EFFECT OF APITEGROMAB ON MOTOR FUNCTION AND PEDICAT AND PROMIS AT 36-MONTHS IN PATIENTS WITH TYPE 2 AND NONAMBULATORY TYPE 3 SPINAL MUSCULAR ATROPHY: COMBINED PRESENTATION OF THE PHASE 2 TOPAZ STUDY

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Author Disclosures

Dr Crawford is lead principal investigator of the TOPAZ trial.

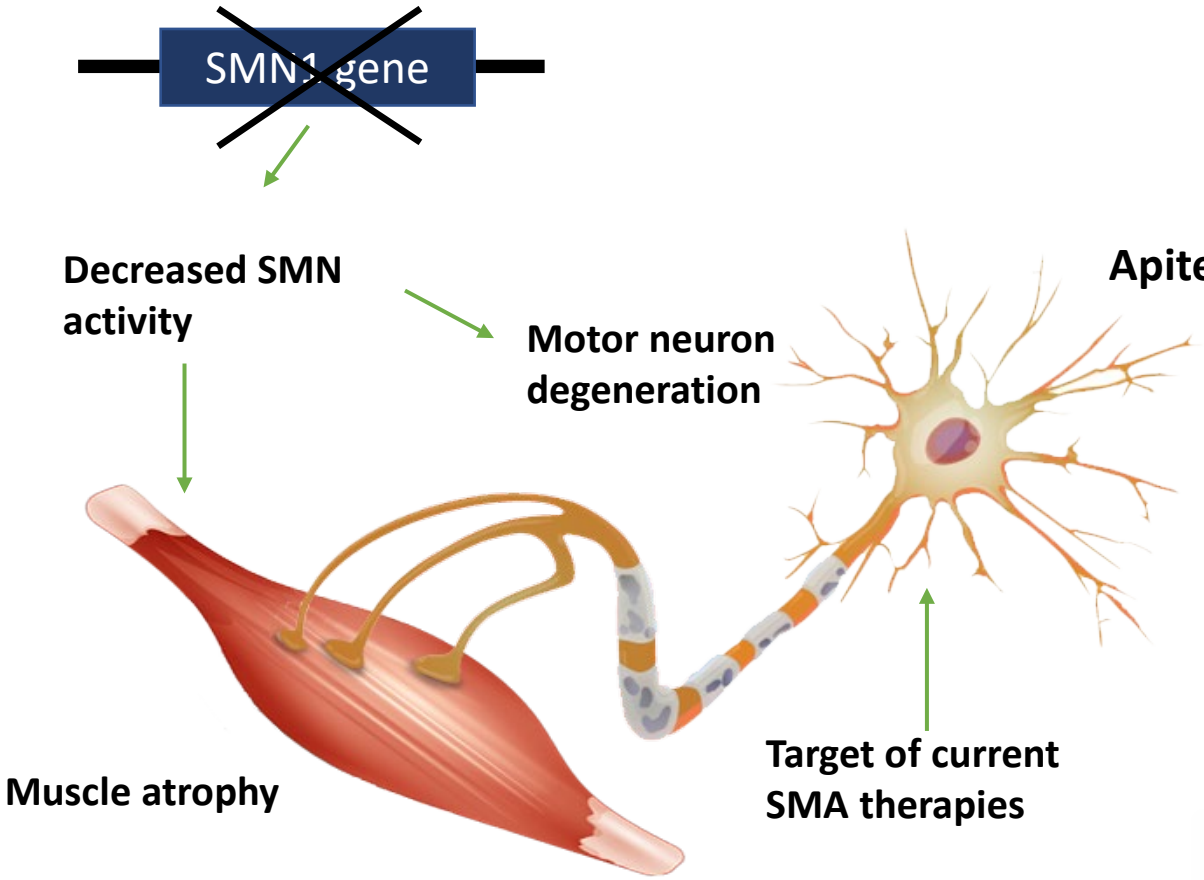
Consulting/Ad Boards:
- AveXis/Novartis
- Biogen
- Pfizer
- Roche/Genentech
- Scholar Rock

