Topaz Extension: 24-Month Efficacy and Safety:

Apitegromab in Patients With Type 2 and Type 3 Spinal Muscular Atrophy (SMA)

Thomas O. Crawford, M.D.

Professor of Neurology and Pediatrics
Johns Hopkins University
On behalf of the entire TOPAZ Study Team

TOPAZ (NCT03921528)

Medical Questions should be sent via email to the following address: medicalinquiry@scholarrock.com

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Author Disclosures

- Dr. Crawford is Lead Principal Investigator of the TOPAZ trial

Consulting/Ad Boards:

- Biogen
- Roche/Genentech
- Avexis / Novartis
- Pfizer

Study Site Investigations:

- Biogen
- Avexis
- Cytokinetics
- Parexel
- Catalyst

Patient Organizations:

- CureSMA
- SMA Foundation
- Muscular Dystrophy Association
- Ataxia Telangiectasia Children's Project

Disclaimers

- The TOPAZ trial is sponsored by Scholar Rock, a biopharmaceutical company developing and investigating apitegromab in a clinical development program for the treatment of Spinal Muscular Atrophy (SMA).
- Apitegromab has not been approved by the US Food and Drug Administration (FDA), the European Commission, or any other health authority.
- The safety and effectiveness of apitegromab have not been established.

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TOPAZ Study Team

PIs:

- Darras, Basil[1]
- Finanger, Erika[2]
- DeVivo, Darryl[3]
- Proud, Crystal[4]
- Tesi-Rocha, Ana Carolina[5]
- Parsons, Julie[6]
- Nance, Jessica[7]
- Castro, Diana[8]
- Cartwright, Michael[9]
- Bernes, Saunder[10]
- Krueger, Jena[11]
- Mercuri, Eugenio[12]
- Sansone, Valeria[13]
- Van der Pol, Ludo[14]
- Nascimento, Andres[15]
- Pitarch Castellano, Inmaculada[16]
- Maczek, Elizabeth[1]
- Pasternak, Amy[1]*
- Gurgel, Brittany[2]
- Zilke, Kirsten[2]
- Rome-Martin, Donielle[3]
- Salazar, Rachel [3]
- Jackson, Elise[4]
- Schuler, Lindsey[4]
- Dunaway Young, Sally[5]*
- Duong, Tina [5]*
- Carry, Terri[6]
- Kelley, Carolyn[6]
- Moore, Meghan[7]
- Vela, Kerry[7]
- Nelson, Leslie [8]*
- Valle, Melanie[8]
- Sink, Teresa[9]

PTs:

- Smith, Emily[9]
- Fern-Bueno, Anna[10]
- Harrington, Andrew[11]
- Linton-Fisher, Robin[11]
- Coratti, Giorgia[12]
- De Sanctis, Roberto[12]
- Morettini, Valentina[13]
- Salmin, Francesca[13]
- Bartels, Bart[14]*
- Van der Woude, Danny[14]
- Medina, Julita[15]
- Moya, Obdulia[15]
- Ibanez Albert, Eugina[16]
- Leon, Juan Carlos[16]
- Montes, Jaqueline*
- Mazzone, Elena*

CRCs:

- Levine, Alexis[1]
- McCarthy, Bryn[2]
- McCary, Isabella[3]
- Karras Conklin, Terrie[4]
- Lum, Tia[5]
- Filar, Lauri[6]
- King-Rennie, Agnes[7]
- Taylor, Leah[8]
- Harris, Summer[9]
- Enriquez, Abigail[10]
- Russell, Christopher[11]
- Vizzino, Maria Rosaria[12]
- Mauro, Luca[13]
- Asselman, Fay-Lynn[14]
- Rodriquez, Alicia[15]
- Lizandra Cortez, Paula[16]

CROs and Vendors:

- Medpace
- Chris Yun
- ChilliPharm
- BBK
- CRECare

Scientific Advisors:

- Day, John W.[17]

ScholarRock Research and Development Teams

1. Boston Children's Hospital; Boston, Mass.; 2. Oregon Health & Science University; Portland, OR.; 3. Columbia Univ.; NY, NY; 4. Children's Hospital of the King's Daughters; Norfolk, Virginia; 5. Tesi-Rocha- Stanford Health Care; Palo Alto, Ca; 6. Children's Hospital; Denver, CO; 7. Johns Hopkins; Baltimore, Maryland; 8. UT Southwestern Medical Center; Dallas, Texas; 9. Wake Forest Baptist Health; Winston Salem, NC; 10. Phoenix Children's Hospital; Phoenix, Az; 11. Spectrum Health; Grand Rapids, MI; 12. Catholic University; Rome, Italy; 13. ASST Grande Ospedale Metropolita Niguarda; Milan, Italy; 14. University Medical Center Utrecht; Netherlands; 15. Hospital Sant Joan de Deu; Barcelona, Spain; 16. Hospital Universitari I Polytecnic la fe; Valencia, Spain; 17. Stanford Neuroscience Health Center; Stanford, Ca. *TOPAZ *Physical Therapist Advisory Board*

