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

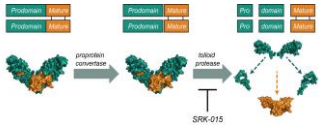
George Nomikos, MD, PhD on behalf of the Scholar Rock SRK-015 team
Scholar Rock, Inc., Cambridge, MA 02139

Poster: 253

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. Preclinical studies demonstrated selective inhibition of myostatin activation, effectively increasing muscle mass and function in a SMA mouse model. The structural basis for SRK-015 binding to pro-/latent myostatin will be presented. No toxicologically significant findings were observed for SRK-015 in rats and nonhuman primates. A Phase 1, healthy volunteer study demonstrated a favorable safety profile of SRK-015 administered intravenously (IV) at all doses tested. The ongoing Phase 2 study evaluates the safety and efficacy of SRK-015 dosed IV every four weeks over a 12-month treatment period. Three distinct and parallel cohorts were enrolled. Cohort 1 enrolled 23 patients (5-21 years old) with ambulatory Type 3 SMA and were treated with 20 mg/kg of SRK-015 as monotherapy or in conjunction with an approved SMN up-regulator. The primary objectives are to assess safety and the mean change from baseline in the Revised Hammersmith Scale (RHS). Cohort 2 enrolled 15 patients (5-21 years old) with Type 2 or non-ambulatory Type 3 SMA, who were already treated with an approved SMN up-regulator. Patients were treated with 20 mg/kg of SRK-015. Cohort 3 enrolled 20 patients with Type 2 SMA, who were at least 2 years old and initiated treatment with an approved SMA up-regulator before turning five. Patients were randomized 1:1 to either 2 mg/kg or 20 mg/kg of SRK-015. For Cohort 2 and Cohort 3, the primary objectives are to assess safety and the mean change from baseline in Hammersmith Functional Motor Scale Expanded (HFMSE). Demographics and baseline characteristics will be provided.

SRK-015: A Fully Human Antibody that Blocks Cleavage of the Myostatin Prodomain

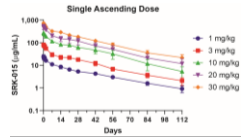


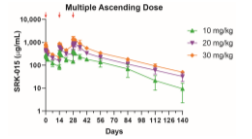
- Activation of myostatin requires two distinct proteolysis events that generate the active mature growth factor
- SRK-015 binds to both pro- and latent myostatin and inhibits tolloid-mediated cleavage of latent myostatin
- SRK-015 does not bind to mature myostatin or any form of GDF11, Activin A, or other TGF-β family members

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	

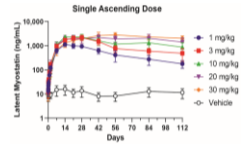
PK Data Support IV Dosing Every 4 Weeks

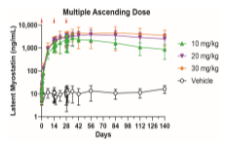




- SRK-015 displayed well-behaved PK profile
- Half-life supports infrequent dosing

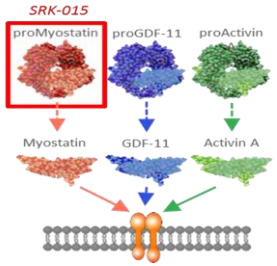
PD Data Demonstrate Target Engagement





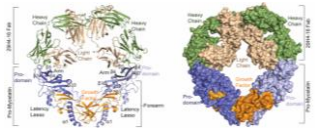
- Robust target engagement observed
- Evidence supports durable target saturation

Selective Targeting of proMyostatin over other Growth Factors



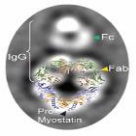
Analyte	SRK-015 Binding Affinity (nM)
ProMyostatin	2.9
Latent Myostatin	2.4
Myostatin	NB
ProGDF11	NB
GDF11	NB
ProActivin A	NB
Activin A	NB
BMP9	NB
BMP10	NB
TGFβ1	NB

NB: no binding detected at 200nM of antibody



An integrated structural biology approach has revealed that SRK-015 binds with both arms of the antibody to the 'arm regions' of the dimeric proMyostatin stabilizing the complex and preventing proteolytic activation.

