Apitegromab, a Novel High-Affinity Anti-proMyostatin Monoclonal Antibody for Treating Spinal Muscular Atrophy: Results of a Phase 2 Interim Analysis.

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18 March 2021

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

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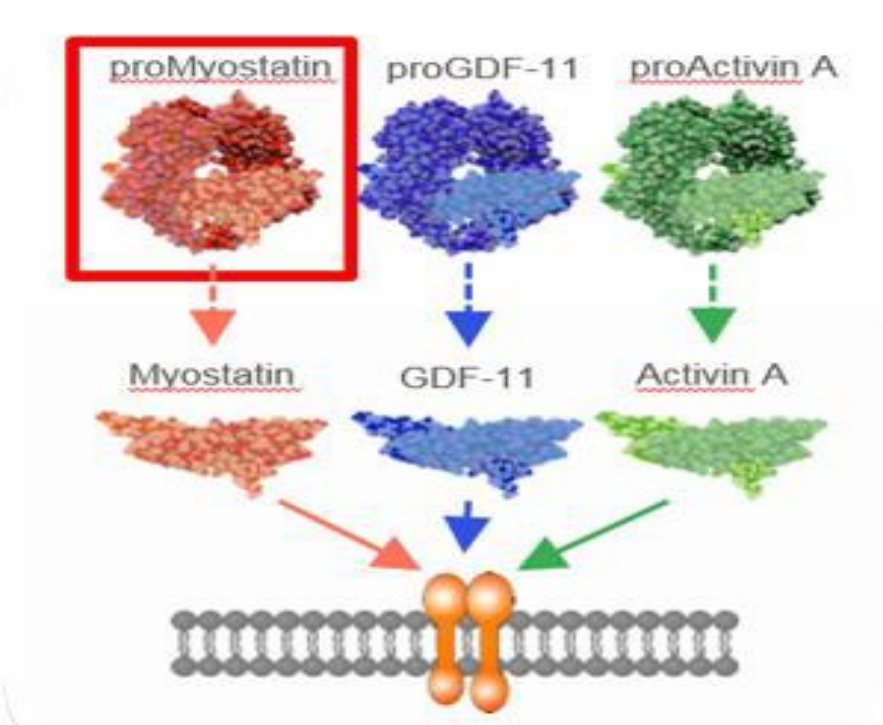
Spinal Muscular Atrophy (SMA) and Myostatin

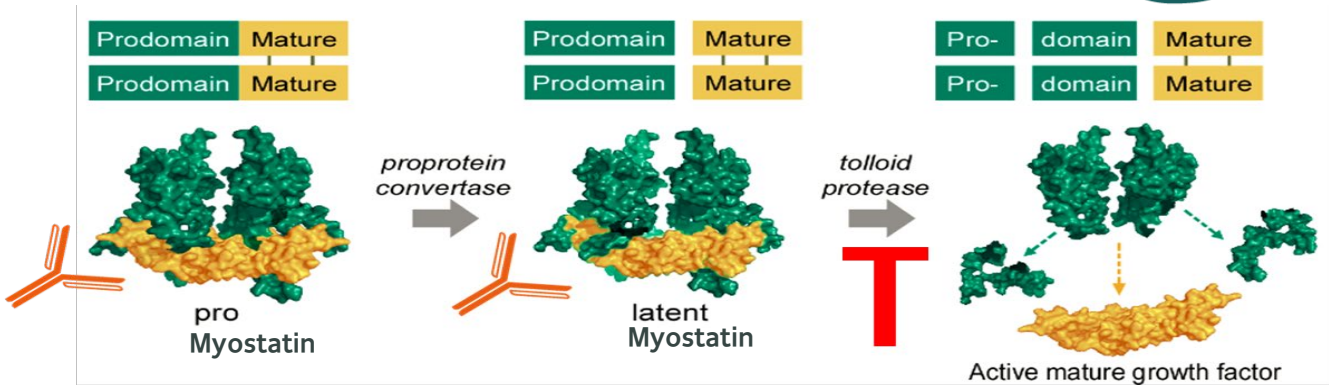
- SMA is a multi system disease: Increasing evidence extends the pathogenic effect of survival motor neuron (SMN) deficiency beyond SMN to include additional cells both within and outside the CNS, whereby numerous peripheral organs and non-neuronal tissues (e.g., cardiovascular system, immune system, gastrointestinal tract, and kidneys) have demonstrated pathological changes in pre-clinical models and patients.[1-6]
- Therapeutic strategies in SMA can be categorized either as SMN-dependent or as SMN-independent therapies. Deletion or mutation of SMN1 is partially compensated by limited expression of SMN protein produced by variable SMN2 copies, which provide a therapeutic target mostly aiming to target SMN2 in the treatment of SMA.[7-9]
- SMN up-regulators improve motor function but patients with SMA still struggle with muscle weakness/motor function.[10-11]
- Current therapies can only incrementally improve SMA symptoms. Thus, there remains a large unmet need for functional improvement.[12]
- Combination therapies may be used in the future to stabilize the disease course and prevent further functional losses.[13-15]
- Myostatin is a growth and differentiation factor that suppresses myoblast proliferation and myofiber hypertrophy.[16]
- As myostatin is a negative regulator of muscle mass, decreased expression of myostatin is associated with improved muscle function and mass in SMA patients.[17]