Types 2/3 SMA: *SMN targeted therapies offer important benefits, but…*

Substantial unmet need remains in this era

- Most patients manifest substantial functional impairment[1,2]
- The greatest improvements with SMN targeted therapies are in the youngest individuals (age < 5)[1,2]
- SMN targeted therapies address neurodegeneration, other approaches to improve motor function are needed[3-5]

1. Mercuri E. *N Engl J Med.* 2018;378:625-35.DOI: 10.1056/NEJMoa1710504; 2. Mercuri, et al. SUNFISH Part 2: Efficacy and safety of risdiplam (RG7916) in patients with Type 2 or NonAmbulatory Type 3 SMA. Presented at the American Academy of Neurology Conference 2020. *Neurology* 2020, 94, 1260. 3. Hua Y et al. Nature. (2011) 478:123–6. doi: 10.1038/nature10485.
4. Sepulveda, P. et al. *Sci Rep 5*, 17535 (2015). https://doi.org/10.1038/srep17535.; 5. Wang Y, Pessin JE. *Curr Opin Clin Nutr Metab Care.* 2013 May;16(3):243-50. doi.; This third-party information is provided for background only and is not intended to convey or imply a comparison to the TOPAZ clinical trial results. SMA=spinal muscular atrophy; SMN=survival motor neuron gene.

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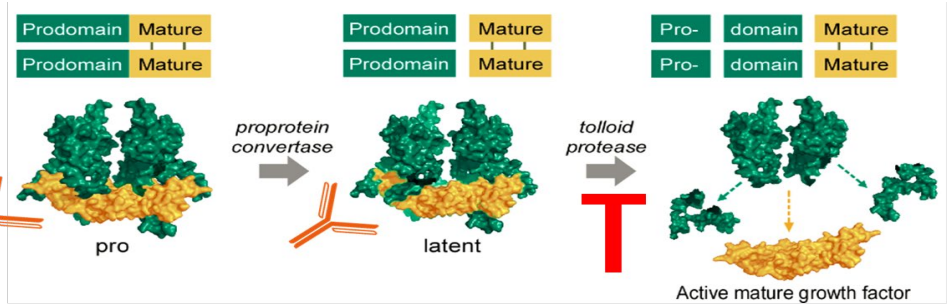
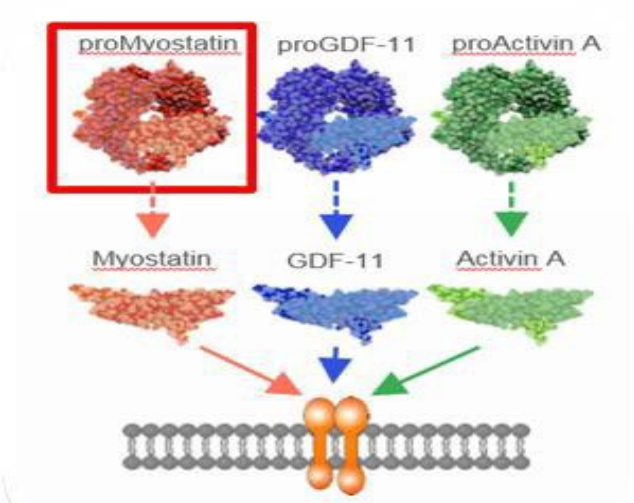
Myostatin Is An Important Negative Regulator Of Skeletal Muscle Growth Whose Inhibition has the Potential to Lead to Improved Muscle Function In Patients With SMA[1,2]

Apitegromab: A Fully Human Monoclonal Antibody That Blocks Cleavage of the Myostatin Prodomain, Thereby Inhibiting Myostatin Activation[2]



- Two distinct proteolysis events necessary to generate active mature myostatin
- Apitegromab binds to both proMyostatin and latent myostatin and inhibits tolloid-mediated cleavage of latent myostatin
- Apitegromab bound latent myostatin is proposed to be pulled from muscle into systemic circulation, and can be measured as part of total circulating myostatin.[3]

Selective Targeting of preproMyostatin, the Myostatin Precursor: Apitegromab does not bind to mature myostatin or any form of GDF11, Activin A, or other TGF-β family[2,3] members



1. Long KK, O'Shea KM, Khairallah RJ, et al. *Hum Mol Genet.* 2019;28:1076-1089. Available: https://pubmed.ncbi.nlm.nih.gov/30481286/
2. Pirruccello-Straub, et al. *Sci Rep.* 2018;8:2292. 3. Dagbay KB, et al. *J Biol Chem.* 2020;295(16):5404-5418.