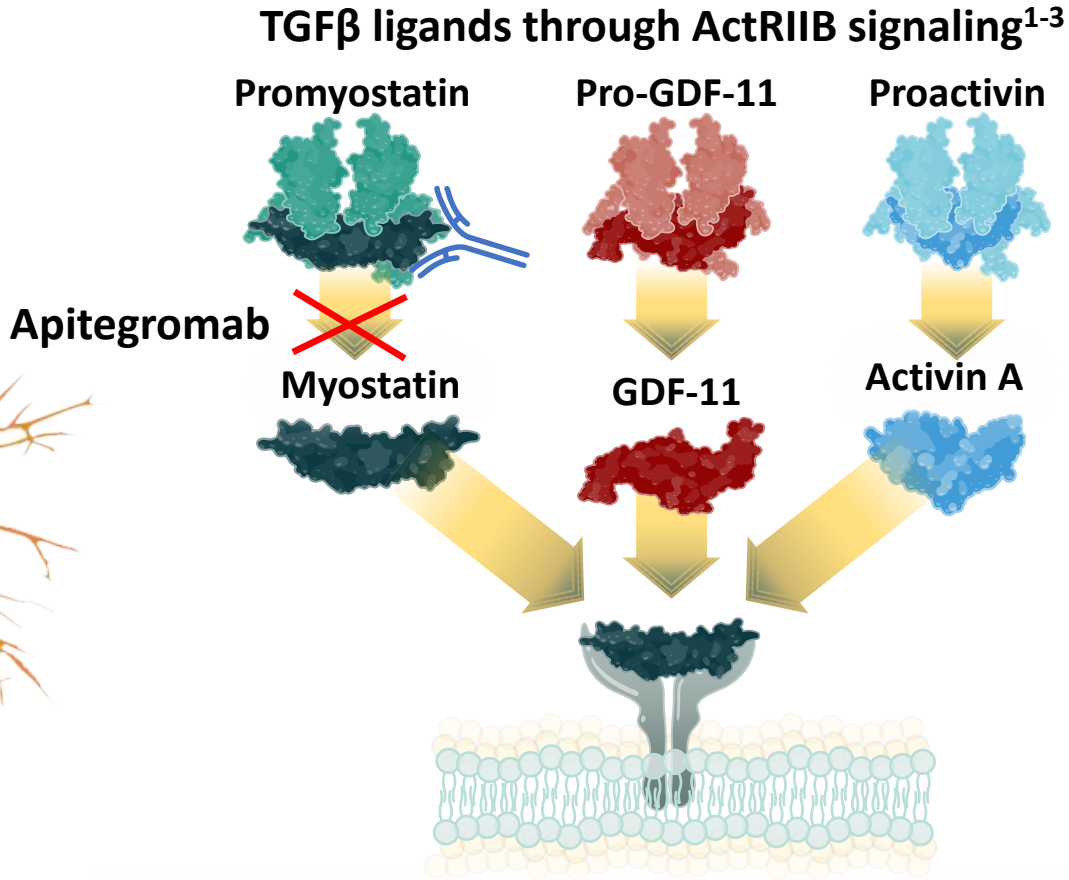
Study Site Investigations:
- AveXis
- Biogen
- Catalyst
- Cytokinetics
- Parexel
- Scholar Rock

Patient Organizations:
- A-T Children's Project®
- Cure SMA
- MDA
- SMA Foundation

A-T, ataxia telangiectasia; MDA, Muscular Dystrophy Association; SMA, spinal muscular atrophy.

Apitegromab is a fully human monoclonal antibody that targets muscle to improve motor function in SMA[1-3]



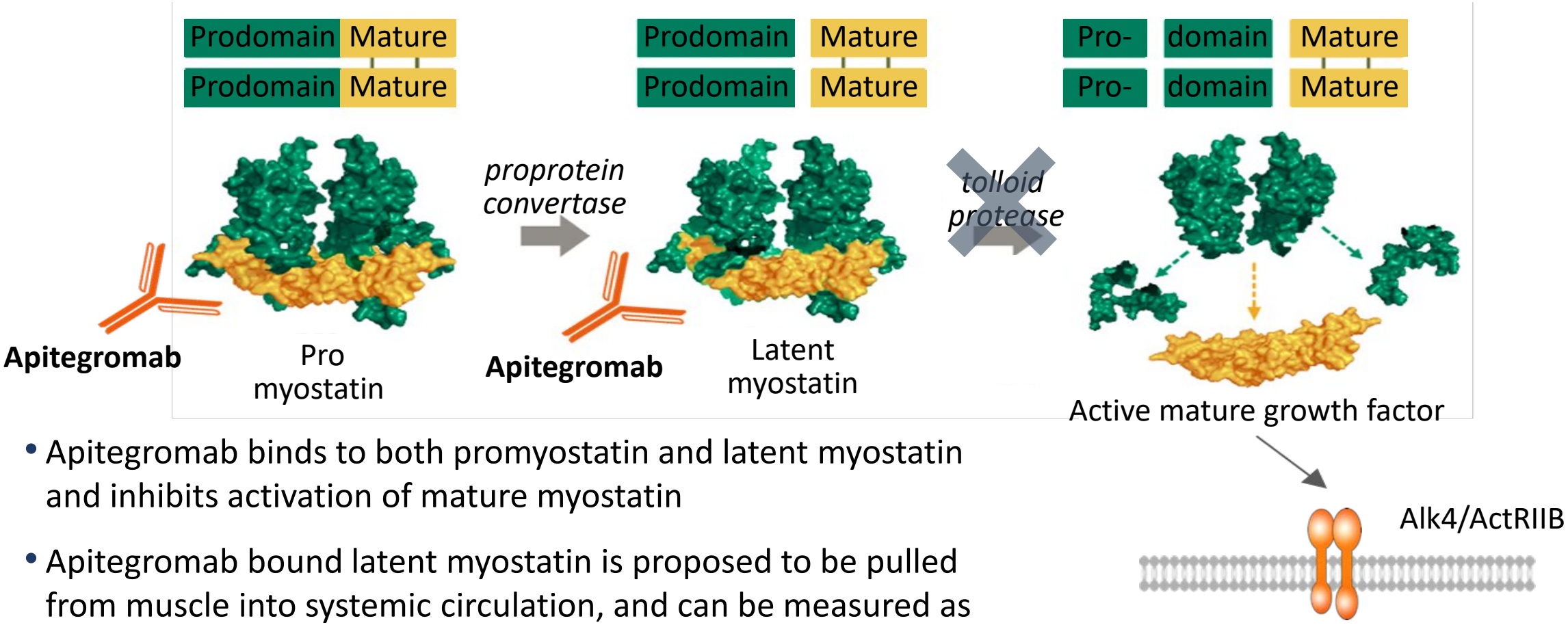


Myostatin is a negative regulator of skeletal muscle growth.
Pro- and latent myostatin are more divergent, thus inhibiting the activation of myostatin avoids unwanted off-target effects of ActRIIB signaling[1]

ActRIIB, activin receptor type 2b; GDF, growth differentiation factor; SMA, spinal muscular atrophy; SMN, survival motor neuron; TGF, transforming growth factor.