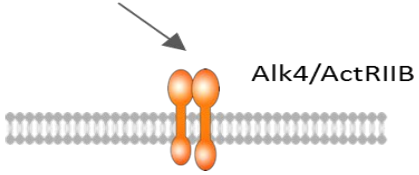
1. Hamilton J G et al. Trends Mol. Med. 2013, 19, 40–50. 2. Farrar MA et al. Ann. Neurol. 2017, 81, 355–368. 3. Schreml J et al. Eur. J. Hum. Genet. 2013, 21, 643–652. 4. Somers E et al. Ann. Neurol. 2016, 79, 217–230. 5. Deguise MO et al. Hum. Mol. Genet. 2017, 26, 801–819. 6. Nery FC et al. Neurol. Genet. 2019, 5, e353. 7. Feldkotter M et al. Am. J. Hum. Genet. 2002, 70, 358–368. 8. Burnett B G et al. Curr. Treat. Options Neurol. 2009, 11, 90–101. 9. Chang J G et al. Proc. Natl. Acad. Sci. USA 2001, 98, 9808–9813. 10. Finkel RS et al. N. Engl J Med. (2017) 377:1723–12. doi: 10.1056/NEJMoa1702752. 11. Hua Y et al. Nature. (2011) 478:123–6. doi: 10.1038/nature10485. 12. Spinraza® (nusinersen) Injection, for Intrathecal Use [Prescribing Information, 2016]. 13.Nash LA et al. Curr Mol Med. (2016) 16:779–92. doi: 10.2174/1566524016666161128113338 14. Tizzano EF et al. Neuromuscul Disord. (2017) 27:883–9. doi: 10.1016/j.nmd.2017.05.011 15. Wirthe B et al. Annu Rev Genomics Hum Genet 2020 Aug 31;21:231-261. 16.Thomas, et al. *J Biol Chem*. 2000;275:40235. 17. Mosher, et al. *PLoS Genet*. 2007;3:e79.

Apitegromab: Anti-ProMyostatin Monoclonal Antibody; A fully human antibody that blocks cleavage of the myostatin prodomain

Selective Targeting of proMyostatin, the Myostatin Precursor







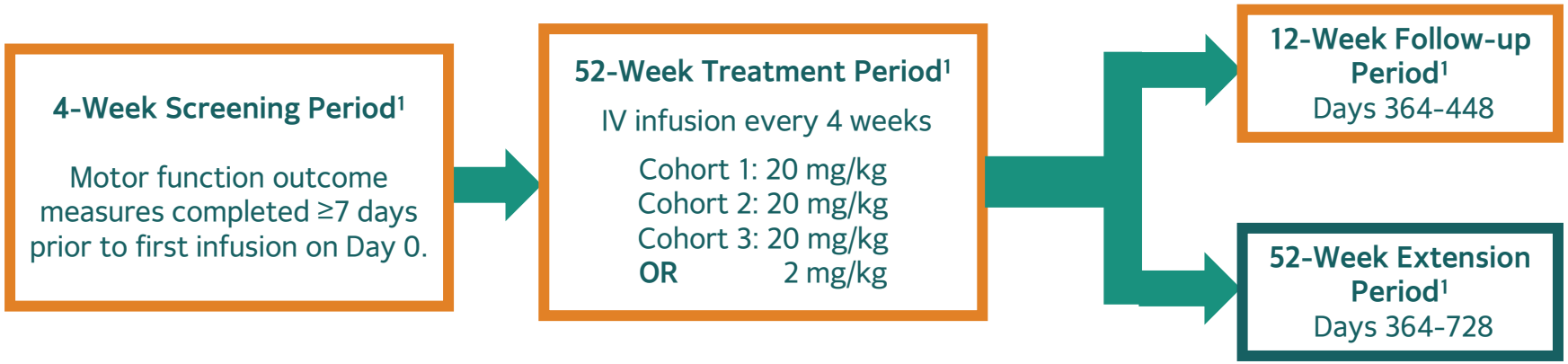
- Activation of myostatin requires two distinct proteolysis events that generate the active mature growth factor
- Apitegromab binds to both proMyostatin and latent myostatin and inhibits tolloid-mediated cleavage of latent myostatin