TOPAZ Phase 2 Trial Design: Three Cohorts to Identify Therapeutic Opportunities

All SMA Types 2/3, cohorts defined by age and present ambulatory status at time of enrollment

	Ambulatory Patients (Revised Hammersmith Scale)	NonAmbulatory Patients (Hammersmith Functional Motor Scale Expanded)	
	Cohort 1	**Cohort 2**	**Cohort 3**
Design	• N = 23; ages 5-21 • Open-label, single-arm • 20 mg/kg apitegromab IV Q4W • 12-month treatment period	• N = 15; ages 5-21 • Open-label, single-arm • 20 mg/kg apitegromab IV Q4W • 12-month treatment period	• N = 20; ages ≥2 • Double-blind, randomized (1:1) to 2 or 20 mg/kg apitegromab IV Q4W • 12-month treatment period
Patients	• **Ambulatory Type 3 SMA** • Two subgroups: 1. Receiving nusinersen 2. Apitegromab monotherapy	• **Type 2 or Type 3 SMA** • **Receiving nusinersen (initiated at age 5 or older)**	• **Type 2 SMA** • **Receiving nusinersen (initiated 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

Apitegromab = non-proprietary name for SRK-015; HFMSE=Hammersmith Functional Motor Scale Expanded; RHS=Revised Hammersmith Scale

Data on file. Scholar Rock, Inc. Cambridge, MA.

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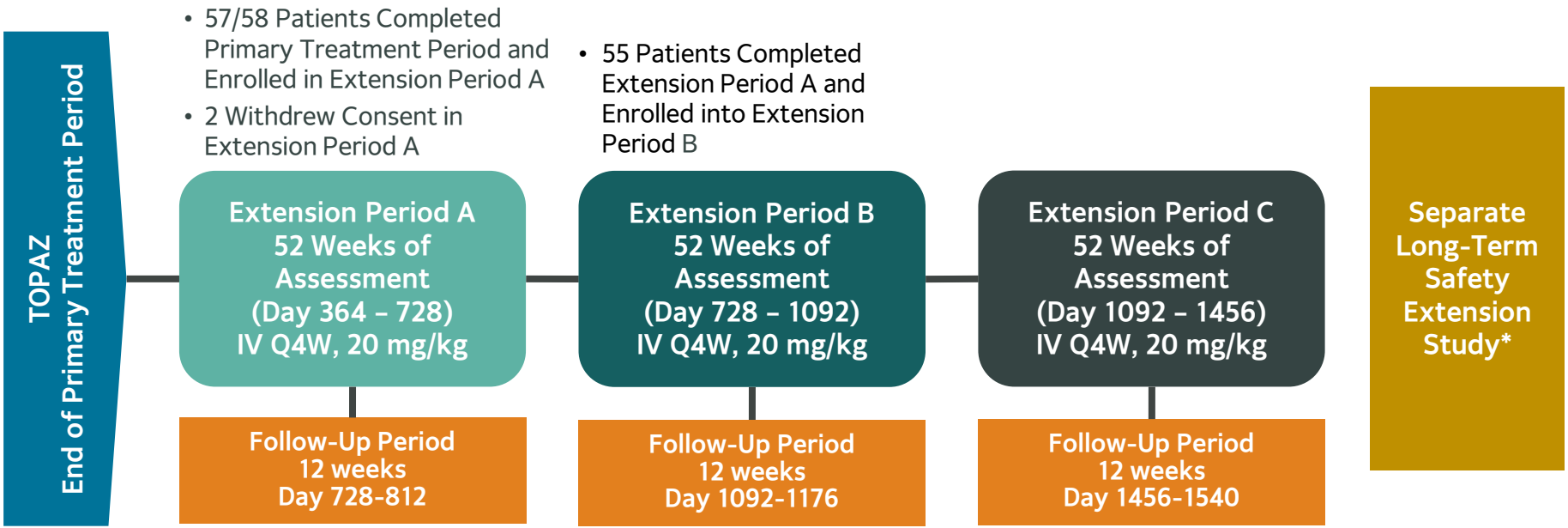
TOPAZ Extension Period Design