A 2.79Å x-ray crystal structure of proMyostatin with an SRK-015 analog (PDB:6UMX) shows 1:1 binding of each myostatin monomer to a Fab



Negative stain EM with the full mAb verified that this stoichiometry was representative of the Drug:Target interaction.

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= 23; 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 • Patients receive SRK-015 in combination with approved SMN up-regulator or as monotherapy	• Type 2 or non-ambulatory Type 3 SMA • Receiving treatment with approved SMN up-regulator	• Type 2 SMA • Initiated treatment with approved SMN up-regulator 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
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
- Cohort 1: Revised Hammersmith Scale (RHS) in ambulatory SMA
- Cohorts 2 and 3: Hammersmith Functional Motor Scale Expanded (HFMSE) in non-ambulatory SMA

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

TOPAZ: Baseline Data

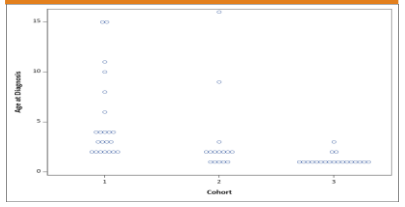
Age (Years) at Informed Consent by Cohort

Cohort	N	Mean	Std	Min	Med	Max
1	23	12.6	4.53	7	13.0	21
2	15	11.7	3.94	8	10.0	19
3	20	4.0	1.23	2	4.0	6
Total	*58*	*9.4*	*5.31*	*2*	*8.0*	21

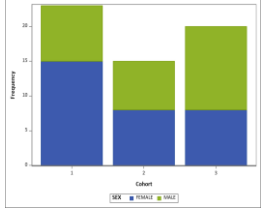
TOPAZ: Baseline Data Continued

[†]Excluded Cohort 1 patients who are not on Nusinersen

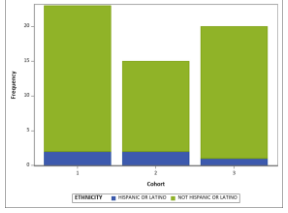
Age (Years) at Diagnosis by Cohort



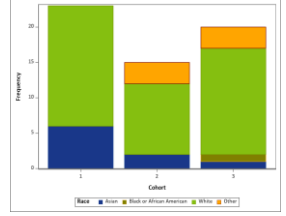
Sex Distribution by Cohort



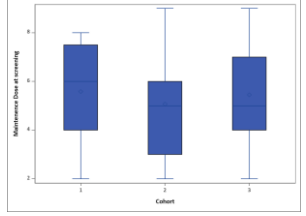
Ethnicity Distribution by Cohort



Race Distribution by Cohort



Maintenance Dose of Nusinersen at Screening[†]



Acknowledgements

The authors thank the healthy volunteers, patients, PIs and SCs in the Phase 1 and 2 trials; SRK-015 preclinical and clinical teams, Myologica LLC, Medpace (Phase 1 trial unit), the SMA Foundation, and Cure SMA.

References

1. Pirruccello-Straub M et al. Sci Rep. 2018; 8(1):2292
2. Long KK et al. Hum Mol Genet. 2019; 28(7):1076-1089
3. Cote SM et al. SLAS Discov. 2020; 25(1):95-103
4. Dagbay KB et al. J Biol Chem. 2020; 295(16):5404-5418

TOPAZ Timelines

- All 3 cohorts fully enrolled
- Interim analysis: 6-month treatment period
- Topline results: 12-month treatment period
- Patients eligible to continue treatment for an additional 12-month extension period
- Results from TOPAZ trial may inform future studies in SMA

SRK-015 has the potential to be the first muscle-directed therapy for patients with SMA