1. Long KK, et al. Hum Mol Genet. 2019;28(7):1077-1088. **2**. Pirruccello-Straub M, et al. Sci Reports. 2018;8(1):2292. **3**. Walker RG, et al. BMC Biol. 2017;15(1):19

Apitegromab inhibits myostatin activation[1,2]

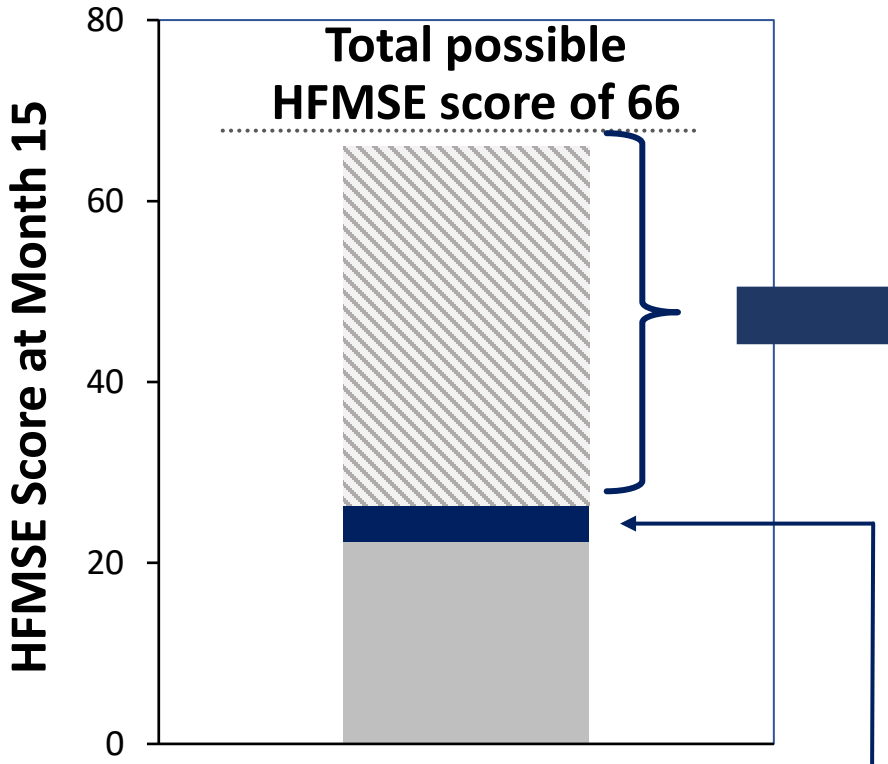


- Apitegromab binds to both promyostatin and latent myostatin and inhibits activation of mature myostatin
- Apitegromab bound latent myostatin is proposed to be pulled from muscle into systemic circulation, and can be measured as part of total circulating myostatin[3]

ActRIIB, activin receptor type 2b; Alk4, activin receptor like kinase 4.

1. Long KK, et al. *Hum Mol Genet*. 2019;28:1076-1089. **2.** Pirruccello-Straub M, et al. *Sci Rep.* 2018;8:2292. **3.** Dagbay KB, et al. *J Biol Chem*. 2020;295(16):5404-5418.

Disease burden persists despite current SMA treatments



Mean improvement in HFMSE in Type 2 and nonambulatory Type 3 SMA in the Phase 3 CHERISH nusinersen trial[1]

Limitations in mobility and daily activities continue[2,3]

HFMSE, Hammersmith Functional Motor Scale–Expanded; SMA, spinal muscular atrophy.

1. Mercuri E, et al. *N Engl J Med* 2018;378:625-635. **2.** Yang M, et al. *Adv Ther*. 2022;39:1915-1958. **3.** Wan HWY, et al. *Orphanet J Rare Dis*. 2020;15:70.

TOPAZ Phase 2 trial design[1,2]

Nonambulatory patients aged at least 2 years (Cohort 3)

- Type 2; started SMN targeted therapy **before** age 5 years
- Apitegromab (2 or 20 mg/kg IV q4w) and nusinersen

Nonambulatory patients aged 5-21 years (Cohort 2)

- Types 2 & 3; started SMN targeted therapy **at** or **after** age 5 years
- Apitegromab (20 mg/kg IV q4w) and nusinersen

Ambulatory patients aged 5-21 years (Cohort 1)

- Type 3
- Apitegromab alone or apitegromab (20 mg/kg IV q4w) and nusinersen

Primary efficacy endpoint:
Mean HFMSE change from baseline at 12 months (Cohorts 2 and 3)
Mean RHS change from baseline at 12 months (Cohort 1)

Data presented today

First 12-month Extension → **Second 12-month Extension** → **Third 12-month Extension**

3-Year Extension Period
All patients in extension periods receive 20 mg/kg apitegromab

Cohorts defined by age and present ambulatory status at time of enrollment.
HFMSE, Hammersmith Functional Motor Scale–Expanded; IV, intravenous; q4w, every 4 weeks; RHS, Revised Hammersmith Scale; SMA, spinal muscular atrophy; SMN, survival motor neuron.
1. Place A, et al. *Eur J Neurol*. 2021;28(suppl 1):207-334 (EPR-184). **2.** Crawford T, et al. Presented at Cure SMA Annual Conference; June 16-19, 2022.