*Patients will be eligible to roll over into separate planned OLE trials

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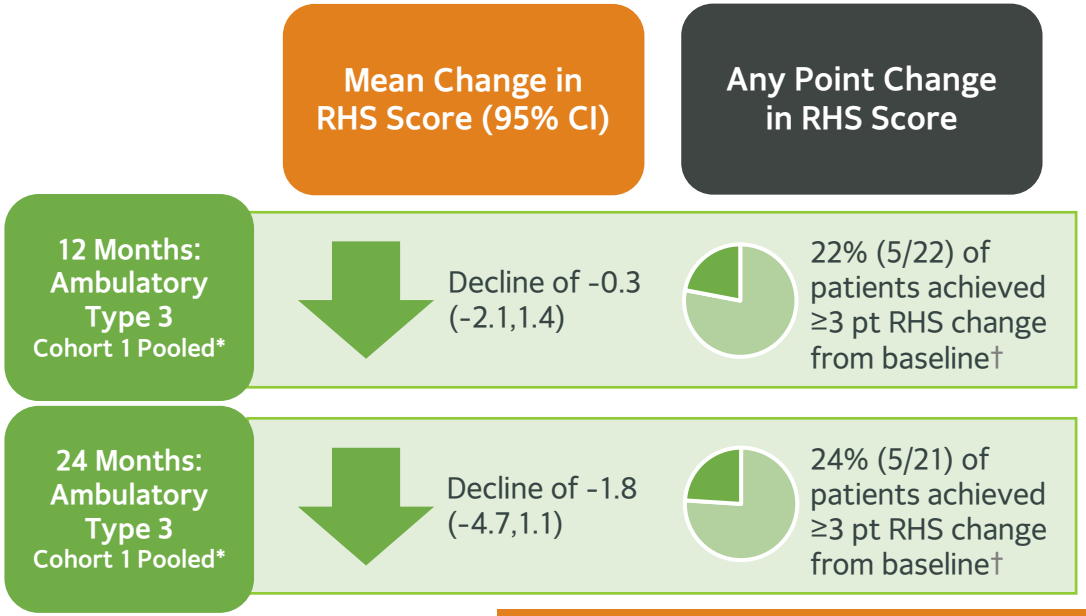
TOPAZ Subject Disposition, Demographics and Baseline Characteristics

		Cohort 1			Cohort 2	Cohort 3	
		20 mg/kg monotherapy	20 mg/kg + nusinersen		20 mg/kg + nusinersen	2 mg/kg + nusinersen	20 mg/kg + nusinersen
N (dosed)	Ambulatory Patients	11	12	NonAmbulatory Patients	15	10	10
Mean age at screening (min, max)		12.1 (7, 19)	13.1 (7, 21)		11.7 (8, 19)	4.1 (2, 6)	3.8 (2, 6)
Mean age at SMA diagnosis (min, max)		5.9 (2, 15)	4.5 (2, 15)		3.1 (1, 16)	1.2 (1, 2)	1.2 (1, 3)
Female (%)		73%	58%		53%	30%	50%
SMN2 Gene Copy* (#, %)							
2		1 (9%)	0 (0%)			1 (10%)	1 (10%)
3		4 (36%)	9 (75%)		11 (73%)	8 (80%)	8 (80%)
4		4 (36%)	1 (8%)		2 (13%)	1 (10%)	0 (0%)
# of maintenance doses of nusinersen at baseline (min, max)		N/A	5.6 (2, 8)		5.1 (2, 9)	5.5 (2, 9)	5.4 (3, 8)
Discontinuation(s)		0	2†		1†	0	0
Scoliosis (#, %)		7 (63.6)	4 (33.3)		11 (73.3)	4 (40%)	3 (30%)
Contracture(s) (#, %)		6 (54.5)	7 (58.3)		13 (86.7)	8 (80%)	4 (40%)
Mean RHS score (min, max)		47.6 (26, 63)	51.3 (43, 62)				
Mean HFMSE score (min, max)					22.7 (13, 39)	26.1 (12, 44)	23.5 (14, 42)

*1 patient answered 3-4, 1 patient answered >4 , both patients are in Cohort 1 treated with 20 mg/kg + nusinersen; data not available for all patients.
†1 cohort 1 patient discontinued study in 12M Treatment Period, 1 cohort 1 patient and 1 cohort 2 patient discontinued during 24M Extension Period A. All discontinuations were for reasons unrelated to study drug.
HFMSE=Hammersmith Functional Motor Scale Expanded; RHS=Revised Hammersmith Scale.
Data on File. Scholar Rock, Inc. Cambridge, MA.

Ambulatory Patients Receiving Apitegromab + SMN Targeted Treatment Suggests Stabilization of Motor Function Over 24 Months[1]



Therapeutic Potential of Apitegromab Observed in a Subset of the Ambulatory Patients: mainly in patients on apitegromab + nusinersen‡

*Observed Case (OC) Analysis includes all patients who had a valid measurement at E14 (Day 728); Inclusive of data from 3 patients in monotherapy who lost ability to ambulate. This analysis does not exclude any patients who missed doses due to COVID-19 related site access restrictions. †Data not shown; RHS, revised Hammersmith scale; 1. Data on File, Scholar Rock, Inc

