



TOPAZ: Phase 2 Study Evaluating Efficacy and Safety of Apitegromab in Later-Onset Spinal Muscular Atrophy; An Interim Analysis

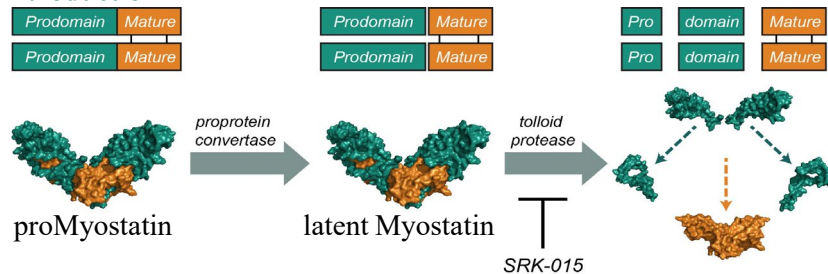
Amy Place^{1,2}, Doreen Barrett¹, Shaun Cote¹, George Nomikos¹, Guochen Song¹, Ryan Iarrobino¹, Yung Chyung¹

¹ ScholarRock Inc. 301 Binney Street, Cambridge, MA; ²Corresponding author; MedicalInquiry@ScholarRock.com <https://scholarrock.com/our-pipeline>

Abstract

Apitegromab (SRK-015) is a fully human, high-affinity anti-proMyostatin monoclonal antibody that binds to human proMyostatin and latent myostatin and inhibits the tolloid-mediated proteolysis step for myostatin activation. As proMyostatin is the predominant form of myostatin in skeletal muscle, apitegromab inhibits myostatin activation directly in target tissues.¹

Introduction²



- Activation of myostatin requires two distinct proteolysis events that generate the active mature growth factor¹
- Apitegromab does not bind to mature myostatin or any form of GDF11, Activin A, or other TGF-β family members¹

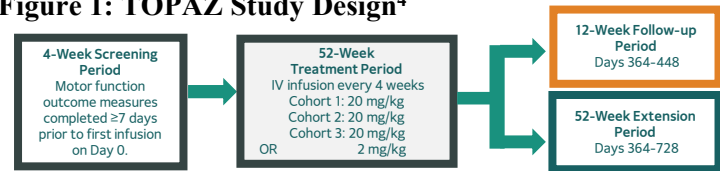
Methods³

TOPAZ (NCT03921528) is a Phase 2, 52-week proof-of-concept study of IV apitegromab treatment as monotherapy or with an approved SMN upregulator (nusinersen) in 58 patients across 16 study sites in the US and EU. The 52-week Treatment Period is followed by a 52-week open-label Extension Period or a 12-week Follow-Up Period. Cohorts 1 and 2 are open-label, while Cohort 3 is a double-blind, randomized arm (Fig 1). A pre-planned interim analysis was conducted following a 6-month treatment period across all three study cohorts (Fig 2; Tables 1 and 2)*.

References: 1. Dagbay KB et al. J Biol Chem. 2020; 295(16):5404-5418; 2. Pirruccello-Straub M et al. Sci Rep. 2018; 8(1):2292; 3. Press release (October 27, 2020), available: www.scholarrock.com; 4. Data on File, Scholar Rock, Inc. Cambridge, MA.

Disclaimer: Apitegromab is an investigational drug candidate being developed and studied for SMA. The effectiveness and safety of apitegromab have not been established. Apitegromab has not been approved by the FDA or any other regulatory authority.

Figure 1: TOPAZ Study Design⁴



	Cohort 1	Cohort 2	Cohort 3
Design	<ul style="list-style-type: none"> N=23; ages 5-21 Open-label, single-arm 20 mg/kg apitegromab IV Q4W 52-week treatment period 	<ul style="list-style-type: none"> N=15; ages 5-21 Open-label, single-arm 20 mg/kg apitegromab IV Q4W 52-week treatment period 	<ul style="list-style-type: none"> N=20; ages ≥2 Double-blind, randomized (1:1) to 2 mg/kg or 20 mg/kg apitegromab IV Q4W 52-week treatment period
Patients	<ul style="list-style-type: none"> Ambulatory Type 3 SMA Patients receive apitegromab in combination with approved SMN up-regulator or as monotherapy 	<ul style="list-style-type: none"> Type 2 or non-ambulatory Type 3 SMA Receiving treatment with approved SMN up-regulator 	<ul style="list-style-type: none"> Type 2 SMA Initiated treatment with approved SMN up-regulator before age 5
Primary Objectives	<ul style="list-style-type: none"> Safety & tolerability Mean change from baseline in RHS 	<ul style="list-style-type: none"> Safety & tolerability Mean change from baseline in HFMSE 	<ul style="list-style-type: none"> Safety & tolerability Mean change from baseline in HFMSE
Secondary Objectives	<ul style="list-style-type: none"> PK & PD effects Immunogenicity 	<ul style="list-style-type: none"> PK & PD effects Immunogenicity 	<ul style="list-style-type: none"> PK & PD effects Immunogenicity Time to therapeutic effect between low and high dose