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

GDF11; Growth differentiation factor 11 also known as BMP11, Alk4/ActRIIB; Aristaless-like homeobox 4/Activin receptor type IIB,

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

Phase 2 Clinical Trial – TOPAZ Objectives and Design



	Cohort 1	Cohort 2	Cohort 3
Design[2]	• n=23; ages 5-21 years • Open-label, single-arm • 20 mg/kg Apitegromab IV Q4W • 52-week treatment period	• n=15; ages 5-21 years • Open-label, single-arm • 20 mg/kg Apitegromab IV Q4W 52-week treatment period	• n=20; ages ≥2 years • Double-blind, randomized (1:1) to 2 mg/kg or 20 mg/kg Apitegromab IV Q4W • 52-week treatment period
Subjects[2]	• 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[2]	• Safety • Mean change from baseline in RHS	• Safety • Mean change from baseline in HFMSE	• Safety • Mean change from baseline in HFMSE

Secondary endpoints: PK and PD effects; Time to therapeutic effect between low and high dose apitegromab in Cohort 3; Immunogenicity

RHS, Revised Hammersmith scale; HFMSE, Hammersmith functional motor scale expanded; mg/kg, milligram/kilogram; n, number; IV, intravenous; Q4W, every 4 weeks; PK, pharmacokinetics; PD, pharmacodynamics

ClinicalTrials.gov Identifier: NCT03921528.

1. Place, et al. Presented: Cure SMA Conference February 5–7, 2020, Evry, France; 2. Data on File. Scholar Rock, Inc

Subject Disposition, Demographics, Baseline Characteristics

	Ambulatory Subjects		Non-ambulatory Subjects		
	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
Dosed subjects, N	11	12	15	10	10
Mean age, years (min, max)	12.1 (7, 19)	13.1 (7, 21)	11.7 (8, 19)	4.1 (2, 6)	3.8 (2, 6)
Female, (%)	73	58	53	30	50
SMN2 Gene Copy, n (%)					
2	1 (9)	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
Baseline nusinersen mean maintenance doses, n	N/A	5.6	5.1	5.5	5.4
Discontinuation	0	1**	0	0	0
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)

**Patient who discontinued study for reasons unrelated to study drug; min, minimum; max, maximum

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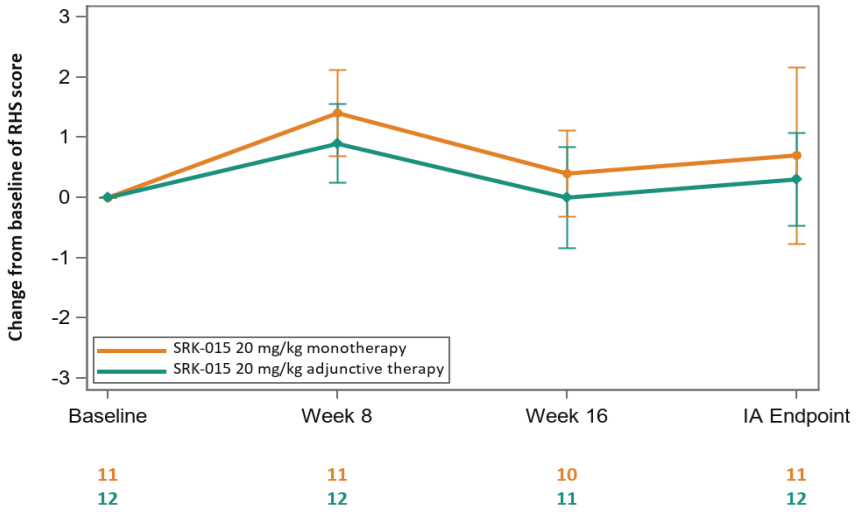
TOPAZ- Mean Baseline Change in Primary Efficacy Endpoints (Hammersmith Scale Scores)

Ambulatory Subjects; (Mean (+/- 1 SE) RHS Scores)