TOPAZ Phase 2 trial baseline characteristics[1,2]

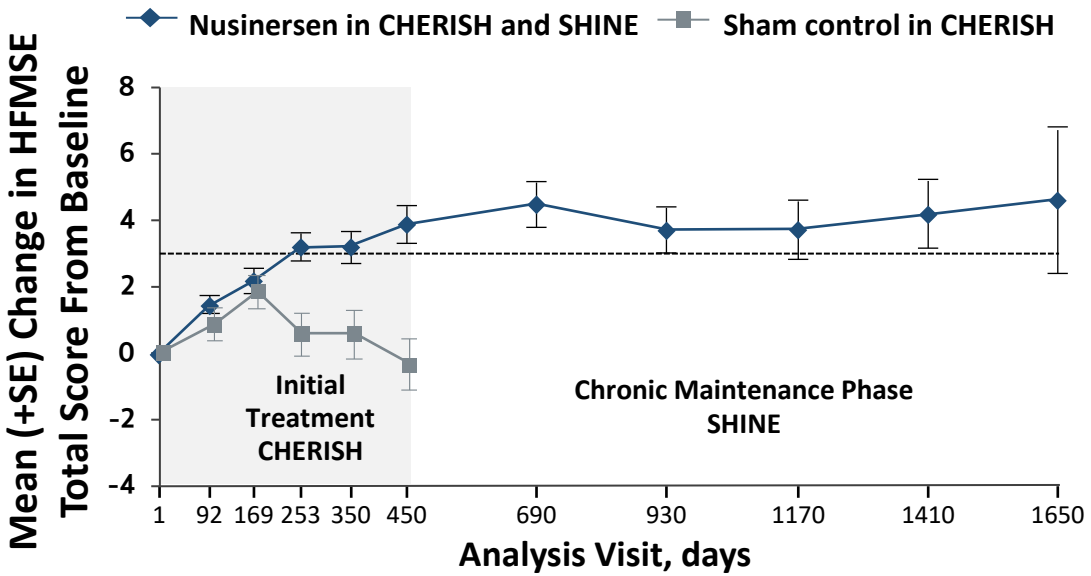
	Nonambulatory Aged at least 2 years (Cohort 3)			Nonambulatory, Aged 5-21 years (Cohort 2)	Ambulatory Aged 5-21 years (Cohort 1)		
	20 mg/kg with nusinersen	2 mg/kg with nusinersen	Pooled	20 mg/kg with nusinersen	20 mg/kg alone	20 mg/kg with nusinersen	Pooled
N	10	10	20	15	11	12	23
Mean age (min, max)	4 (2, 6)	4 (2, 6)	4 (2, 6)	12 (8, 19)	12 (7, 19)	13 (7, 21)	13 (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)			
Prior nusinersen, months Mean (min, max)*		24 (10, 34)		25 (12, 39)	N/A	20 (12, 28)	N/A
No. of patients with 2, 3, or 4 *SMN2* copies*	1, 8, 0	1, 8, 1	2, 16, 1	0, 11, 2	1, 4, 4	0, 9, 1	1, 13, 5

*****_SMN2_ copy numbers were not available for all patients. All discontinuations were for reasons unrelated to study drug.
HFMSE, Hammersmith Functional Motor Scale–Expanded; max, maximum; min, minimum; RHS, Revised Hammersmith Scale; SMN, survival motor neuron.
1. Crawford T, et al. *Neuromuscul Disord*. 2022;32(Suppl1):S86-S87. P102. **2.** Crawford T, et al. Presented at Cure SMA Annual Conference; June 16-19, 2022.

Motor function with SMN therapies appear to plateau after initial gains

Change in HFMSE over four years with nusinersen[1]

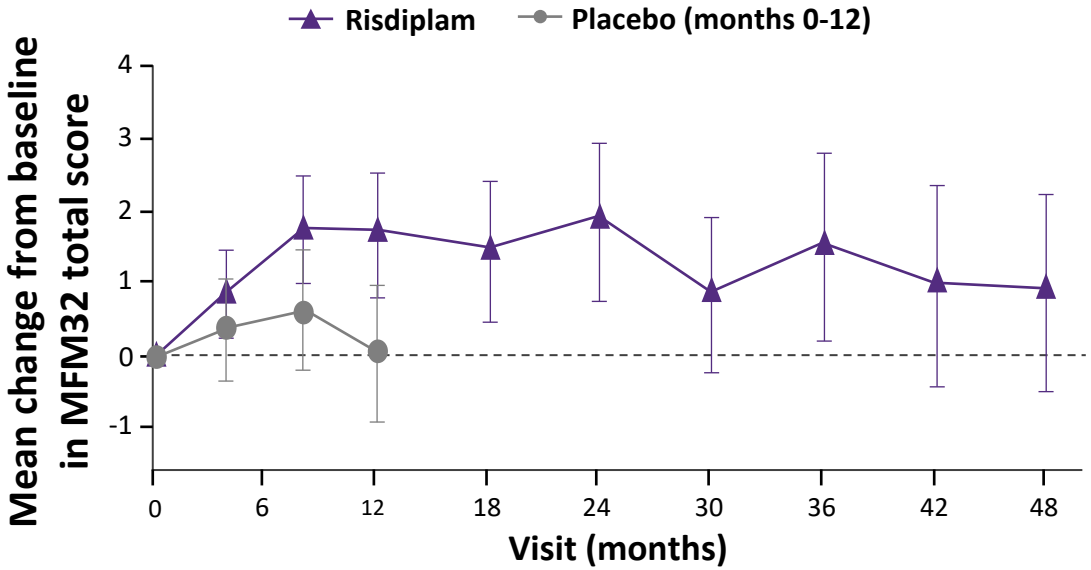
Overall population aged 2-12 years



Nusinersen n=	84	82	84	84	83	76	83	83	79	61	20
Placebo n=	42	41	41	42	42	39					

Change in MFM over four years with risdiplam[2]

