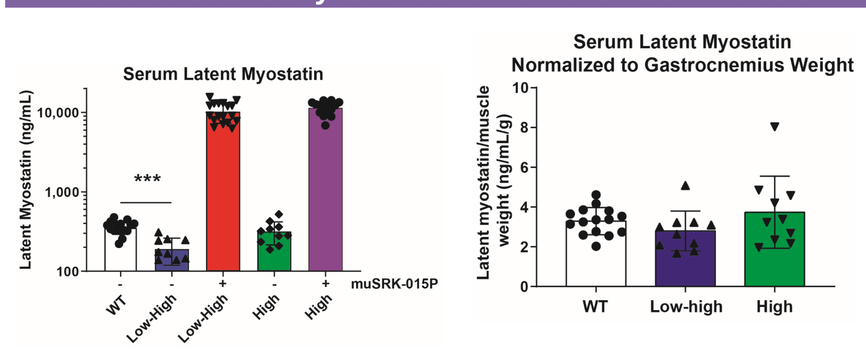
- 44%-51% increase in maximal torque (at ≥ 40Hz) of the plantarflexor muscle group
- Greater percentage of large muscle fibers

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



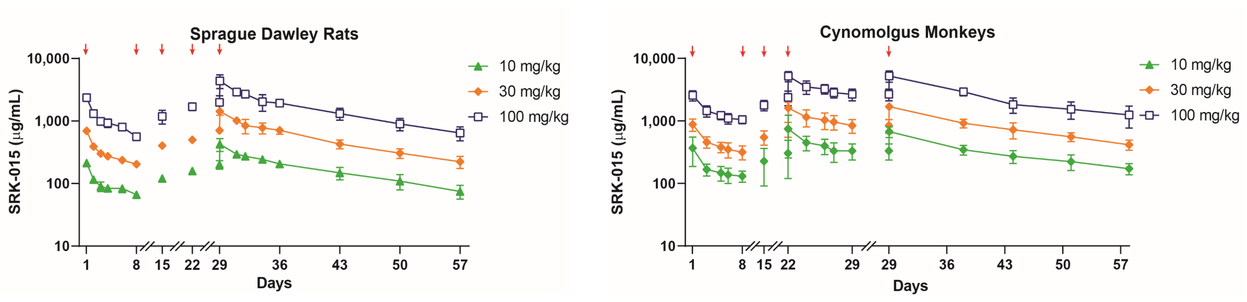
- 20%-30% increase in maximal torque (at ≥ 40Hz) of the plantarflexor muscle group
- Greater percentage of large muscle fibers

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



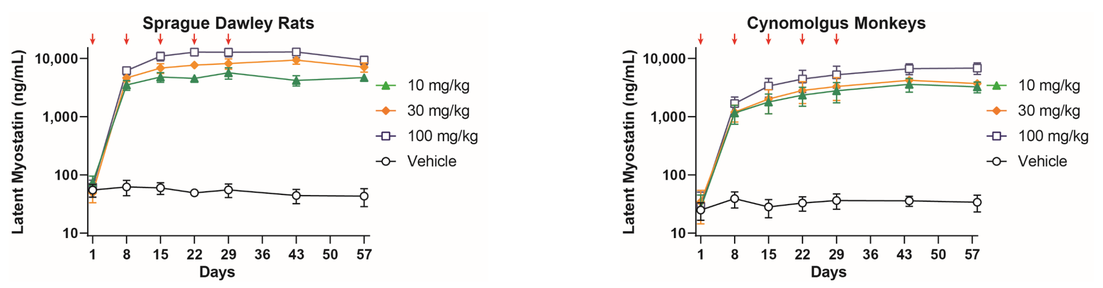
- Achieved multi-fold increase in serum latent myostatin levels
- Confirms presence of target in disease setting
- Lower latent myostatin levels in the SMA group may be attributable to reduced overall muscle mass

SRK-015 displays well-behaved 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

PD data demonstrates target engagement across animal species

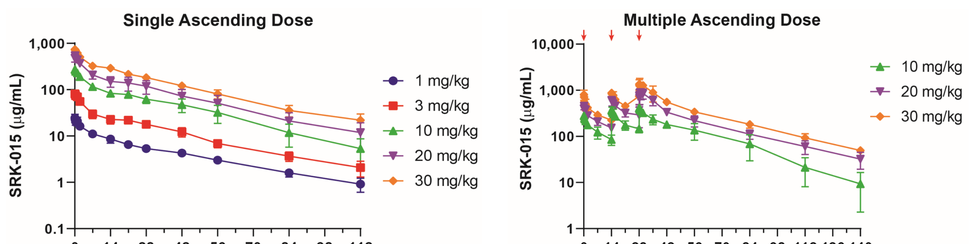


- Latent myostatin accumulation following repeat dose IV administration of SRK-015
- Latent myostatin levels appear to plateau at all doses suggesting target saturation
- No meaningful change observed with placebo (vehicle)

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

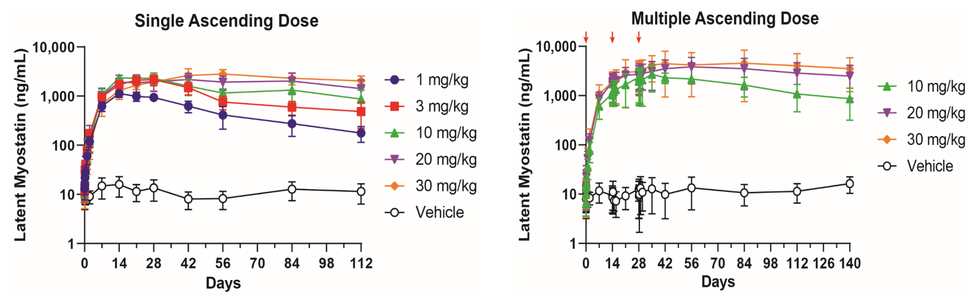
	Single Ascending Dose (SAD)	Multiple Ascending Dose (MAD)
Design	Double-blind, placebo-controlled 3:1 randomization	Double-blind, placebo-controlled 3:1 randomization
Subjects	40 Adult healthy volunteers (Ages 18-55)	26 Adult healthy volunteers (Ages 18-55)
Dosing	Single doses at: 1, 3, 10, 20, or 30 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 Supports Dosing Every 4 Weeks



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

PD Data Demonstrates 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 • Open-label, single-arm • 20 mg/kg SRK-015 IV Q4W • 12-month treatment period	• N= 15; ages 5-21 • Open-label, single-arm • 20 mg/kg SRK-015 IV Q4W • 12-month treatment period	• N= 20; ages ≥2 • Double-blind, randomized (1:1) to 2 mg/kg or 20 mg/kg SRK-015 IV Q4W • 12-month treatment period
Subjects	• Ambulatory Type 3 SMA	• Type 2 or non-ambulatory Type 3 SMA • Receiving treatment with approved SMN upregulator	• Type 2 SMA • Initiated treatment with approved SMN upregulator before age 5
Primary Objectives	• Safety • Mean change from baseline in RHS	• Safety • Mean change from baseline in HFMSE	• Safety • Mean change from baseline in HFMSE

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

- Hammersmith Functional Motor Scale Expanded (HFMSE) in non-ambulatory SMA
- Revised Hammersmith Scale (RHS) in ambulatory SMA

Secondary efficacy endpoints include

- 6-minute Walk Test (6MWT)
- Revised Upper Limb Module (RULM)

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