Apitegromab in Spinal Muscular Atrophy (SMA):

An Analysis of Multiple Efficacy Endpoints in the TOPAZ Trial

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On behalf of the entire TOPAZ Study Team

TOPAZ (NCT03921528)

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

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Author Disclosures

Dr. Crawford is lead principal investigator of the TOPAZ trial

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- Roche/Genentech
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- Biogen
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- Cytokinetics
- Parexel
- Catalyst

Patient Organizations

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

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Disclaimers

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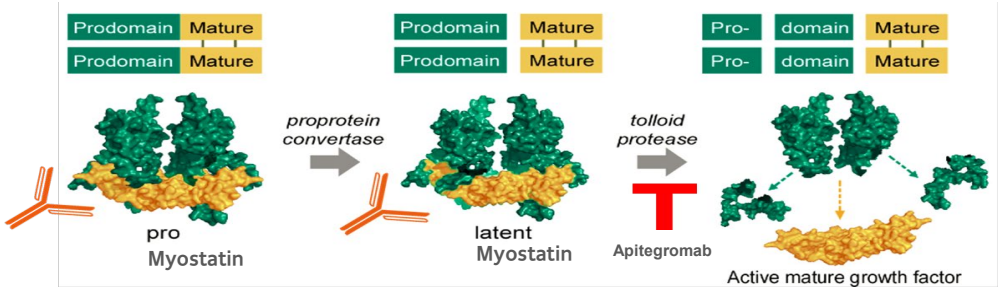
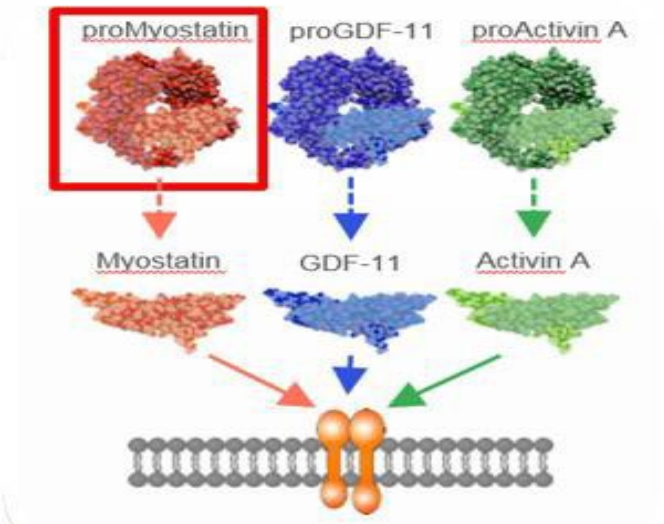
Myostatin Is An Important Negative Regulator Of Skeletal Muscle Growth Whose Inhibition Leads To Improved Muscle Function In Patients With SMA[1,2]

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



- Activation of myostatin requires two distinct proteolysis events to generate the active mature growth factor
- Apitegromab binds to both proMyostatin and latent myostatin and inhibits tolloid-mediated cleavage of latent myostatin
- It is proposed that apitegromab bound latent myostatin is pulled from muscle into systemic circulation, and this is measured as part of total myostatin in circulation.[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]



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.

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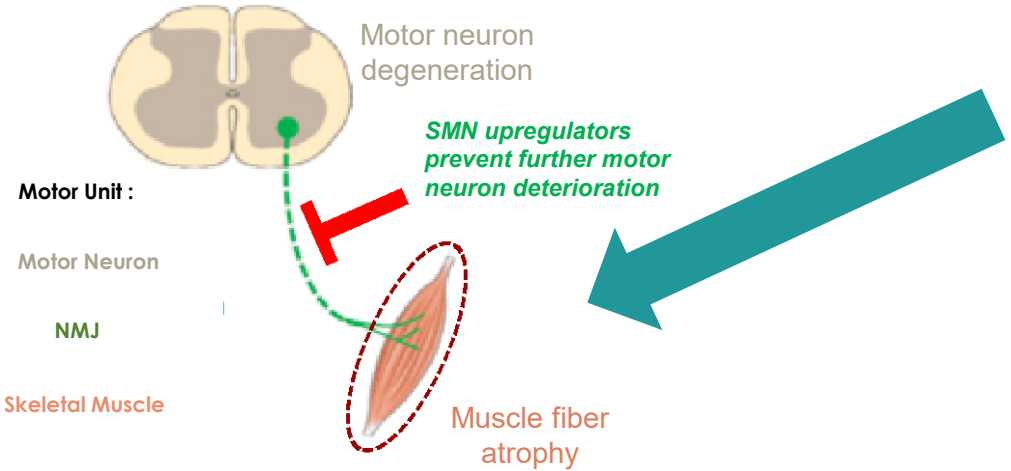
Apitegromab: A Potential Muscle-Directed Therapy
Intended to Complement SMN Upregulators