Table 1: TEAEs; All cohorts: most frequently reported⁴

TEAEs ≥ 5	Cohort 1	Cohort 2	Cohort 3
Preferred Term (PT)	20 mg/kg, monotherapy (n=11)	20 mg/kg, adjunctive therapy (n=12)	Total (n=23)
Subjects with any TEAE	10 (90.9)	9 (75.0)	19 (82.6)
Headache	5 (45.5)	3 (25.0)	8 (34.8)
Upper respiratory tract infection	3 (27.3)	2 (16.7)	5 (21.7)
Pyrexia	1 (9.1)	0	1 (4.3)
Nasopharyngitis	1 (9.1)	1 (8.3)	2 (8.7)
Cough	1 (9.1)	2 (16.7)	3 (13.0)

Interim Analysis Summary: Results support the potential of Apitegromab to be the first muscle-directed therapy for patients with SMA

- Motor function improvements were observed in the primary efficacy endpoints at 6-months
- Dose response in primary endpoint was observed at 6 months: higher improvements over BL in high dose compared to low dose arm
- Supportive PK/PD results; high dose - higher drug exposure and target engagement
- Incidence and severity of AEs were consistent with underlying patient population and background therapy
- Topline study results are due in Q2 2021

Figure 2: TOPAZ Interim Analysis Results; change from baseline in primary efficacy endpoints [Hammersmith scores; mean (+/- 1 SE)]⁴

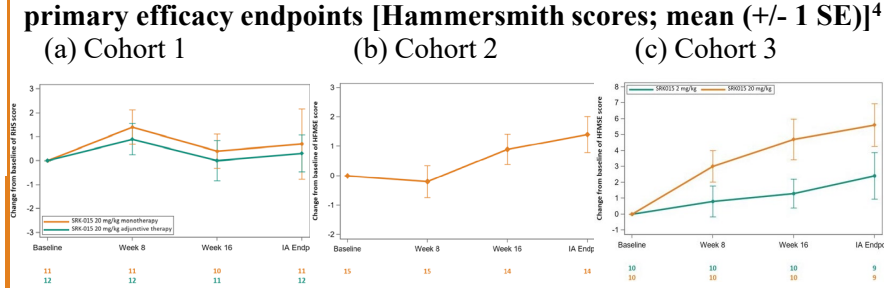


Table 2: TOPAZ Interim Analysis Results; mean improvements from baseline in HFMSE/RHS observed in each of the 3 cohorts⁴

	Ambulatory Subjects (RHS)			Non-Ambulatory Subjects (HFMSE)	
	Cohort 1		Cohort 2	Cohort 3	
	20 mg/kg pooled (n=23)	20 mg/kg monotherapy (n=11)	20 mg/kg +nusinersen (n=12)	20 mg/kg +nusinersen (n=14)	20 mg/kg +nusinersen (n=9)
Mean baseline change (95% CI)	0.5 (-1.1, 2.2)	0.7 (-2.5, 4.0)	0.3 (-1.4, 2.0)	1.4 (0.1, 2.7)	2.4 (-0.9, 5.8)
≥1-pt increase, n (%)	12/23 (52)	7/11 (64)	5/12 (42)	10/14 (71)	6/9 (67)
≥3-pt increase, n (%)	6/23 (26)	4/11 (36)	2/12 (17)	3/14 (21)	4/9 (44)

67% of total patients achieved ≥1 pnt increase in Hammersmith scores³
35% of total patients achieved ≥3 pnt increase in Hammersmith scores³

Acknowledgements

The authors thank the patients, PIs and SCs in the Ph 2 trial; and the apitegromab preclinical and clinical teams.

* Three patients (one in Cohort 2 and two in Cohort 3) each missed three doses of apitegromab and the six-month interim analysis timepoint due to COVID-19-related site access restrictions; the six-month timepoint from these patients was not included in the interim analysis; TEAE, treatment emergent adverse events (defined as AEs that started after the first dose of study drug or started prior to the administration of study drug and worsen in severity/grade or relationship to investigational medication after the administration of study drug); IV, intravenous; GDF11, Growth differentiation factor 11 also known as BMP11; TGF-β, Transforming growth factor β; PI, Principal Investigator; SC, study coordinator; PK, pharmacokinetic; PD, pharmacodynamic; SMN, Survival motor neuron 1; RHS, Revised Hammersmith scale; HFMSE, Hammersmith functional motor scale expanded; CI, confidence interval; SE, Standard error; SMA, spinal muscular atrophy; mg/kg, milligram/kilogram

