TOPAZ

Apitegromab, a Novel, Investigational, High-Affinity Anti-pro Myostatin Monoclonal Antibody for Treating Spinal Muscular Atrophy (SMA):

Topline Phase 2 PK/PD Related to Efficacy

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On behalf of the TOPAZ Study Team and the Scholar Rock Development Team

ScholarRock

Scholar Rock Disclosures and Disclaimers

- TOPAZ trial is sponsored by Scholar Rock, a biopharmaceutical company developing and investigating apitegromab for SMA
- Apitegromab is an investigational product candidate that is currently being evaluated in a clinical trial for the treatment of spinal muscular atrophy.
- Apitegromab 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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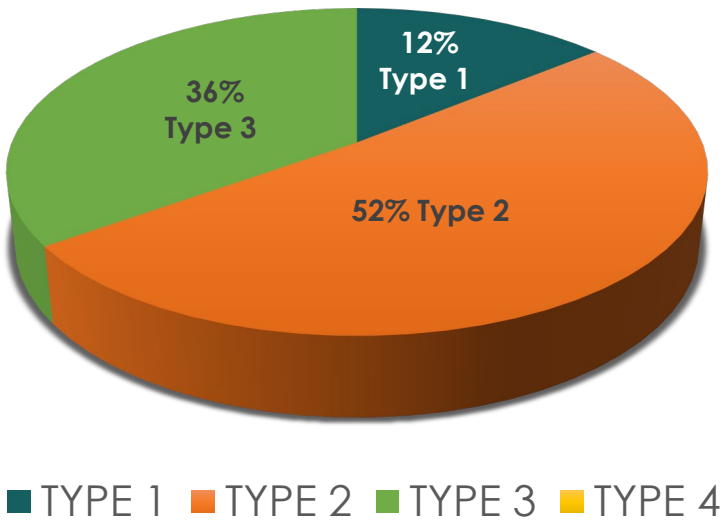
Spinal Muscular Atrophy (SMA) Is a Neuromuscular Disease of Chronic, Lifelong Progressive Pathology With a High Unmet Need Despite Current Foundational Therapy[1-7]

Overall Prevalence of SMA: 30,000-35,000 in US and EU[1]

RELATIVE PREVALENCE AMONG PATIENTS LIVING WITH SMA[1]



Type 2:
- Infant-onset; often fatal

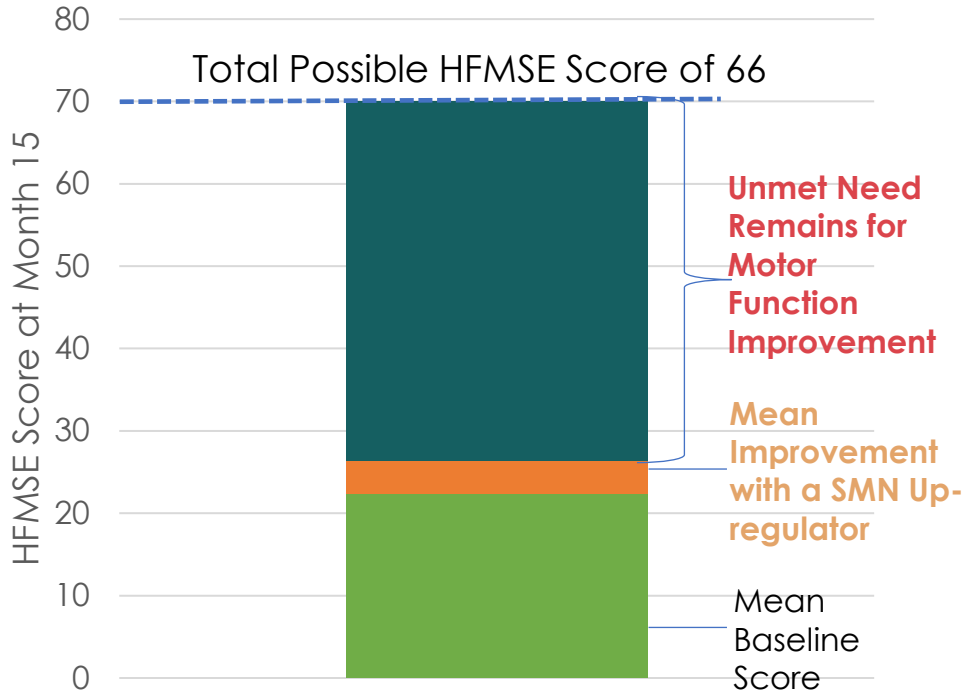
Type 2 and nonambulatory Type 3:
- Later-onset but still early childhood
- Severe deficits in motor function