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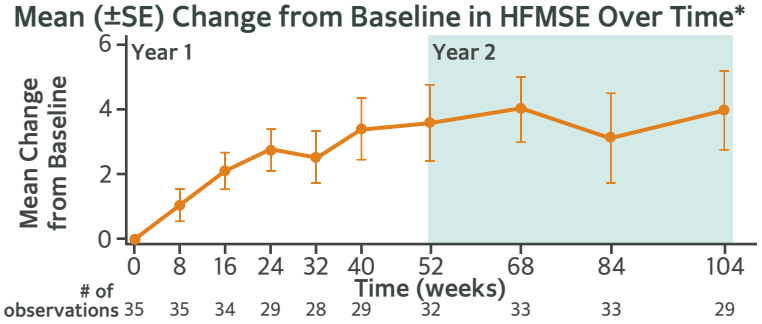
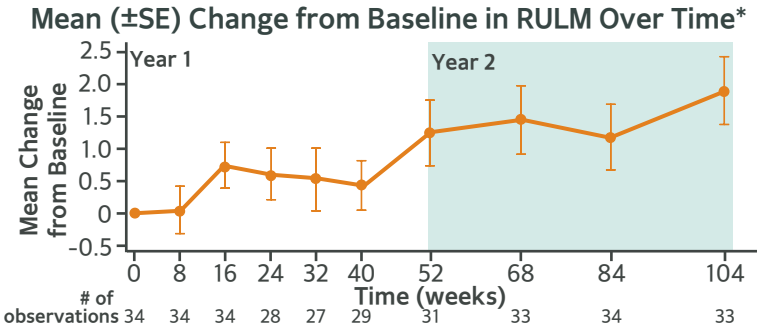
NonAmbulatory Patients Continue to Improve in Motor Function Over 24 Months of Apitegromab Treatment

	At 12 months*	At 24 months*
Mean Change in HFMSE (95% CI):	Increase of 3.6 (1.2, 6.0)	Increase of 4.0 (1.5, 6.5)
≥1 pt point change in HFMSE:	Achieved in 72% (23/32) of patients	Achieved in 62% (18/29) of patients
≥3 pt point change in HFMSE:	Achieved in 42% (13/32) of patients	Achieved in 45% (13/29) of patients
Mean Change in RULM score (95% CI):	Increase of 1.3 (0.2, 2.3)	Increase of 1.9 (0.8, 3.0)
≥1 pt point change in RULM:	Achieved in 48% (15/31) of patients	Achieved in 61% (20/33) of patients
≥2 pt point change in RULM:	Achieved in 40% (12/31) of patients	Achieved in 45% (15/33) of patients





Apitegromab + SMN targeted treatment in NonAmbulatory patients with Types 2 and 3 SMA (age 2-21) for 24 months demonstrated durable improvement in motor function (HFMSE) and continued increases in RULM scores.

*Observed Case (OC) Analysis includes all patients who had a valid measurement at E14 (Day 728).; OC analysis included patients treated with 2 mg/kg as well as 20 mg/kg of apitegromab. This analysis does not exclude any patients who missed doses due to COVID-19 related site access restrictions. Error bars represent SEM. CI, Confidence Interval; 1. Data on File, Scholar Rock, Inc.

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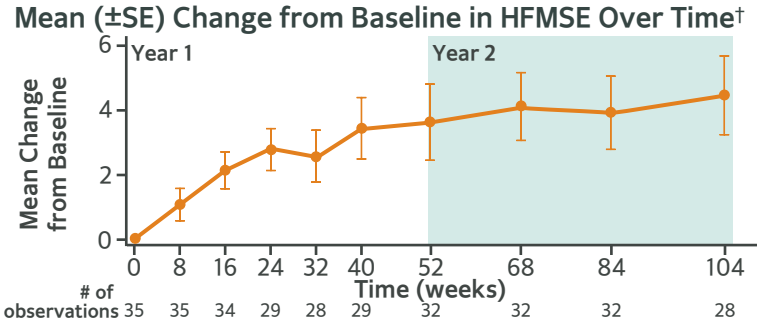
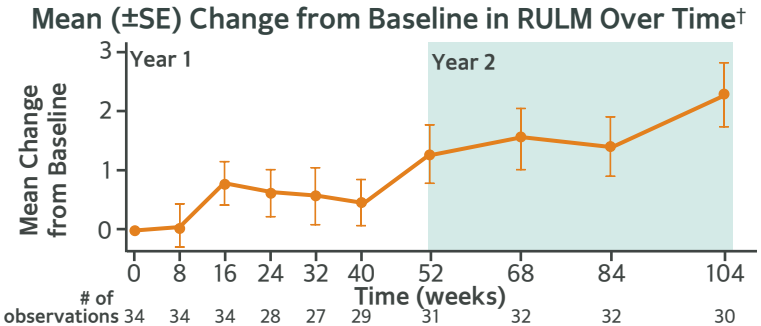
NonAmbulatory Patients Continue to Improve in Motor Function Over 24 Months of Apitegromab Treatment, Excludes Measurements Taken After Scoliosis Surgery