Overall population aged 2-25 years



Risdiplam n=	115	113	113	112	107	103	85	100	101	98
Placebo n=	59	57	58	58						

HFMSE, Hammersmith Functional Motor Scale–Expanded; MFM, motor function measure; SE, standard error; SMN, survival motor neuron.

1. Mercuri E, et al. Presented at: World Muscle Society Congress 2020, P257. **2.** Oskoui M, et al. Presented at: 2021 Muscular Dystrophy Association Clinical & Scientific Conference; March 15-18, 2021. Poster 80.

Improved HFMSE at 12 months in Phase 2 TOPAZ study

Post hoc analysis of nonambulatory groups

Type 2 & nonambulatory Type 3 SMA (Apitegromab 20 mg/kg)	**Aged 2-12 years** (n=16*)
Primary efficacy endpoint at 12 months: Mean HFMSE change from baseline, (95% CI)	**+4.4 (1.3, 7.4)**
Participants with ≥1-point increase in HFMSE, n (%)	**13 (81%)**
Participants with ≥3-point increase in HFMSE, n (%)	**9 (56%)**

HFMSE gains also notable in individuals who started nusinersen at ≥5 years old:

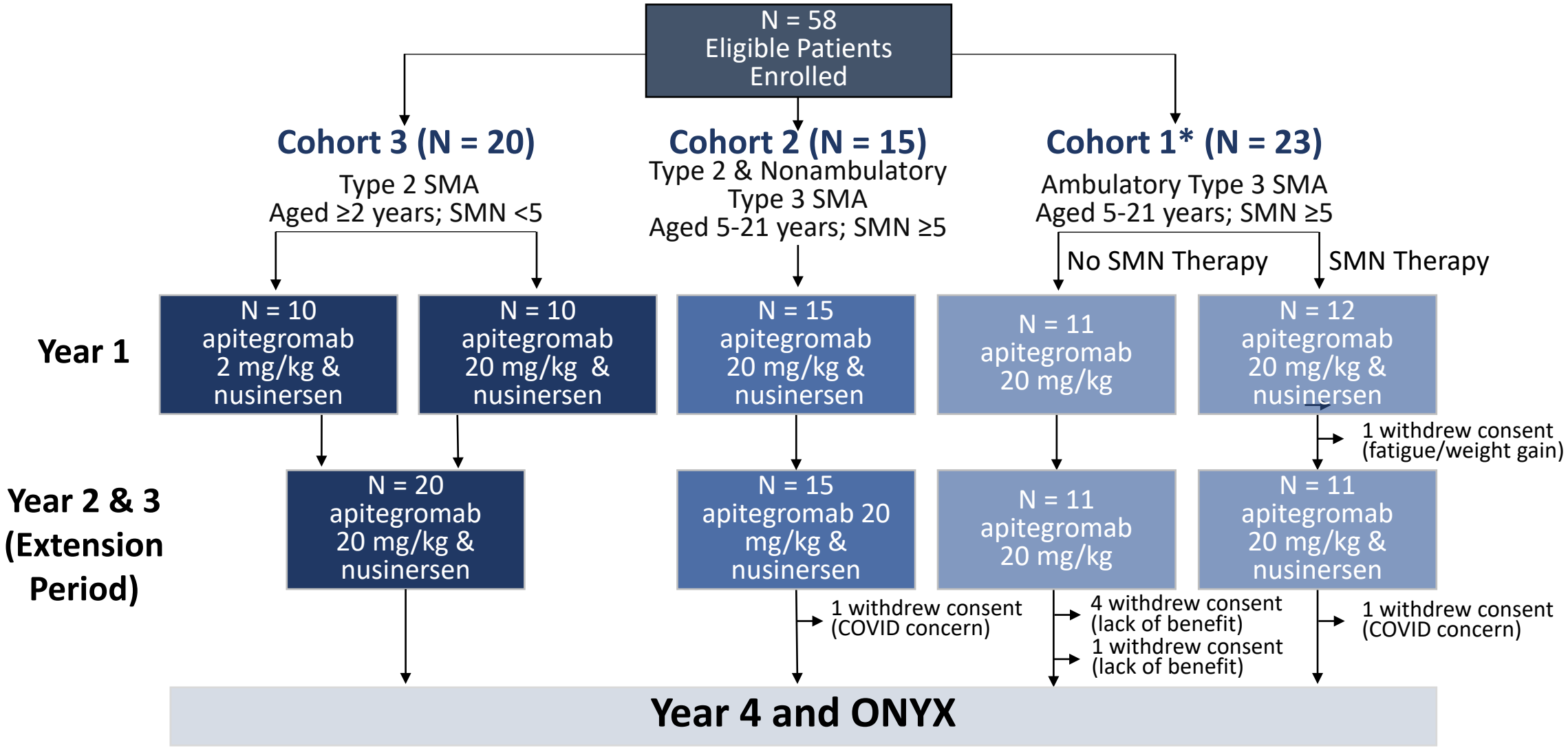
- 75% (6/8) with ≥1-point increase
- 50% (4/8) with ≥3-point increase

***For 12-month endpoint, if participants skipped 3 consecutive doses due to site restrictions caused by COVID-19, records after dose skipping were excluded from analysis. The last observation carried forward was used for other missing data.