SMN upregulators *target one part of the motor unit, the* motor neurons[1]



Adapted from images courtesy of the SMA Foundation

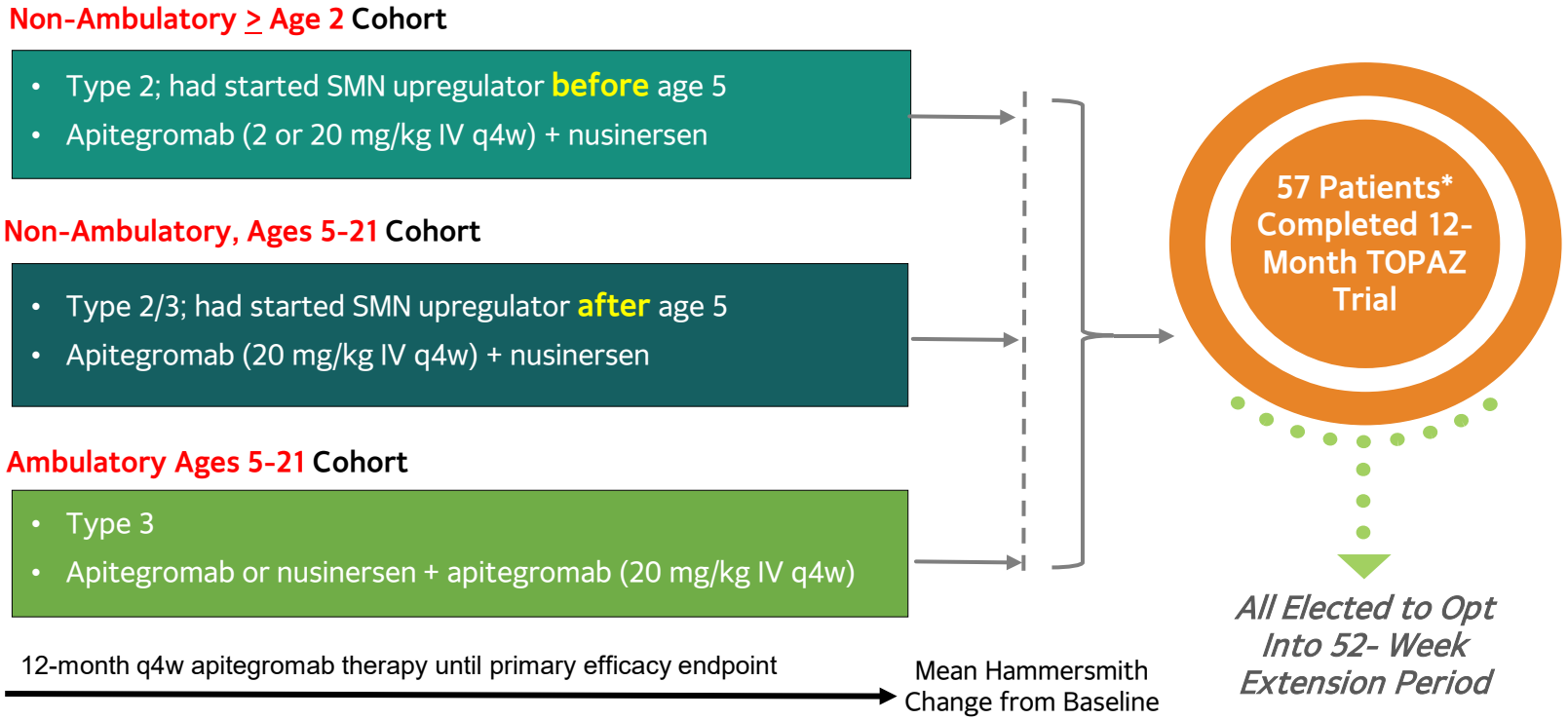
Apitegromab *targets* muscle-specific regulation of contractile protein mass*[2-4]

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

* Based on Animal Model Data; 1. Adapted from: 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; 4. Dagbay KB, et al. J Biol Chem. 2020;295(16):5404-5418.