	At 12 months*	At 24 months†
Mean Change in HFMSE (95% CI):	Increase of 3.6 (1.2, 6.0)	Increase of 4.4 (2.0, 6.9)
≥1 pt point change in HFMSE:	Achieved in 72% (23/32) of patients	Achieved in 64% (18/28) of patients
≥3 pt point change in HFMSE:	Achieved in 42% (13/32) of patients	Achieved in 46% (13/28) of patients
Mean Change in RULM score (95% CI):	Increase of 1.3 (0.2, 2.3)	Increase of 2.3 (1.2, 3.4)
≥1 pt point change in RULM:	Achieved in 48% (15/31) of patients	Achieved in 67% (20/30) of patients
≥2 pt point change in RULM:	Achieved in 40% (12/31) of patients	Achieved in 50% (15/30) of patients



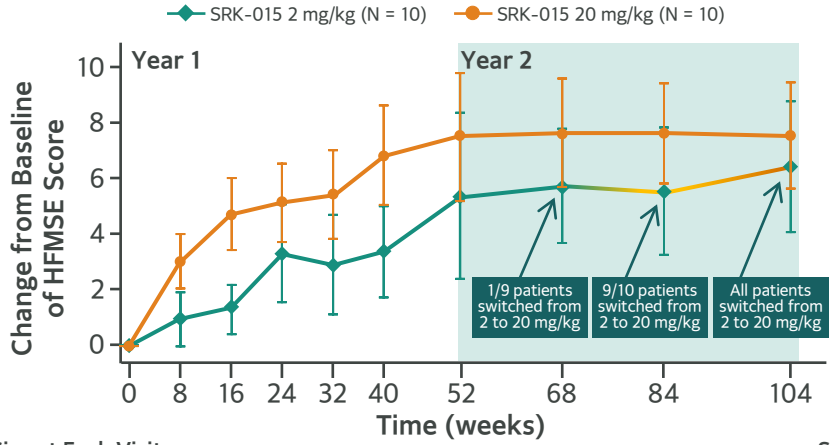


Apitegromab + SMN targeted treatment in NonAmbulatory patients with Types 2 and 3 SMA (age 2-21) for 24 months demonstrated durable improvement in motor function (HFMSE) and continued increases in RULM scores.

*Observed Case (OC) Analysis includes all patients who had a valid measurement at E14 (Day 728).; OC analysis included patients treated with 2 as well as 20 mg/kg of apitegromab. This analysis does not exclude any patients who missed doses due to COVID-19 related site access restrictions. †24 month Sensitivity Analysis excludes from the OC Analysis any HFMSE data following scoliosis surgery in TOPAZ. Of the three Non-Ambulatory patients who had scoliosis surgery, data from one was excluded and the other two did not have valid HFMSE assessments. Error bars represent SEM. CI, Confidence Interval; 1. Data on File, Scholar Rock, Inc..

High Dose Outperforms Low Dose in HFMSE & RULM, but Switchover to High Dose Closes the Gap in NonAmbulatory Patients in Cohort 3

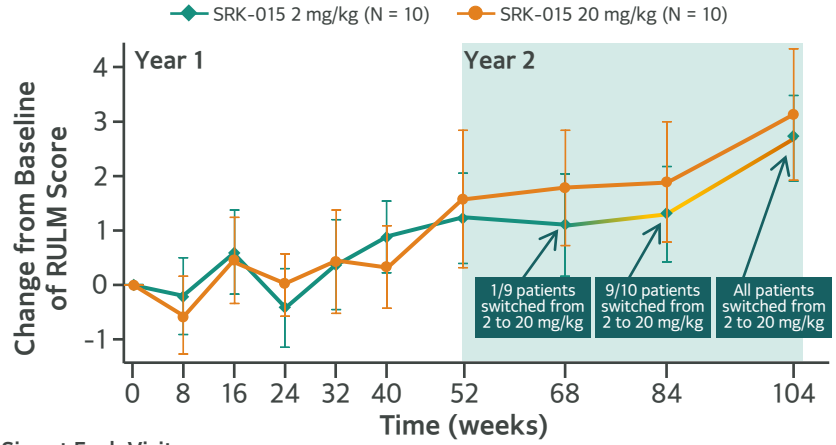
Mean (±SE) Change From Baseline in HFMSE Score Over Time (Cohort 3)*



Sample Size at Each Visit

2 mg/kg	10	10	10	7	8	9	9	9	10	10
20 mg/kg	10	10	10	8	8	10	8	10	10	8

Mean (±SE) Change From Baseline in RULM Score Over Time (Cohort 3)*



Sample Size at Each Visit

2 mg/kg	10	10	10	7	8	9	9	10	10	10
20 mg/kg	9	9	9	7	7	9	7	9	9	8

Dose Response Observed Over 24 Months

*24 month Sensitivity Analysis excludes from the OC Analysis any HFMSE data following scoliosis surgery in TOPAZ. Of the three NonAmbulatory patients who had scoliosis surgery, data from one was excluded and the other two did not have valid HFMSE assessments. Error bars represent SEM. Data on File, Scholar Rock, Inc.