Ambulatory Type 3:
- Limited mobility and substantial morbidity

Type 4:
- Population not well-characterized

Muscle Function in SMA[2]

Hammersmith Functional Motor Scale Expanded (HFMSE)



Mean Improvement in HFMSE score experienced by patients with later-onset SMA*

Limitations of existing treatments and specific subpopulations who may be refractory or intolerant to treatment exist.[8]

* In the Phase 3 CHERISH trial of SOC; 1. SMA Foundation Overview. http://www.smafoundation.org/wp-content/uploads/2012/03/SMA-Overview.pdf.; Accessed April 18, 2021; ; 2. Mercuri E et al.; N Engl J Med 2018; 378:625-635; DOI: 10.1056/NEJMoa1710504; 3. SMN1 gene. Genetics Home Reference. NIH. https://ghr.nlm.nih.gov/gene/SMN1. Accessed December 18, 2019 4. Werlauff U, Vissing J, Steffensen BF. Neuromuscul Disord. 2012;22(12):1069-1074. 5. Deymeer F, et al. Neurology. 2008;71:644-649 . 6. Wadman RI,, et al. Eur J Neurol. 2018;25(3):512-518. 7. Montes J, et al. PLoS One. 2018;13(6):e01996573. 8. SMA Voice of the Patient Report. https://www.curesma.org/wp-content/uploads/2018/01/SMA-VoP-for-publication-1-22-2018.pdf, Accessed April 18, 2021

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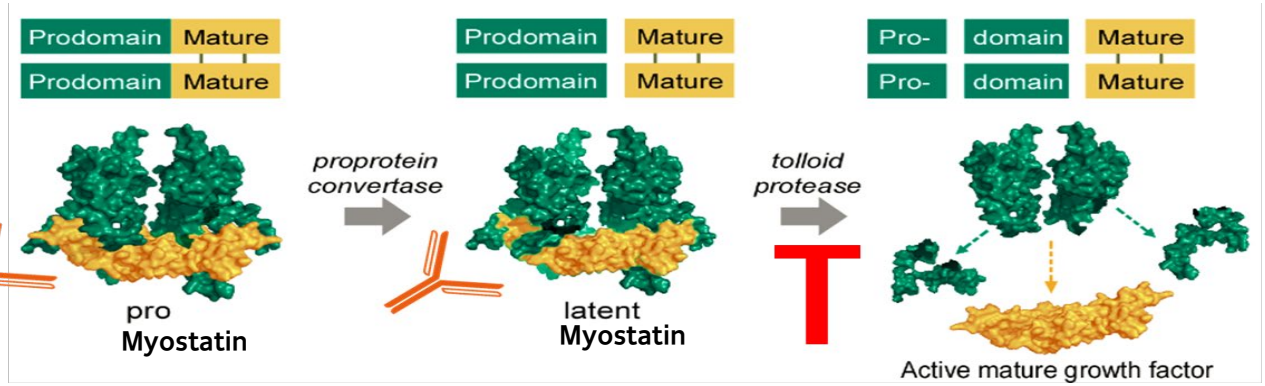
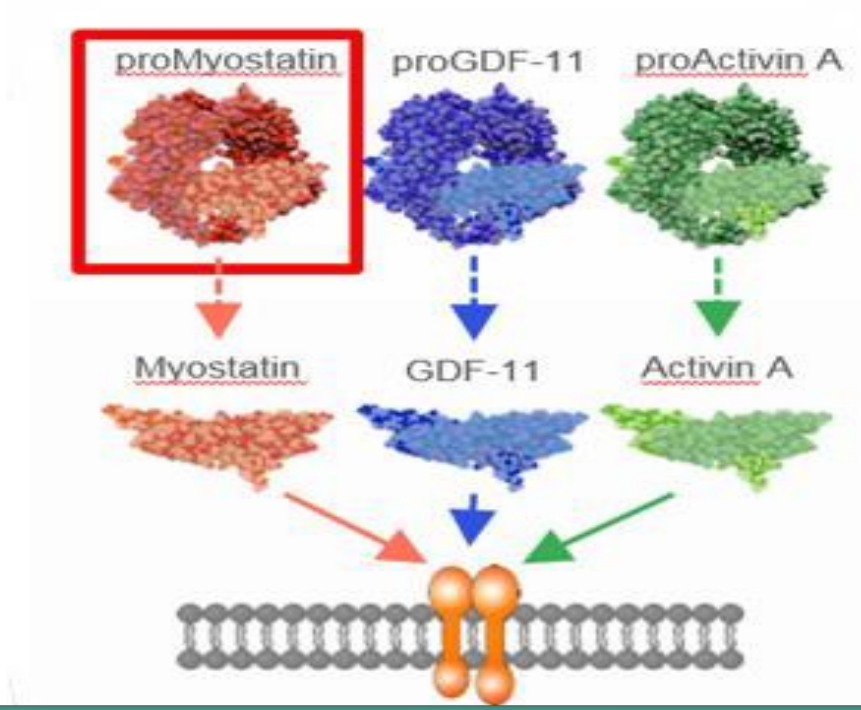
Myostatin Is An Important Negative Regulator Of Skeletal Muscle Growth Whose Inhibition Leads To Improved Muscle Function In Patients With SMA[1,2]



