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

George Nomikos, MD, PhD
VP, Head of Medical Research
Scholar Rock, Inc.

Cure SMA
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Disclaimer

- SRK-015 is an investigational product candidate that is currently being evaluated in a clinical trial

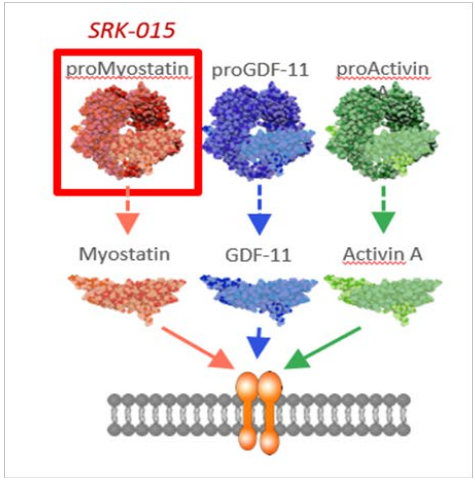
- SRK-015 has not been approved by the U.S. Food and Drug Administration (FDA), the European Commission, or any other health authority, and the safety and effectiveness of this molecule have not been established

Disclosures

- George Nomikos is an employee of Scholar Rock and owns equity in the company.

SRK-015 is a Fully Human Monoclonal Antibody that Specifically Inhibits Myostatin Activation

Selective Targeting of ProMyostatin, the Myostatin Precursor



- SRK-015 does not bind to mature myostatin or any form of GDF11, Activin A, or other TGF-β family members

The Scholar Rock Approach

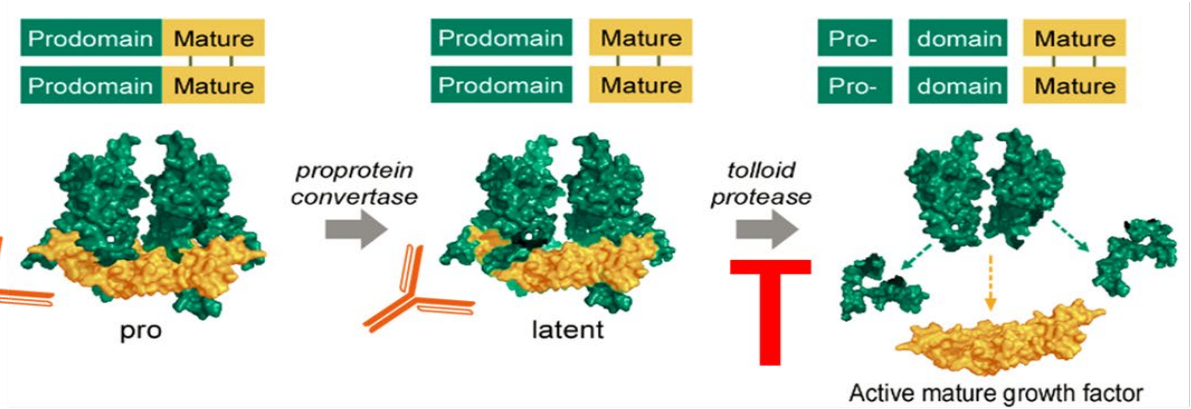
Identity between Myostatin and GDF11

Mature growth factor	Prodomain
90%	47%

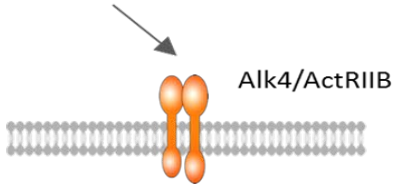
Superior selectivity due to sequence divergence of prodomains

Pirruccello-Straub, et al., Sci Rep (2018) 8:2292

SRK-015 Blocks Cleavage of the Myostatin Prodomain



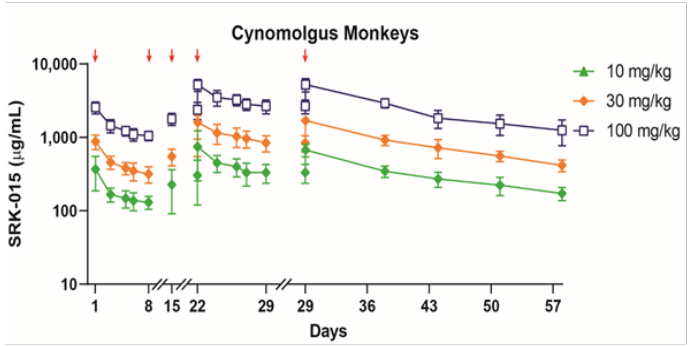
- Activation of myostatin requires two distinct proteolysis events that generate the active mature growth factor
- SRK-015 binds to both proMyostatin and latent myostatin and inhibits tolloid-mediated cleavage of latent myostatin