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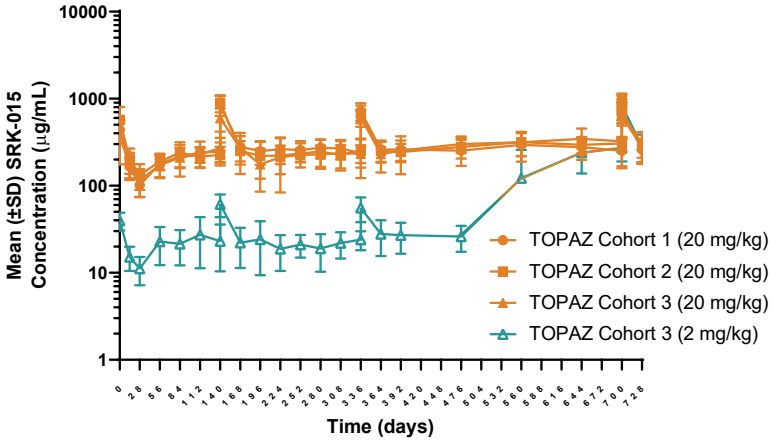
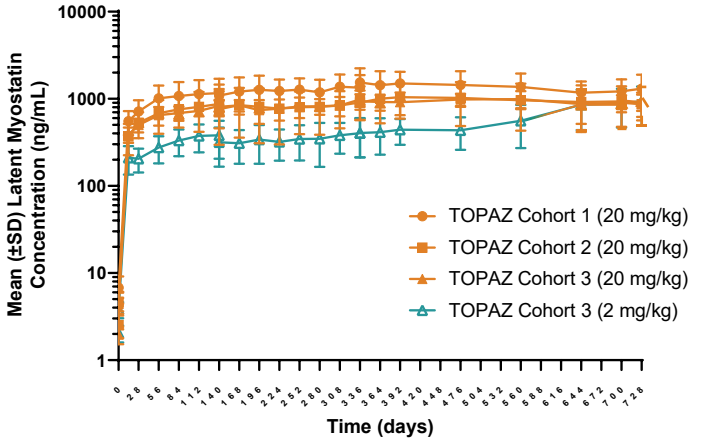
PK and PD Data are Consistent With Clinically Observed Dose Response

Pharmacokinetics* (PK)



- Well-behaved PK profile consistent with that commonly observed with monoclonal antibodies
- Drug exposure was dose proportional

Target Engagement [Pharmacodynamics (PD)]



- Target engagement by apitegromab was confirmed
- Low-dose (2 mg/kg) yielded lower level of target engagement and did not achieve full target saturation

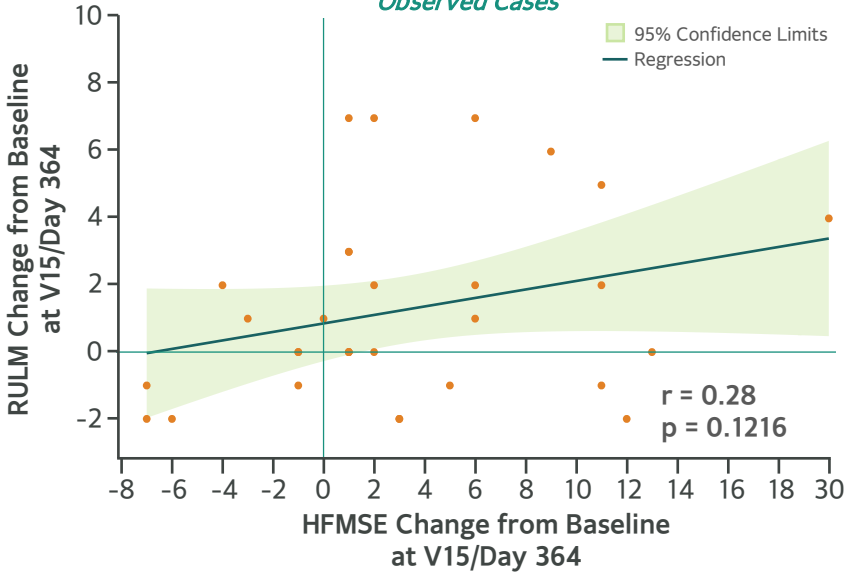
Higher drug exposure and target engagement reached when Cohort 3 low-dose patients switched from 2 mg/kg to 20 mg/kg

*Starting at day 28, measures are predose trough levels.
Data on File. Scholar Rock, Inc. Cambridge, MA.