- 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**

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



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

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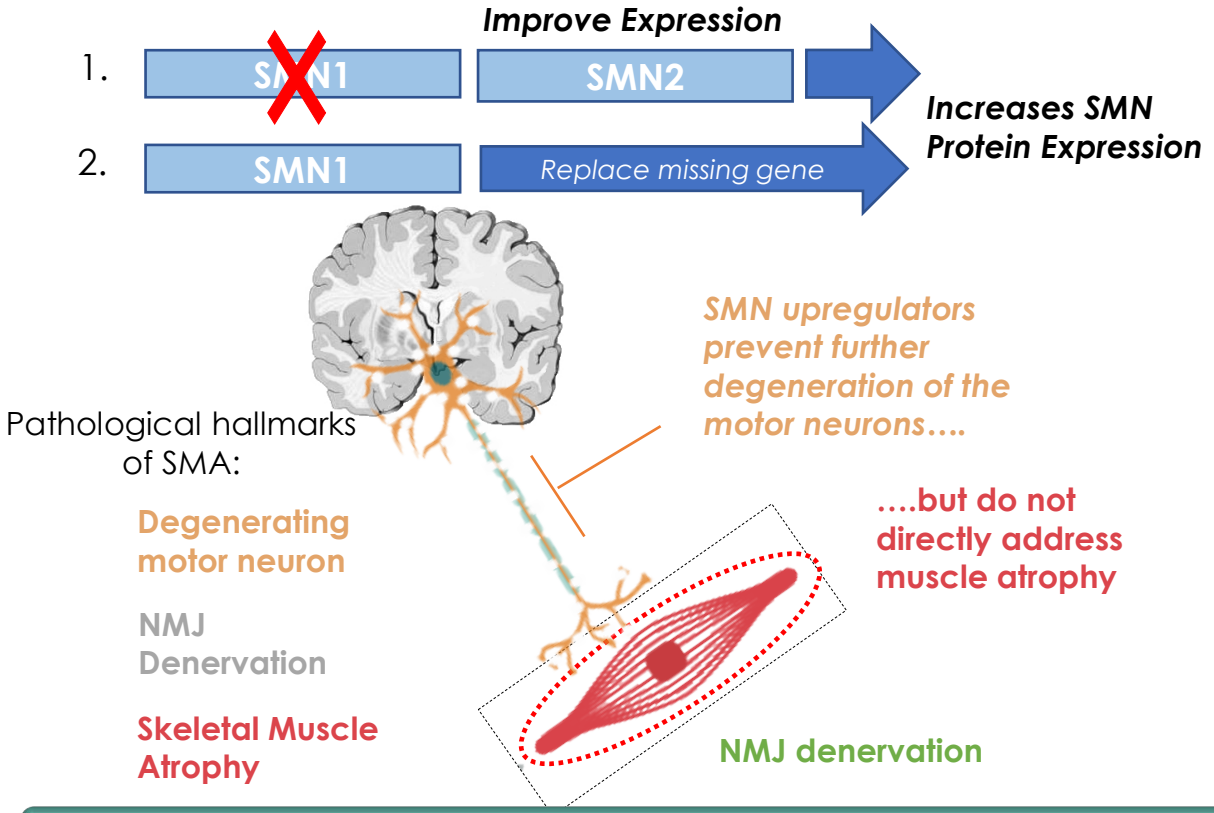
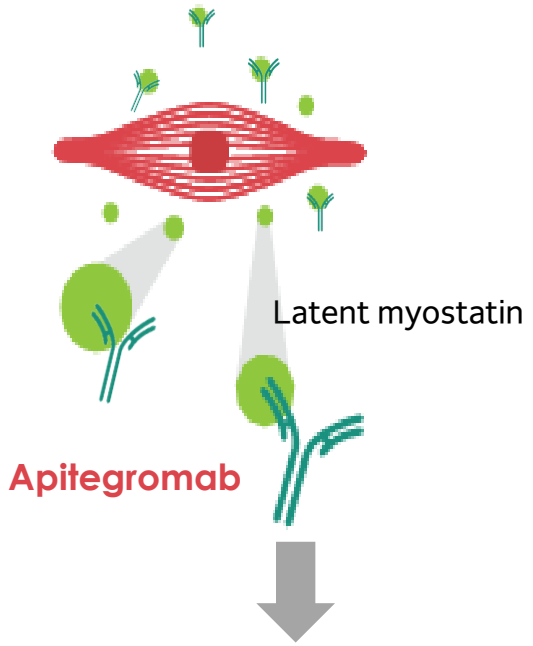
1. Long KK, O'Shea KM, Khairallah RJ, et al. Hum Mol Genet. 2019;28:1076-1089. Available: https://pubmed.ncbi.nlm.nih.gov/30481286/ 2. Pirruccello-Straub, et al. Sci Rep. 2018;8:2292.