TOPAZ Phase 2 Trial Design: Three pilot cohorts to identify therapeutic opportunities

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



*Excludes one patient from Cohort 1 who discontinued from the trial; Place A, et al. Eu J Neurol. 2021;28(Suppl1) 207–334:(EPR-184).

TOPAZ Baseline Characteristics

Patients were well into chronic maintenance phase of background therapy

	Non Ambulatory Age ≥2			Non Ambulatory Ages 5-21	Ambulatory Ages 5-21		
	Higher dose 20 mg/kg	Lower dose 2 mg/kg	Pooled	20 mg/kg +nusinersen	Monotherapy 20 mg/kg	With nusinersen 20 mg/kg	Pooled
N	**10**	**10**	**20**	**15**	**11**	**12**	**23**
Mean age (min, max)	3.8 (2, 6)	4.1 (2, 6)	4.0 (2, 6)	11.7 (8, 19)	12.1 (7, 19)	13.1 (7, 21)	12.6 (7, 21)
Mean RHS (min, max)					48 (26, 63)	51 (43, 62)	50 (26, 63)
Mean HFMSE (min, max)	24 (14, 42)	26 (12, 44)	25 (12, 44)	23 (13, 39)			
# of maintenance Nusinersen doses: Mean (min, max)*	**5.4 (3, 8)**	**5.5 (2, 9)**	**5.5 (2, 9)**	**5.1 (2, 9)**	**N/A**	**5.6 (2, 8)**	**N/A**
# of patients with 2,3, or 4 copies of SMN2‡	1, 8, 0	1, 8, 1	2, 16, 1	0, 11, 2	1, 4, 4	0, 9, 1	1, 13, 5
Discontinuation(s)	0	0	0	0	0	1†	1†

Nusinersen treated patients received ~2 years of nusinersen maintenance treatment at baseline

*Patients on average received ~2 years of nusinersen treatment at baseline and ~3 years of nusinersen treatment by the end of the TOPAZ study (12-months).†Patient who discontinued study for reasons unrelated to study drug. Place A, et al. Eu J Neurol. 2021;28(Suppl1) 207–334:(EPR-184); ‡Intent-to-treat analysis

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

	NonAmbulatory Patients HFMSE				Ambulatory Patients RHS
	Type 2; Age ≥2 Cohort*			Type 2/3; Ages 5-21 Cohort*	Type 3 Cohort†
Primary Analysis ITT Population‡	Apitegromab (2 mg/kg) +nusinersen	Apitegromab (20 mg/kg) +nusinersen	Pooled (n=17)	Apitegromab (20 mg/kg) +nusinersen	Apitegromab (20 mg/kg) Pooled
% (n) patients ≥3-pt increase in motor function	56% (5/9)	63% (5/8)	59% (10/17)	29% (4/14)	22% (5/23)
Topline Summary per Cohort	**NonAmbulatory, Type 2 Apitegromab (20 mg/kg) -Motor Function Improvements:** • Majority of patients >60% experienced ≥ 6-point gains in HFMSE • 38% experienced > 10-point gains in HFMSE • +7.1 point mean improvement in HFMSE (95% CI 1.8, 12.5)			**NonAmbulatory, Type2/3; difficult-to-treat cohort: younger subset with greater Motor Function Increases** • A post-hoc exploration showed 50% of patients in the younger subset (5-12 years) experienced >3-point increases in HFMSE • A +1.6 (-1.3, 4.6) mean improvement in HFMSE in younger (5-12 year) cohort vs mean +0.6 (-1.4, 2.7) improvement overall	**Ambulatory, Type 3; Apitegromab (20 mg/kg) -Motor Function Improvements:** • Majority of patients maintained or improved RHS from baseline • Majority of patients showed stabilization (the goal of treatment where natural history suggests decline is common) with a mean pooled RHS score from baseline of -0.3 (-2.1, 1.4)[2]

A 3-point HFMSE clinically meaningful increase represent improvements in 2 or 3 motor skills[3]
A 6-point increase in HFMSE represents improvements in 3 to 6 motor skills[3]