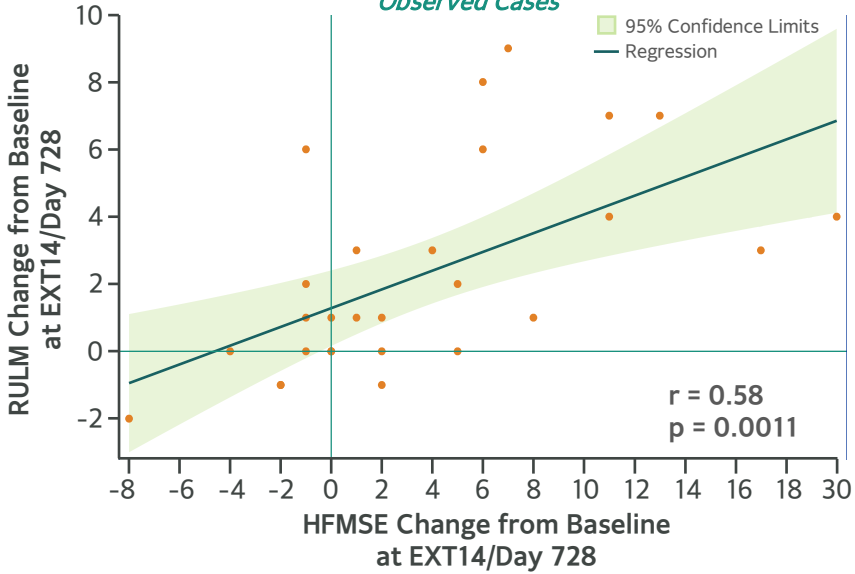
Relationship of HFMSE to RULM Tightens Over 2 Years:
NonAmbulatory Cohorts

Over 2 years, most patients had improvements in both HFMSE & RULM, suggesting durability of effect

RULM and HFMSE Change from Baseline at 12 Months
Observed Cases



RULM and HFMSE Change from Baseline at 24 Months
Observed Cases



*Observed Case (OC) 24 month Analysis includes all patients who had a valid measurement at extension visit 14 (Day 728).; OC analysis included patients treated with 2 mg/kg as well as 20 mg/kg of apitegromab. This analysis does not exclude any patients who missed doses due to COVID-19 related site access restrictions. The 12-month graph displays all patients who had a valid measurement at visit 15 (Day 364). 1. Data on File, Scholar Rock, Inc..

No New Serious Safety Risks Identified Over 2 Years of Treatment

Treatment-Emergent Adverse Events (TEAEs)*	Apitegromab 2 mg/kg dose (N=10) n (%)	Apitegromab 20 mg/kg dose (N=48) n (%)	Total (N=58) n (%)
Any TEAE	10 (100)	45 (93.8)	55 (94.8)
Any Serious TEAE	3 (30)	11 (22.9)	14 (24.1)
Any TEAE leading to study drug discontinuation	0 (0.0)	1 (2.1)	1 (1.7)
Any Grade 3 (severe) or higher TEAE	2 (20)	9 (18.8)	11(19)

- The incidence and types of TEAEs were consistent with the underlying disease or nusinersen therapy
- The 5 most common TEAEs were headache, pyrexia, upper respiratory tract infection, cough, and nasopharyngitis
- No deaths or suspected unexpected serious adverse reactions (SUSARs) reported
- Adverse events continue to be reported as mostly mild to moderate in severity, as observed during the 12-month analysis
- No new serious risks identified to date

*Notes: % = 100 x n/N
Treatment-emergent adverse events (TEAEs) are defined as AEs that start after the first dose of study drug or start prior to the administration of study drug and worsen in severity/grade or relationship to investigational medication after the administration of study drug; Data on File. Scholar Rock, Inc. Cambridge, MA.

Summary of TOPAZ Extension Period: 24-Month Data

- The results of these data are relevant for informing the therapeutic hypotheses being evaluated in the Phase 3 SAPPHIRE trial and thus could increase interest for this randomized double-blind, placebo-controlled study now in progress.
- NonAmbulatory Types 2/3 SMA: motor function gains with apitegromab treatment show durability at 24 months
  - Sustained increases in motor function (HFMSE & RULM) over 2 Years
  - Continued improvements in RULM throughout 2 years
  - Correlation between HFMSE & RULM tightens in 2nd year
  - High dose outperforms low dose in HFMSE & RULM, but switchover to high dose closes the gap
  - Consistent PK & PD dose response
- Stabilization of motor function over 2 years in ambulatory subjects with apitegromab + nusinersen
  - Potential motor function gains in subgroups
- No new serious safety risks identified over 2 years of apitegromab treatment
- **Many thanks to all the patients who participate in these studies, caregivers/families, healthcare professionals & patient advocacy groups**