Apitegromab May Represent A Novel MOA to Possibly Improve and Maintain Neuromuscular Integrity and Function Throughout Life

SMN upregulators directly address motor neuron degeneration but not muscle atrophy[1]



Apitegromab is a potential muscle-directed approach aimed at improving muscle atrophy and motor function[2,3]



- Myostatin is a negative regulator of skeletal muscle growth
- Apitegromab is a fully human, monoclonal antibody that specifically binds to proforms of myostatin, which include promyostatin and latent myostatin, thereby inhibiting myostatin activation

Aim to improve motor function by inhibiting myostatin activation with apitegromab

Safe treatments that stabilize the disease course and prevent further functional losses are valued by SMA patients.[3]

Adapted from: 1. SMA Foundation Overview. http://www.smafoundation.org/wp-content/uploads/2012/03/SMA-Overview.pdf.; Accessed April 18, 2021; 2. Long KK, et al. *Hum Mol Genet*. 2019;28(7):1077-1088; 3. Pirruccello-Straub M, et al. *Sci Reports*. 2018;8(1):2292. doi:10.1038/s41598-018-20524-9.; *Apitegromab is an investigational product candidate under development.; *apitegromab = SRK-015*

TOPAZ Trial Design: Three pilot cohorts to identify therapeutic opportunities

All SMA Types 2/3, groups defined by age and present ambulatory status

Ambulatory Cohort

- Ambulatory Type 3 (age 5-21)
- Monotherapy or with nusinersen Apitegromab (20 mg/kg IV q4w)

Non-Ambulatory, Ages 5-21 Cohort

- Type 2/3; Age 5-21; had started SMN upregulator **after** age 5
- Apitegromab (20 mg/kg IV q4w) + nusinersen

Non-Ambulatory > Age 2 Cohort

- Type 2; Age ≥ 2; had started SMN upregulator **before** age 5
- Apitegromab (2 or 20 mg/kg IV q4w) + nusinersen

12-months monthly apitegromab therapy until primary efficacy endpoint

Mean Hammersmith Score Change from Baseline

57 Patients* Completed 12-Month TOPAZ Trial

All Elected to Opt Into 52- Week Extension Period

*Excludes one patient from Cohort 1 who discontinued from the trial.; Data on File. Scholar Rock, Inc; Apitegromab is an investigational product candidate under development; HFMSE=Hammersmith Functional Motor Scale Expanded for SMA; RHS=Revised Hammersmith Scale for SMA

The Data Support That Apitegromab Stabilizes And Improves Motor Function In Patients With Later-onset SMA

Ambulatory Cohort: Majority Maintained or Improved RHS Scores from Baseline[1]

Ambulatory Type 3 SMA	Pooled (n=23) Apitegromab (20 mg/kg) + nusinersen or monotherapy
Mean change from baseline in RHS (95% CI)	-0.3 (-2.1, 1.4)
# (%) patients achieving ≥0-pt increase in RHS	13/23 (57%)
# (%) patients achieving ≥1-pt increase in RHS	9/23 (39%)
# (%) patients achieving ≥3-pt increase in RHS	5/23 (22%)

- TOPAZ results demonstrate functional stabilization or improvement in ambulatory patients
- Stabilization is defined as a ≥0-point increase, which is the goal of treatment for those with more established disease[2]
- Potential signal of motor function benefit in ambulatory type 3, where natural history suggests decline is common[2]
  - Increases from baseline of up to 8-points observed

Nonambulatory; Age 5-21 Cohort: Majority of Patients Attained Increases in HFMSE[1]

Non-Ambulatory; Age 5-21 Cohort Type 2/3	Apitegromab (20 mg/kg) + nusinersen**(n=14)
Mean change from baseline in HFMSE (95% CI)	+0.6 (-1.4, 2.7)
# (%) patients with ≥1-pt increase in HFMSE	9/14 (64%)
# (%) patients with ≥3-pt increase in HFMSE	4/14 (29%)
# (%) patients with ≥5-pt increase in HFMSE	2/14 (14%)