**4 patients (1 in Cohort 2 and 3 in Cohort 3) each missed 3 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;* †Includes 2 patients in monotherapy and 2 patients in apitegromab + nusinersen subgroup who maintained RHS score (0-point change from baseline); ‡Intent-to-treat analysis excluded 1 patient (per prespecified approach) who missed 3 doses due to COVID-19 related site access restrictions; 1 patient who had inadvertently been enrolled who was receiving (and continued to receive) an acetylcholinesterase inhibitor was removed, which is not permitted per the trial protocol*; 1.* Place A, et al. Eu J Neurol. 2021;28(Suppl1) 207–334:(EPR-184).; 2. C Vuillerot et al. Archives of Physical Medicine and Rehabilitation 2013;94:1555–61. 3. Rouault F, et al. Neuromuscul Disord 2017;27:428-38.

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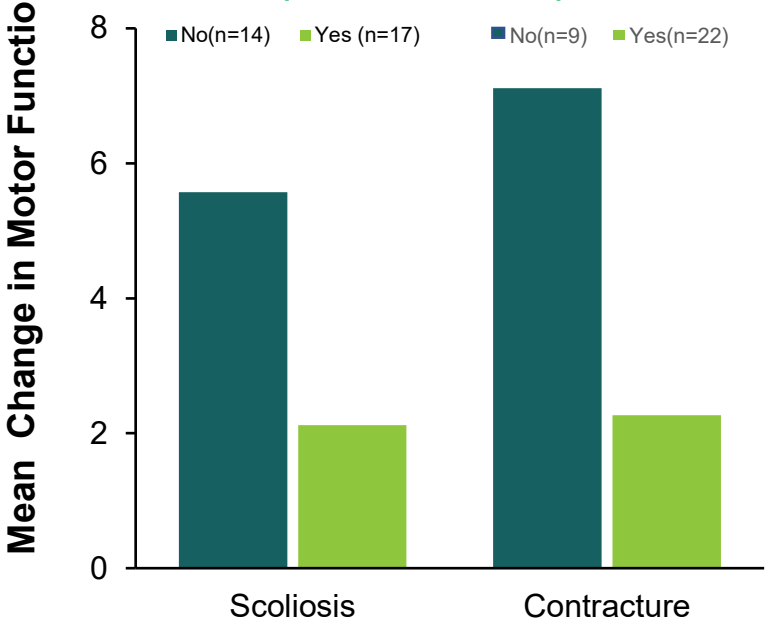
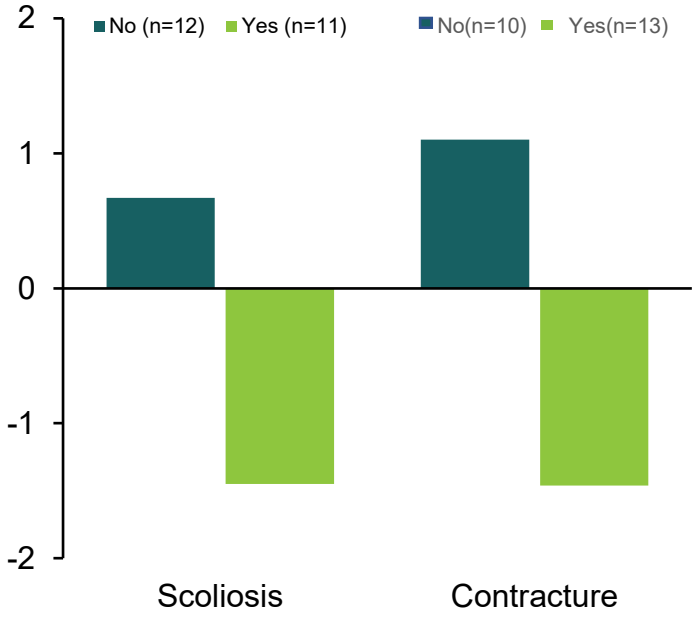
Greater improvements in Hammersmith Scores Inversely Correlate With Characteristics of Advanced Disease- Scoliosis & Contractures

NonAmbulatory Type 2 & Type 2/3 SMA (Pooled HFMSE)*



Ambulatory Cohort Type 3 SMA (Pooled RHS)†



Patients who skipped 3 consecutive doses due to site restrictions due to COVID-19 were excluded; *Std Scoliosis (7.7) min-7, max 20, Std (5.4) min -7, max 13; *Std Contracture (7.1) min-3, max 20, Std (2.3) min -7, max 13; †Std Scoliosis (0.7) min-4, max 4, Std (-1.5) min -12, max 8; †Std Contracture (1.1) min-2, max 4, Std (-1.5) min -12, max 8; Exploratory analysis; Data on File, Scholar Rock, Inc