CI, confidence interval; COVID-19, coronavirus disease 2019; HFMSE, Hammersmith Functional Motor Scale–Expanded; SMA, spinal muscular atrophy.

Crawford T et al. Presented at Muscular Dystrophy Association, 2021 Clinical & Scientific Conference; March 22, 2023.

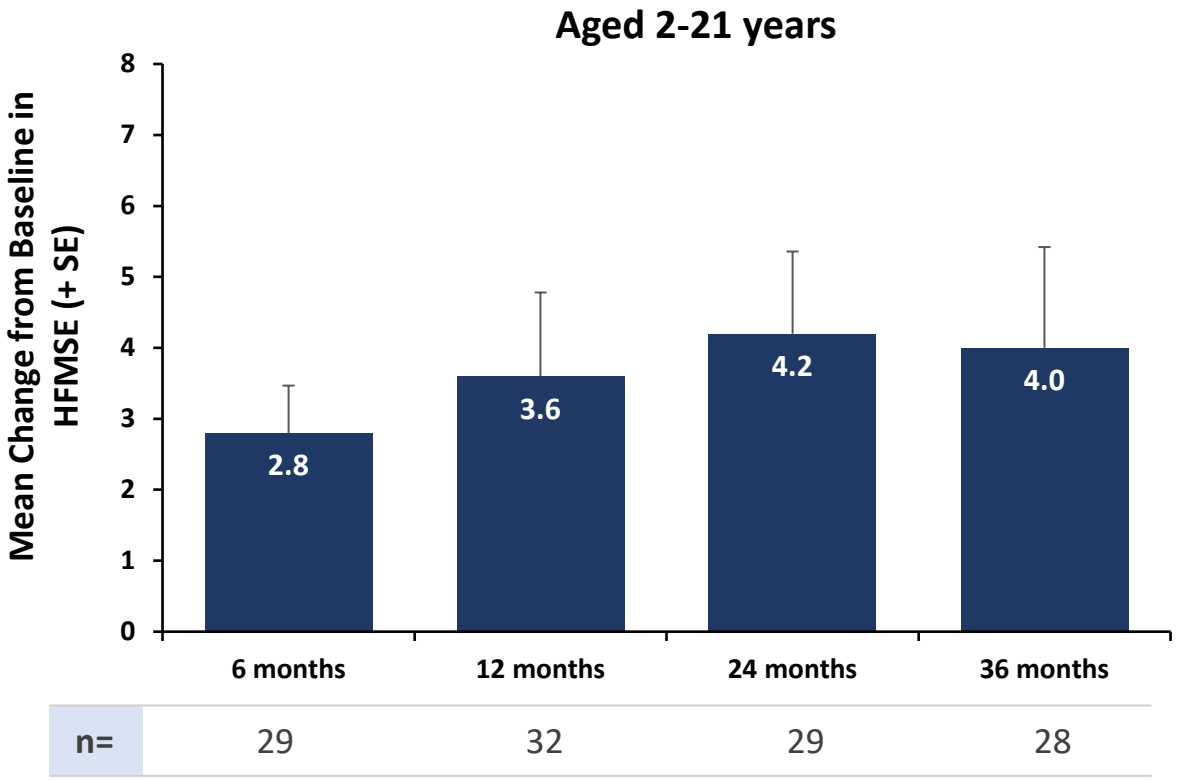
TOPAZ Phase 2 study patient disposition



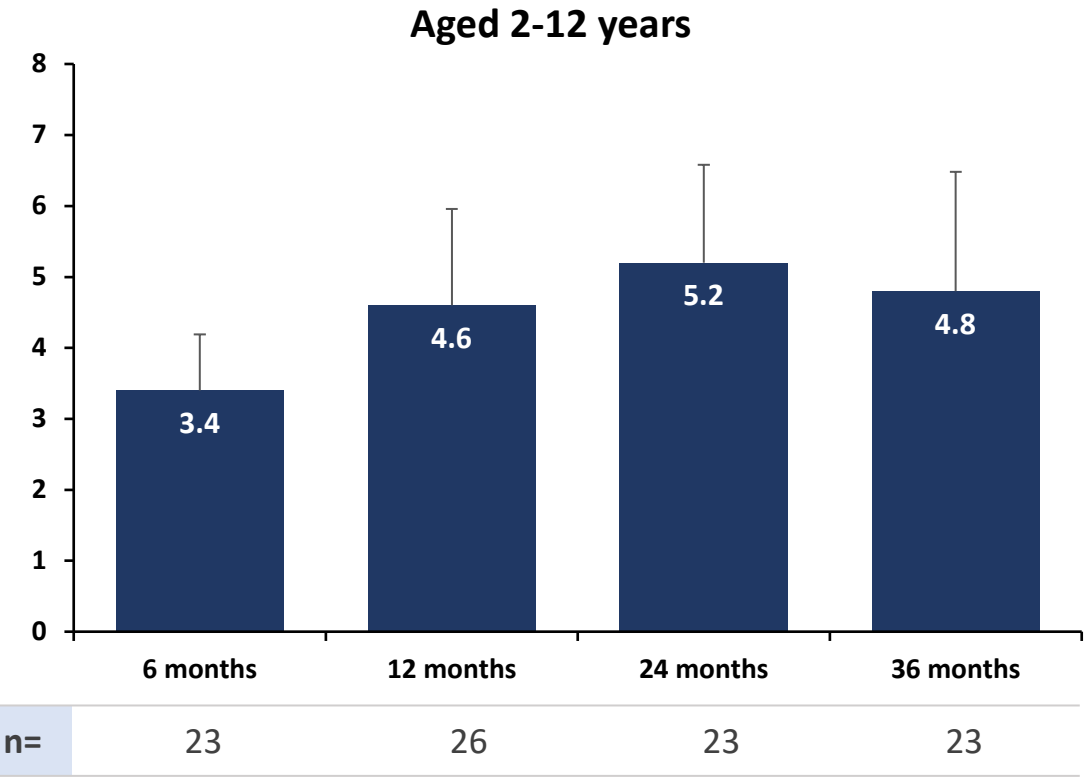
*Patients stratified based on previous treatment with approved SMN therapy.
COVID-19, coronavirus 2019; SMA, spinal muscular atrophy; SMN, survival motor neuron.