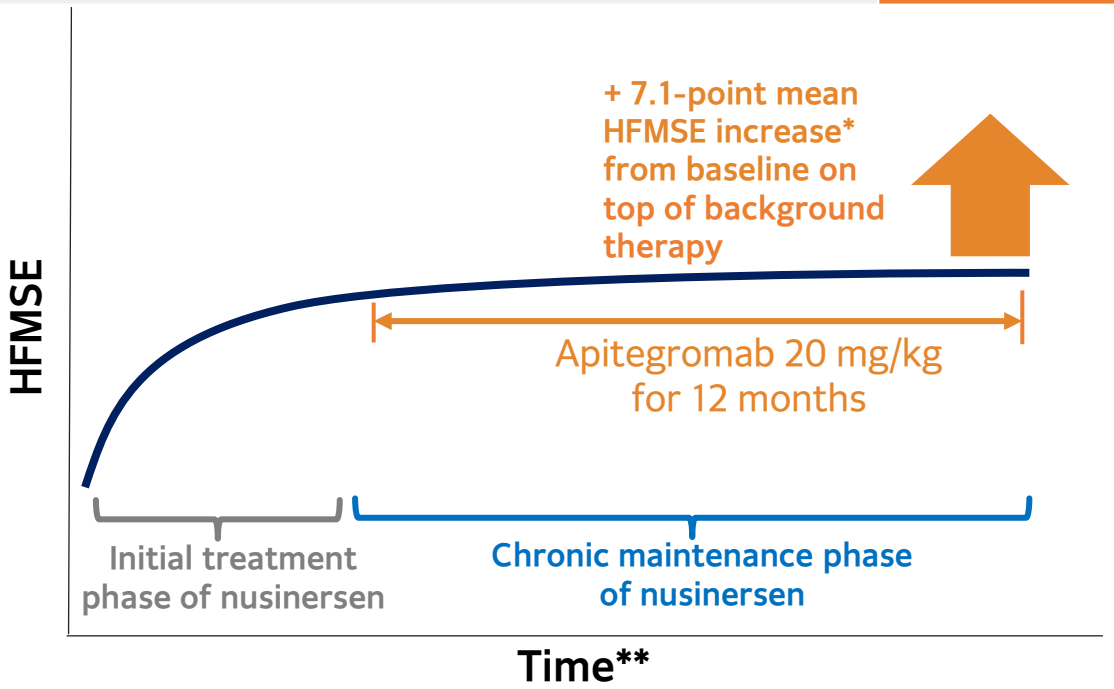
- Majority of patients attained increases in HFMSE
  - Improvements seen even with this difficult to treat older patient population[2]
- Previous SOC data suggest older patients on average observe steeper declines and rarely observe a 3-point increase in HFMSE[3]
  - Relatively larger HFMSE effects in age ≤12 years subgroup
  - 50% of ≤12-year old patients experienced ≥3-point increase in HFMSE†

A 3-point change on the HFMSE is agreed upon by experts to represent a clinically meaningful two or three skills change.[4]
A 6-point improvement reflects achievements in three to six motor skills.[4]

Intent to Treat Population; *Includes 2 patients in monotherapy and 2 patients in apitegromab + nusinersen subgroup who maintained RHS score (0-point change from baseline); **Patient had concomitant exposure to an acetylcholinesterase inhibitor, which is not permitted per the TOPAZ trial protocol; 1. Data on file. Scholar Rock, Inc. Cambridge, MA; 2. C Vuillerot et al. Archives of Physical Medicine and Rehabilitation 2013;94:1555-61; 3. Mercuri E et al.; N Engl J Med 2018; 378:625-635; DOI: 10.1056/NEJMoa1710504; 4. Swoboda KJ et al. PLoS One 2010;5(8):e12140-e12140;
Apitegromab is an investigational product candidate under development.

Non-ambulatory ≥ 2 years SMA Patients: Significant HFMSE Increases Attained with Apitegromab[1]

Non-ambulatory ≥ 2 Years Type 2 SMA*	Apitegromab 20 mg/kg + nusinersen (n=8)	Apitegromab 2 mg/kg + nusinersen (n=9)	Pooled (n=17)
Mean change from baseline in HFMSE (95% CI)	+7.1 (1.8, 12.5)	+5.3 (-1.5, 12.2)	+6.2 (2.2, 10.1)
# (%) patients achieving ≥1-pt increase in HFMSE	7/8 (88%)	7/9 (78%)	14/17 (82%)
# (%) patients achieving ≥3-pt increase in HFMSE	5/8 (63%)	5/9 (56%)	10/17 (59%)
# (%) patients achieving ≥5-pt increase in HFMSE	5/8 (63%)	5/9 (56%)	10/17 (59%)