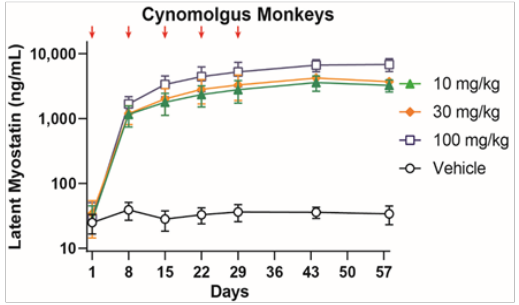
Pirruccello-Straub, et al., Sci Rep (2018) 8:2292

SRK-015 Displays a Favorable PK Profile in Nonhuman Primates with Robust PD (Target Engagement)

SRK-015 PK



SRK-015 PD (Target Engagement)



SRK-015 displays similar PK and PD profiles across animal species

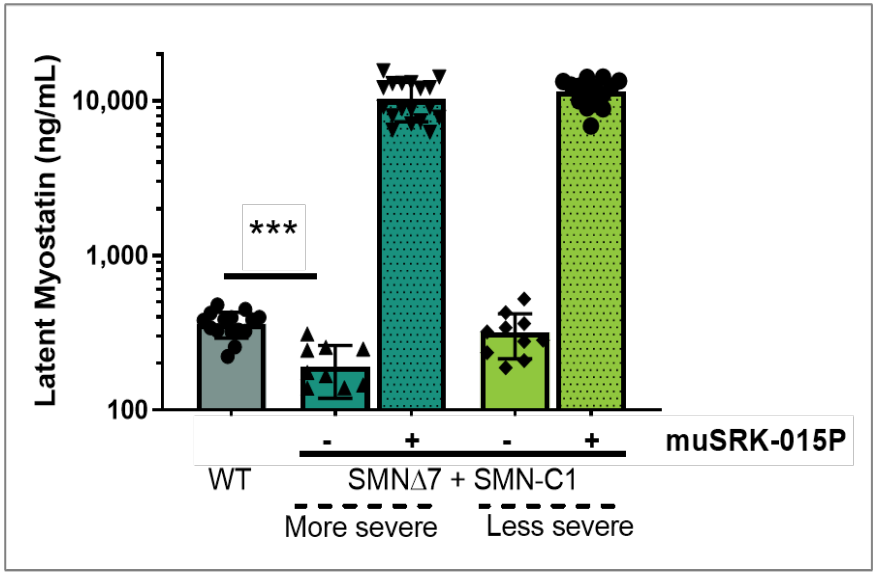
- Maximum serum concentration achieved 1-hour postdose
- Relative dose-proportional accumulation

- Latent myostatin levels increased with increasing doses (in a less than dose-proportional manner)
- Latent myostatin levels appear to plateau at all doses, suggesting target saturation

Data on file

muSRK-015P Robustly Engages Latent Myostatin in a Mouse Model of SMA (SMNΔ7)

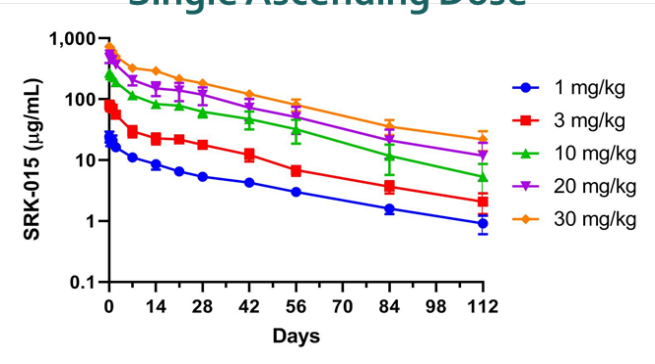
- Basal serum latent myostatin levels correlate with disease severity (based on the use of varying doses of SMN-C1), confirming presence of target in a disease setting
- muSRK-015P results in robust accumulation of latent myostatin in serum, independently of basal levels
- In both severity models, inhibition of myostatin activation increases muscle strength