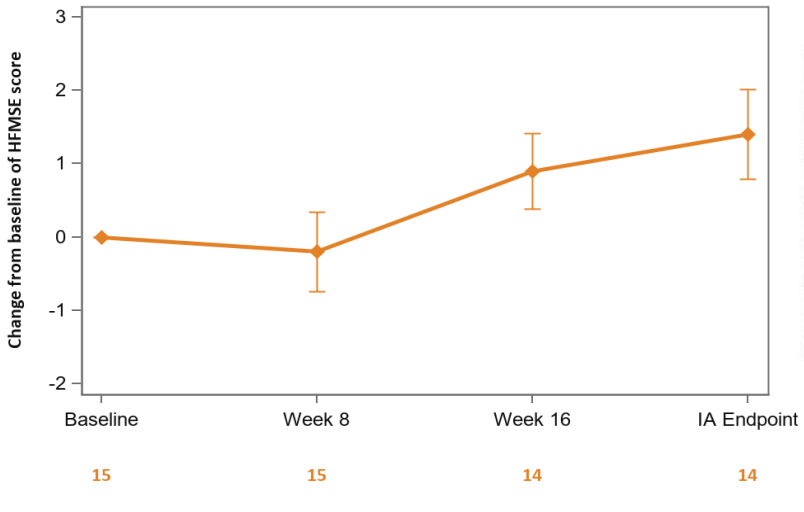
Non-ambulatory Subjects; (Mean (+/- 1 SE) HFMSE Scores)

Cohort 1



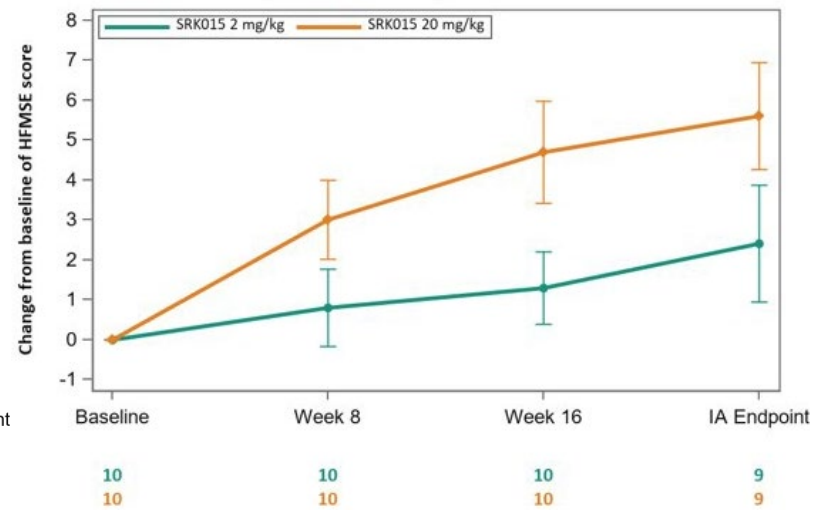
- Observed comparable effects between Apitegromab monotherapy and add-on subgroups

Cohort 2*



- Improvements from baseline in HFMSE scores progressively increased over time.

Cohort 3*



- The high-dose arm numerically outperformed low-dose arm across all timepoints.

No Plateau (or steady-state) was observed up to the 6-month interim analysis timepoint

*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; RHS, Revised Hammersmith Scale; HFMSE, Hammersmith Functional Motor Scale; SE, standard error; IA, interim analysis

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TOPAZ Interim Analysis: Proof-of-Concept

Multiple lines of evidence supporting the clinical efficacy

	Ambulatory Subjects (RHS)			Non-Ambulatory Subjects (HFMSE)		
	Cohort 1			Cohort 2	Cohort 3	
	20 mg/kg monotherapy (n=11)	20 mg/kg +nusinersen (n=12)	20 mg/kg pooled (n=23)	20 mg/kg +nusinersen (n=14)	2 mg/kg +nusinersen (n=9)	20 mg/kg +nusinersen (n=9)
Mean baseline change (95% CI)	0.7 (-2.5, 4.0)	0.3 (-1.4, 2.0)	0.5 (-1.1, 2.2)	1.4 (0.1, 2.7)	2.4 (-0.9, 5.8)	5.6 (2.5, 8.7)
≥1-pt increase, n (%)	7/11 (64)	5/12 (42)	12/23 (52)	10/14 (71)	6/9 (67)	9/9 (100)
≥3-pt increase, n (%)	4/11 (36)	2/12 (17)	6/23 (26)	3/14 (21)	4/9 (44)	6/9 (67)

- Mean improvements from baseline in HFMSE/RHS observed in each of the 3 cohorts.
- Substantial proportion of patients in each cohort attained ≥3-point improvement in HFMSE/RHS.
- Dose response demonstrated in Cohort 3 (randomized, double-blind, parallel arm design).
  - Greater improvements in HFMSE scores for high dose arm across evaluated timepoints.
  - Supportive PK/PD results; high dose led to higher drug exposure and target engagement.