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Nonambulatory Cohorts:
Substantial RULM Improvements with Apitegromab[1]

	Nonambulatory Patients (Hammersmith Functional Motor Scale Expanded; HFMSE)			
Primary Analysis (ITT population)	**Type 2/3; Ages 5-21 Cohort***	**Type 2; Age ≥2 Cohort***		
	Apitegromab (20 mg/kg) +nusinersen	Apitegromab (2 mg/kg) +nusinersen	Apitegromab (20 mg/kg) +nusinersen	Pooled
% (n) patients achieving ≥2-pt improvements from Baseline in Revised Upper Limb Motor (RULM) Function	36% (5/14)	33% (3/9)	29% (2/7)	31% (5/16)

A 2-point increase in RULM is considered clinically meaningful[2]

Mean improvements in RULM from baseline: Type 2, ≥2y: +1.0 (-1.7, 3.7) and Type 2/3, 5-21y: +1.2 (95% CI-0.5, 2.9); *Intent-to-treat analysis excluded 1 patient (per prespecified approach) who missed 3 doses due to COVID-19 related site access restrictions; 1 patient who had inadvertently been enrolled who was receiving (and continued to receive) an acetylcholinesterase inhibitor was removed, which is not permitted per the trial protocol; 1. Data on file. Scholar Rock, Inc.; 2. Coratti G, et al. Muscle Nerve 2019; 59: 426–430.

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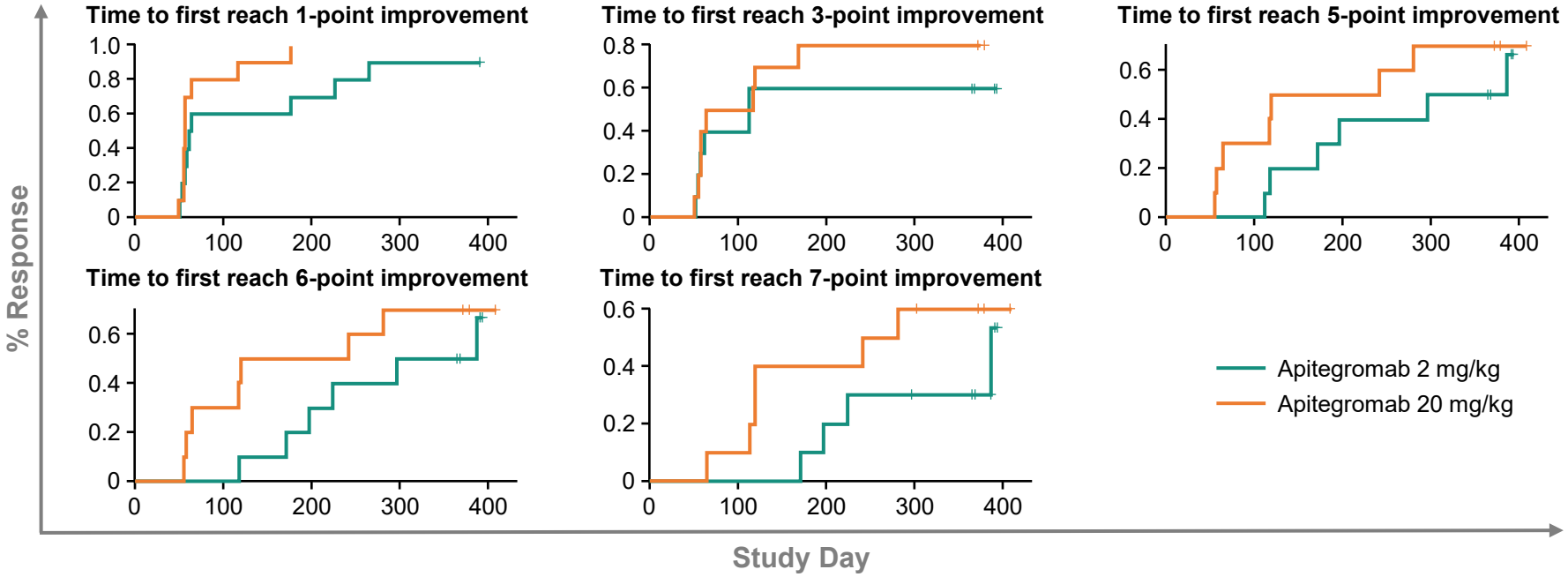
Type 2 Nonambulatory ≥ Age 2 Cohort: Both Dosage Groups Manifest Early Benefit, A Greater Latency Of The Low Dose Cohort Supports Apitegromab Attributable Effect



Dose Responsive Improvement in Time to Reach HFMSE Motor Function Benefit
Benefits in both dosage groups manifested as early as 2 months following treatment initiation.