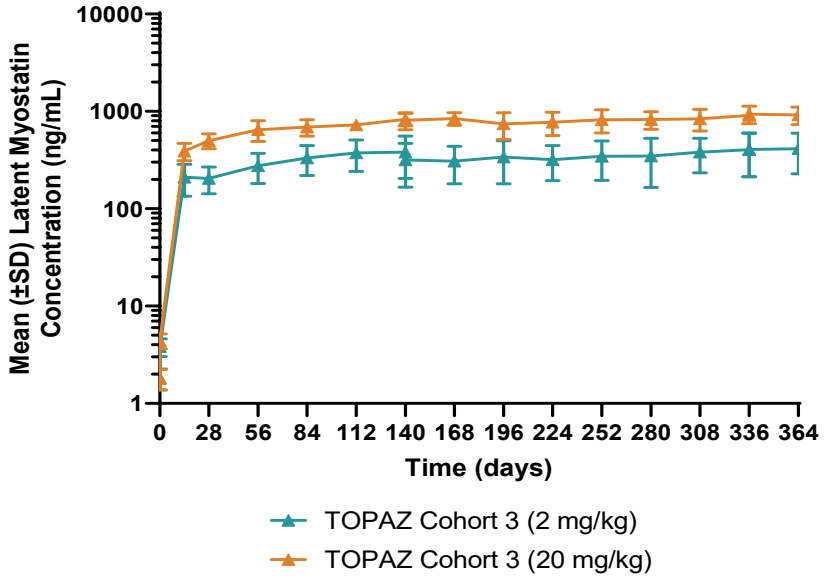


- This magnitude of increase not seen with other therapies at this stage and have demonstrated a plateau effect during chronic maintenance phases[2]
- Previous studies suggest significant HFMSE increases do not occur in younger patients with non-ambulatory Type 2/3 SMA following first year of nusinersen treatment[2]
  - 63% experienced ≥5-point gains in HFMSE with apitegromab
  - 38% of the 20 mg/kg arm showed >10-point gain in HFMSE

*This was a primary intent-to-treat (ITT) analysis that, as prespecified, excluded 2 patients who missed 3 doses due to COVID-19 related site access restrictions. An all-patients analysis that included those 2 patients had similar results as this primary ITT analysis.; **Analysis of all 10 patients, including the 2 patients who missed 3 doses due to COVID-19 related site access restrictions showed improvements of >10 point gain in HFMSE. **The HFMSE time course plot for background nusinersen effect is hypothetical and intended for illustrative purposes only. The data presented here do not reflect any cross-trial comparisons.; 1. Data on File. Scholar Rock, Inc; 2. Mercuri E, et.al. N Engl J Med. 2018;378:625-635.

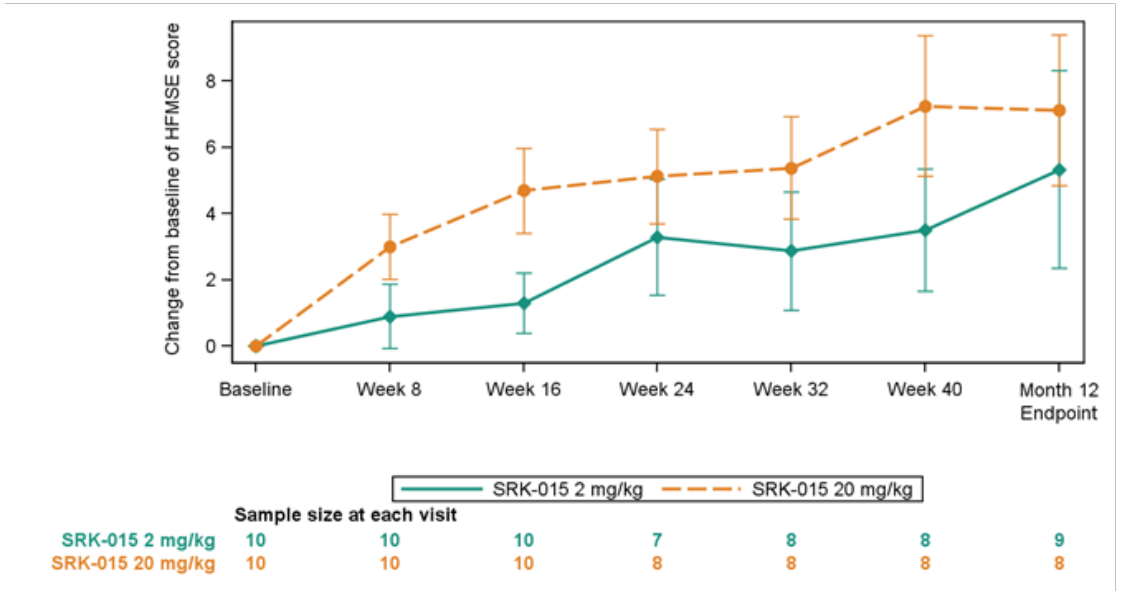
Non-Ambulatory ≥ 2 Years SMA Cohort: Dose Response Observed in Pharmacodynamic & Efficacy Data[1]