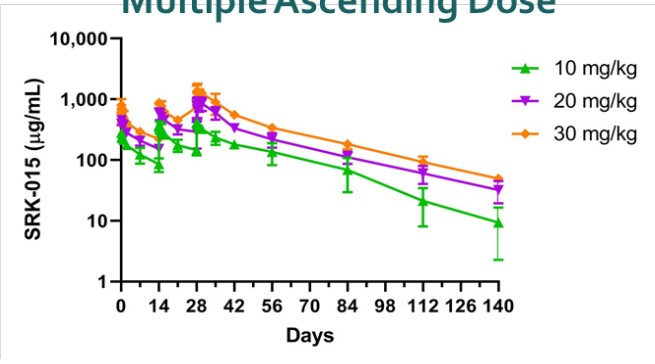
Long, et al., Hum Mol Genet (2018) 28:1076

SRK-015 Phase 1 Study in Healthy Volunteers: PK Data Support Dosing Every 4 Weeks

Single Ascending Dose



Multiple Ascending Dose



SRK-015 Displayed Well-Behaved PK Profile

- Minimal variability observed, consistent with that commonly observed with monoclonal antibodies
- Dose-proportional serum drug exposure

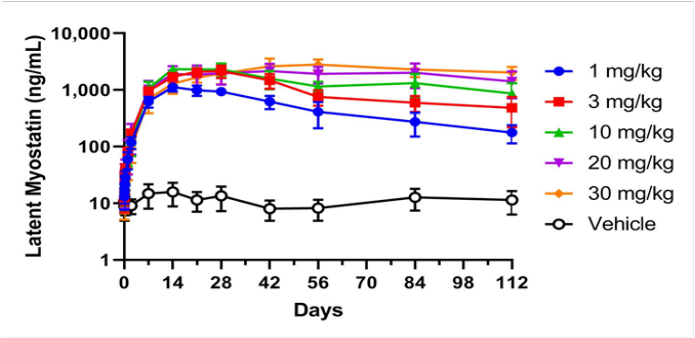
Half-Life Supports Infrequent Dosing

- Serum half-life of 23-33 days across dose groups
- Supports planned evaluation of once every 4-week dosing in the Phase 2 trial

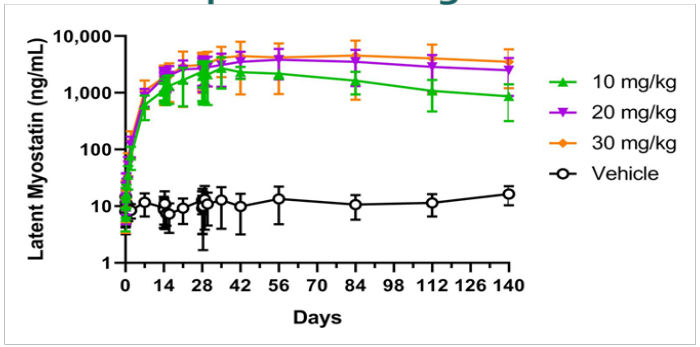
Data on file

SRK-015 Phase 1 Study in Healthy Volunteers: PD Data Demonstrate Robust Target Engagement

Single Ascending Dose



Multiple Ascending Dose



Robust Target Engagement Observed

- Single doses led to marked increases in serum concentrations of latent myostatin

Evidence Supports Durable Target Saturation

- Peak latent myostatin levels plateaued, starting with a single dose at 3 mg/kg, suggesting target saturation
- Plateau was sustained, demonstrating durability of effect

No apparent safety signals observed

- No antidrug antibodies were detected

PK/PD results informed Phase 2 dosing regimen

Data on file

SRK-015 Phase 2 Trial (TOPAZ) Design

	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
Patients	• Ambulatory Type 3 SMA • Receiving treatment with approved SMN upregulator or as monotherapy	• 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

www.clinicaltrials.gov
NTC03921528

RHS: Revised Hammersmith Scale
HFMSE: Hammersmith Functional Motor Scale Expanded

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