EFFECT OF APITEGROMAB ON MOTOR FUNCTION AT 36-MONTHS IN PATIENTS WITH TYPE 2 AND NONAMBULATORY TYPE 3 SPINAL MUSCULAR ATROPHY

Improvements in motor function outcomes by HFMSE scores are sustained over 36 Months



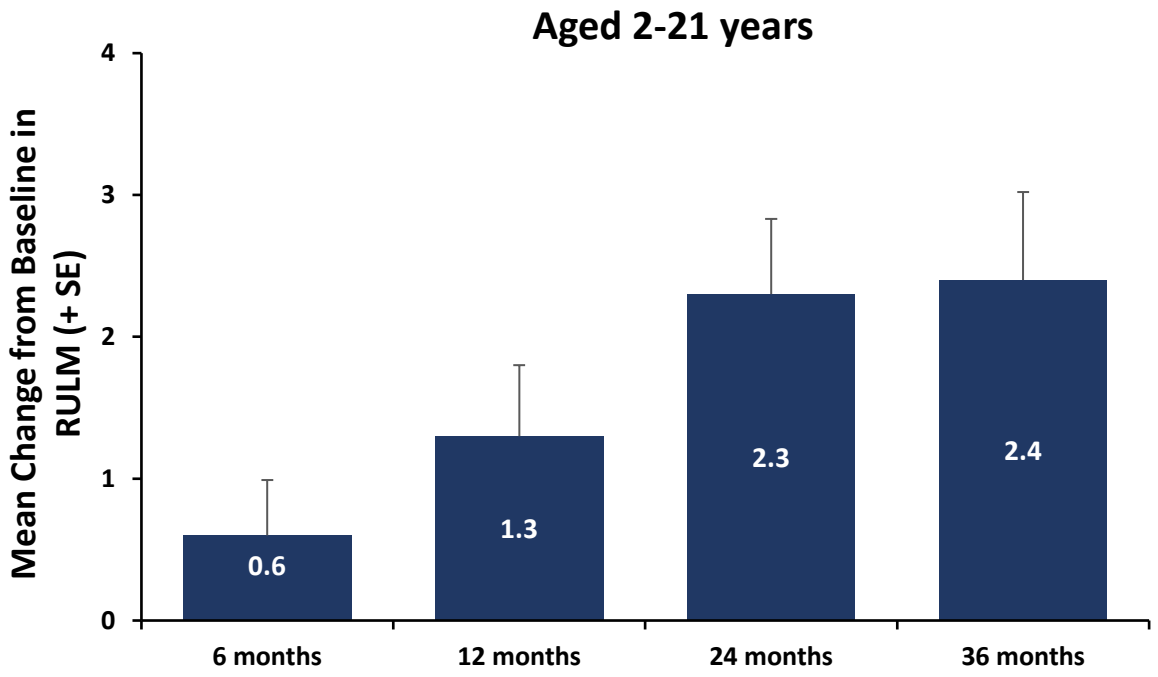
n=	29	32	29	28



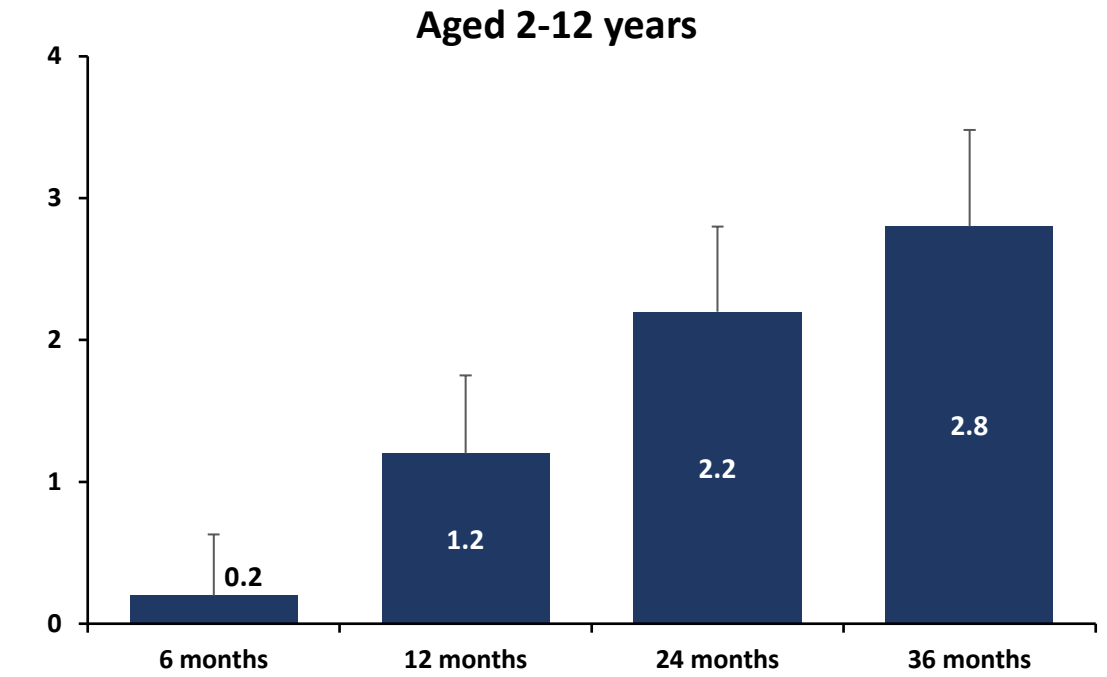
n=	23	26	23	23

This analysis population included patients receiving either low dose (2 