All points beyond 3 are Exploratory analysis; Data on File, Scholar Rock, Inc

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

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
- Anti-drug 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.
- Five most frequently reported TEAEs*: headache (24%), upper respiratory tract infection (22%), pyrexia (22%), cough (22%), and nasopharyngitis (21%).

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; Place A, et al. Eu J Neurol. 2021;28(Suppl1) 207–334:(EPR-184).

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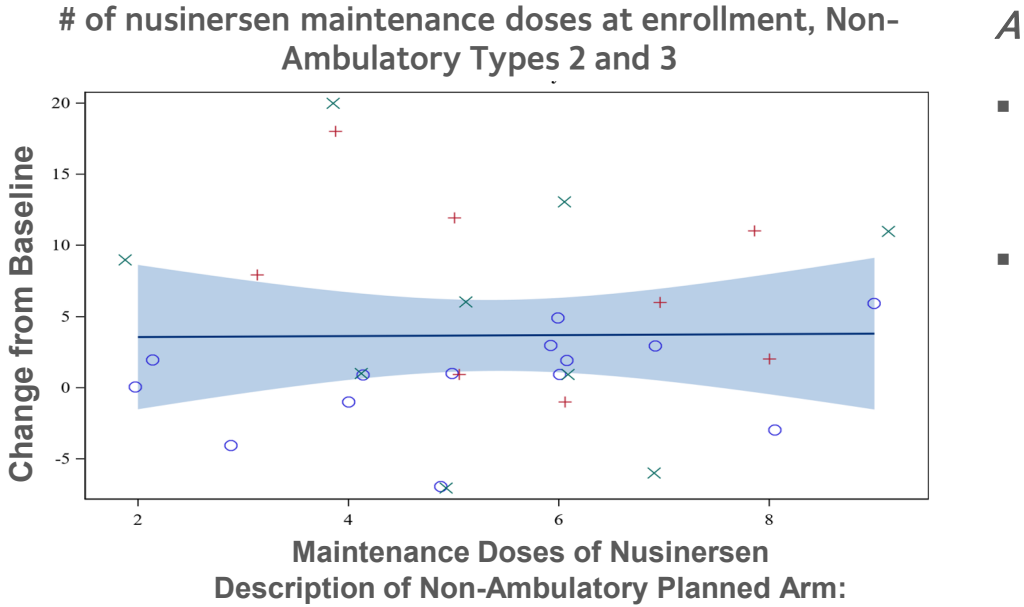
Summary

- Motor function improvements were observed in the primary and secondary efficacy endpoints in the Phase 2 TOPAZ clinical trial at 12 months.
- Dose responsive improvement in time to reach motor function confirmed apitegromab benefit on top of underlying nusinersen benefit.
- Positive correlation of improvement in motor milestone score with SMA severity and inverse relationship with age and characteristics of advanced disease such as scoliosis and contractures.
- The information presented here may be helpful in understanding patient response to apitegromab treatment.
- Apitegromab has the potential to be the first muscle-directed therapy to address motor function impairment in patients with SMA.
- **Many thanks to all the patients who participate in these studies, and their caregivers/families, healthcare professionals and patient advocacy groups**

Backup

A Post-hoc Analysis of Prior Nusinersen Treatment Duration…

No correlation with HFMSE in Non-Ambulant patients



Across both non-ambulatory cohorts in TOPAZ…

- Patients enrolled in TOPAZ were already in the chronic maintenance phase of nusinersen
- No correlation observed between the duration of prior nusinersen therapy and 12- month HFMSE changes

Further evidence suggesting that HFMSE increases in TOPAZ may be attributable to apitegromab than nusinersen

Data on File; ScholarRock Inc.; Patients skipped 3 or more doses due to COVID-site restrictions excluded; Apitegromab is an investigational product candidate under development.

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