HFMSE, Hammersmith Functional Motor Scale Expanded; RHS, Revised Hammersmith Scale.
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Treatment-Emergent Adverse Events (TEAEs) - All Cohorts

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)	20 mg/kg (n=15)	2 mg/kg (n=10)	20 mg/kg (n=10)	Total (n=20)
Subjects with any TEAE	10 (90.9)	9 (75.0)	19 (82.6)	13 (86.7)	9 (90.0)	8 (80.0)	17 (85.0)
Headache	5 (45.5)	3 (25.0)	8 (34.8)	3 (20.0)	2 (20.0)	1 (10.0)	3 (15.0)
Upper respiratory tract infection	3 (27.3)	2 (16.7)	5 (21.7)	2 (13.3)	3 (30.0)	3 (30.0)	6 (30.0)
Pyrexia	1 (9.1)	0	1 (4.3)	2 (13.3)	3 (30.0)	5 (50.0)	8 (40.0)
Nasopharyngitis	1 (9.1)	1 (8.3)	2 (8.7)	2 (13.3)	2 (20.0)	3 (30.0)	5 (25.0)
Cough	1 (9.1)	2 (16.7)	3 (13.0)	1 (6.7)	2 (20.0)	3 (30.0)	5 (25.0)
Vomiting	0	1 (8.3)	1 (4.3)	1 (6.7)	3 (30.0)	3 (30.0)	6 (30.0)
Nausea	1 (9.1)	2 (16.7)	3 (13.0)	1 (6.7)	2 (20.0)	1 (10.0)	3 (15.0)
Dizziness	3 (27.3)	1 (8.3)	4 (17.4)	2 (13.3)	0	0	0
Rash	1 (9.1)	0	1 (4.3)	1 (6.7)	2 (20.0)	2 (20.0)	4 (20.0)
Influenza	0	0	0	2 (13.3)	2 (20.0)	0	2 (10.0)
Diarrhea	0	1 (8.3)	1 (4.3)	0	2 (20.0)	1 (10.0)	3 (15.0)
Nasal congestion	1 (9.1)	0 (0.0)	1 (4.3)	1 (6.7)	0	2 (20.0)	2 (10.0)
Fall	2 (18.2)	2 (16.7)	4 (17.4)	0 (0.0)	0	0	0
Ear infection	0	0	0	1 (6.7)	2 (20.0)	0	2 (10.0)
Rhinorrhea	1 (9.1)	0	1 (4.3)	0	1 (10.0)	1 (10.0)	2 (10.0)
Tonsillar hypertrophy	2 (18.2)	0	2 (8.7)	0	1 (10.0)	0	1 (5.0)
Muscle spasms	0	2 (16.7)	2 (8.7)	0	1 (10.0)	0	1 (5.0)
Musculoskeletal pain	0	0	0	3 (20.0)	0	0	0

- **Incidence and severity of adverse events were consistent with underlying patient population and background therapy**

TEAEs were 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.

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Apitegromab May Have Therapeutic Potential in SMA:
TOPAZ 6 Month Interim Analysis Clinical Data Demonstrates Initial Proof of Concept

A dose response in the primary efficacy endpoint was demonstrated in the randomized, double-blind non-ambulatory cohort (Cohort 3)

- High dose Apitegromab attained a 5.6 point mean improvement over baseline at 6-months compared to low dose (2.4 point mean)

Motor function improvements were observed across all three treatment cohorts in the primary efficacy endpoints (Hammersmith scale scores) at 6-months

- 35% of total patients achieved ≥3 point increase in Hammersmith scores
- 67% of total patients achieved ≥1 point improvement in Hammersmith scores
    - Most subjects observed a ≥1-pt increase in Hammersmith scores
        - Cohort 1: 52% (pooled)
        - Cohort 2: 71%
        - Cohort 3: 100% high dose, 67% low dose

Incidence and severity of adverse events were consistent with underlying patient population and background therapy

- Most frequent reported adverse events were headache and upper respiratory tract infections

Apitegromab has the potential to be the first muscle-directed, SMN-independent therapy for patients with SMA, as an adjunct to background SMN upregulator treatment

- 52-week data may enable evaluation for potential durability and further improvements in motor function

First clinical data showing the potential therapeutic benefits of Scholar Rock's innovative scientific platform of inhibiting the activation of latent myostatin

Topline Results from the TOPAZ trial are due in Q2 2021 and may inform future studies in SMA

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Thank you!

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