Target Engagement



- Both 2 mg/kg and 20 mg/kg doses yielded high levels of **target engagement** (>100-fold increase from baseline)
- 20 mg/kg dose offers relatively higher magnitude of target engagement than 2 mg/kg dose
- The largest fold-change in latent myostatin from baseline was observed in the Younger NonAmbulatory high dose Type 2 Cohort

Mean (±SEM) change from baseline in HFMSE scores



- Both 2 mg/kg and 20 mg/kg doses had sizable dose dependent HFMSE increases already on chronic maintenance nusinersen
- 20 mg/kg dose numerically offered greater HFMSE increases than 2 mg/kg dose across all timepoints
- Continuous and durable improvements observed through 12 months

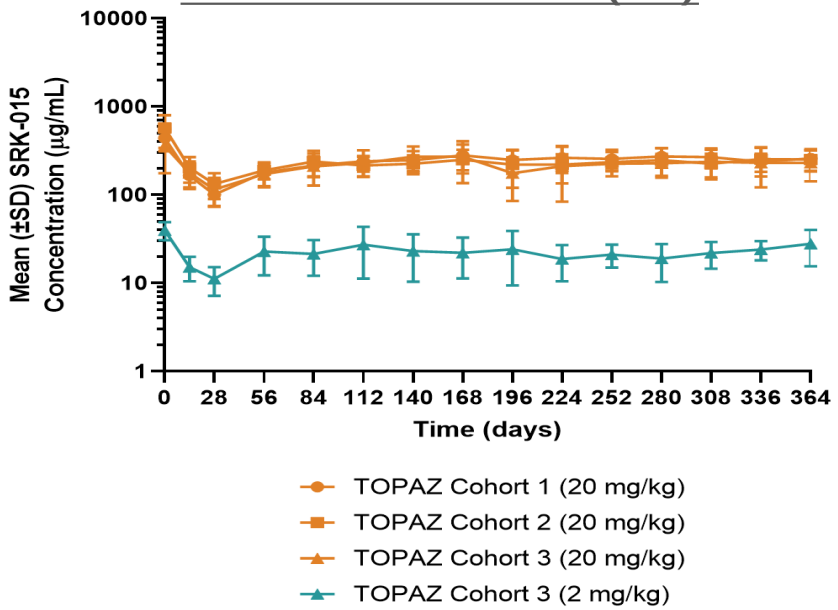
Both doses demonstrated activity, with greater target engagement and efficacy observed with 20 mg/kg

1. Data on File. Scholar Rock, Inc.; Apitegromab is an investigational product candidate under development.

Target Engagement Was Achieved With Durability Of Effect Observed Through 12-month Treatment Timeframe Across All Cohorts

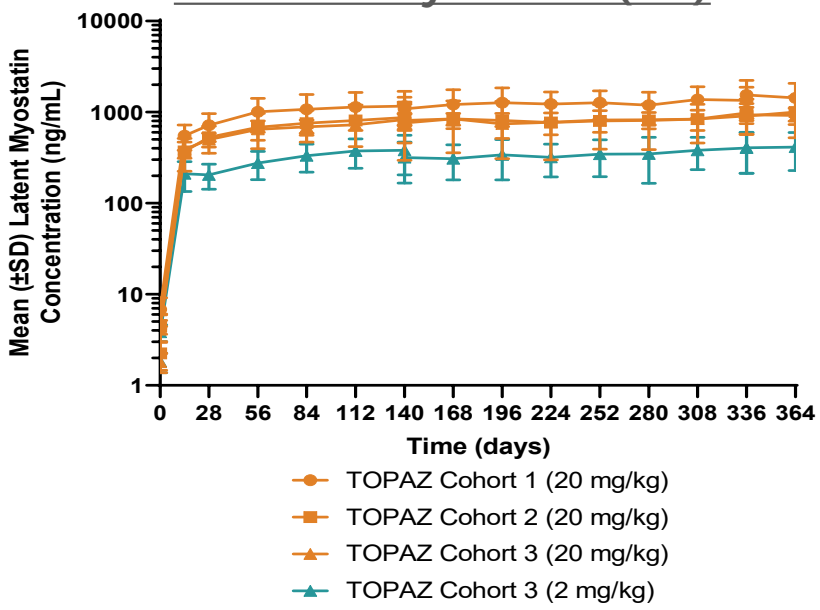
Pharmacokinetic and Pharmacodynamic Data are Supportive of Clinically Observed Dose Response

Pharmacokinetics* (PK)



- Dose-proportional and sustained drug exposure following chronic administration of apitegromab

Pharmacodynamics (PD)



- Both 2 mg/kg and 20 mg/kg doses yielded high levels of target engagement (>100-fold increase from baseline) assessed by serum latent myostatin levels
- 20 mg/kg dose offers higher levels of target engagement than 2 mg/kg dose
- The Ambulatory cohort had the highest average baseline latent myostatin concentrations

High dose (20 mg/kg) yielded higher levels of drug exposure and target engagement than low dose (2 mg/kg)

4 patients (1 in Cohort 2 and 3 in Cohort 3) each missed 3 consecutive doses of apitegromab during the 12-month treatment period due to COVID-19-related site access restrictions and were not included in the **primary analysis. Patient level data are still under analysis; Durability of Response Observed Despite Missed Doses.*

**Starting at day 28, measures are predose trough levels*

Data on File. Scholar Rock, Inc. Cambridge, MA. Apitegromab is an investigational product candidate under development.

Safety Results from TOPAZ 12-Month Top-Line Analysis Support Evaluation of Apitegromab in Phase 3 Trial[1]

Treatment-emergent adverse events (TEAEs)	Apitegromab 2 mg/kg (n=10)	Apitegromab 20 mg/kg (n=48)	Total (n=58)
Any TEAE	9 (90.0%)	44 (91.7%)	53 (91.4%)
Any Serious TEAE	1 (10.0%)	4 (8.3%)	5 (8.6%)
Any TEAE leading to study drug discontinuation	0 (0.0%)	1 (2.1%)	1 (1.7%)
Any Grade 3 (severe) or higher TEAE	0 (0.0%)	3 (6.2%)	3 (5.2%)

- SAEs, Grade 3 AEs and AE leading to early study discontinuation were all assessed by investigators as unrelated to study drug
- Five most frequently reported TEAEs*: headache (24%), pyrexia (22%), upper respiratory tract infection (22%), cough (22%), and nasopharyngitis (21%).
- Antidrug antibodies (ADA) were present at low titers following apitegromab treatment in 3 out of 58 enrolled patients. No apparent impact on drug exposure was observed and was not associated with any hypersensitivity reactions.

Incidence and severity of AEs were consistent with the underlying patient population and background therapy

*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.TEAE rates are across all patients in TOPAZ trial; *Notes: % = 100 x n/N; 1.* Data on File. Scholar Rock, Inc. Apitegromab is an investigational product candidate under development.

TOPAZ Topline Results Demonstrate that Apitegromab Improves Motor Function in Patients with Later-Onset SMA[1]

- ✓ **Non-Ambulatory; ≥ 2 Years, SMA Type 2 Cohort: HFMSE improvement in both high- and low-dose arms; dose response demonstrated**
  - Mean +7.1-point increase in HFMSE on top of SOC with high dose (20 mg/kg dose)
  - High dose led to higher drug exposure and target engagement than low dose (2 mg/kg)
- ✓ **Non-Ambulatory; Ages 5-21, SMA Type 2/3 Cohort: Increases in HFMSE Scores in a subset of patients**
  - 64% of patients showed improvement ≥1-pt increase in HFMSE,
  - Relatively larger improvements in age <12 years subgroup (50% with a >3-point increase)
- ✓ **Ambulatory, SMA Type 3 Cohort: RHS scores maintained or improved in subsets of patients in both the monotherapy and add-on to nusinersen groups**
- ✓ **No safety signals nor concerns have been identified from 12-month topline results**
- ✓ **PK: Dose-proportional and sustained drug exposure; PD: Dose-dependent and sustained target engagement**
- ✓ **Anti-drug antibodies were present in postdose samples in 3/58 total subjects at low titers (>1:64); no impact on PK/PD**
- ✓ **The 12-month topline results support further evaluation of apitegromab in a Phase 3 trial**
- ✓ **Topline results highlight therapeutic potential of apitegromab in patients with SMA**
- ✓ **Fast Track Designation granted for the treatment of patients with SMA; having previously received Orphan Drug and Rare Pediatric Disease designations from the FDA and priority medicines, PRIME, and Orphan Medicinal Product designations from the EMA for the treatment of SMA[2]**

1. Data on File. Scholar Rock, Inc.; 2. Scholar Rock Press Release; May 24, 2021 Apitegromab is an investigational product candidate under development.

THANK YOU!!

Many thanks to all the patients who participate in these studies and their families, healthcare professionals and the support of patient groups

Please Send an Email with Your Medical Questions to the Following Address: medicalinquiry@scholarrock.com