mg/kg) or high dose (20 mg/kg) apitegromab (inclusive of patients in Cohort 3 who transitioned from 2 mg/kg to 20 mg/kg in Year 2).
This analysis excludes data post scoliosis surgery from six patients. Error bars represent SE.
RULM, Revised Upper Limb Module; SE, standard error.

Improvements in motor function outcomes by RULM scores are sustained over 36 months



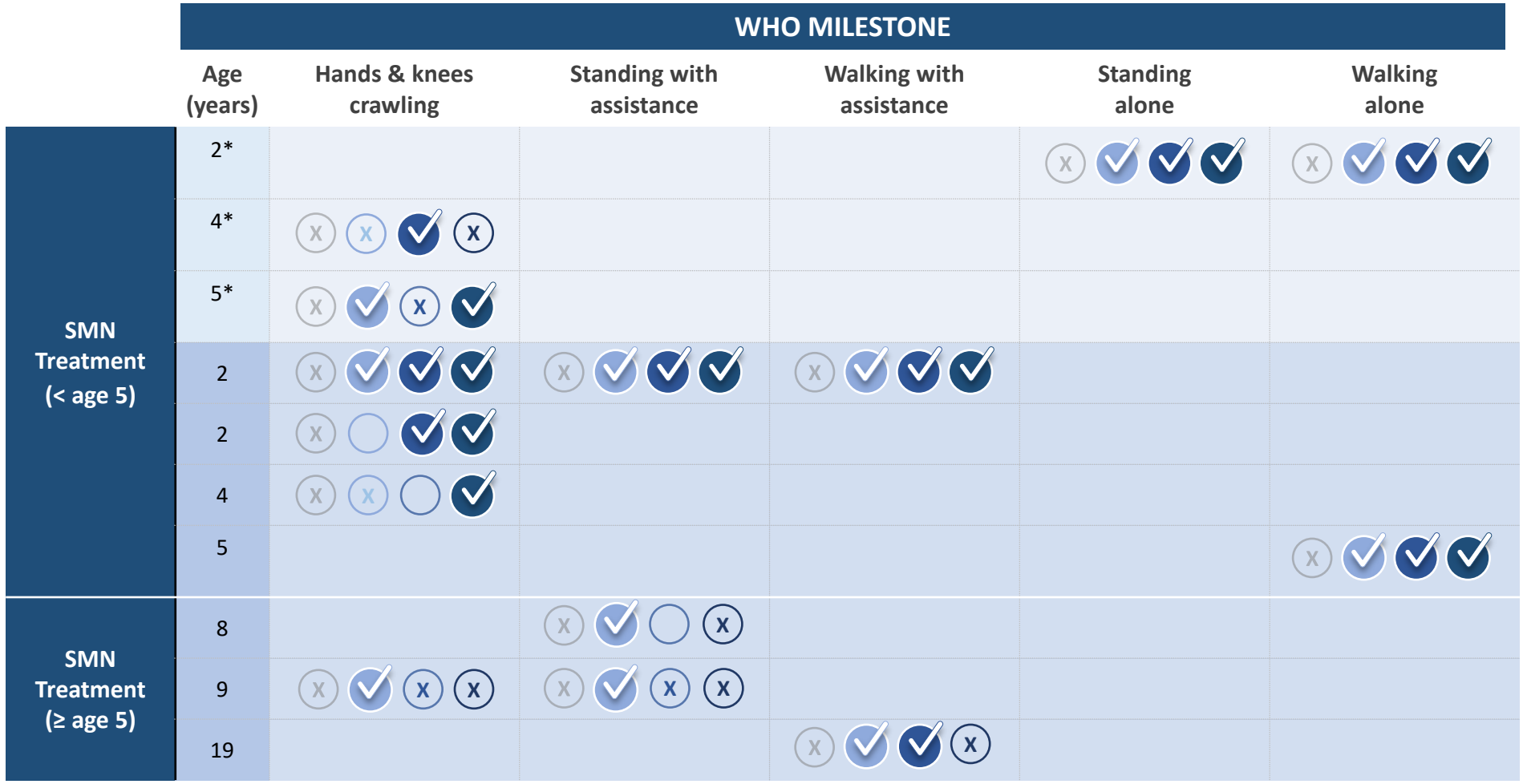
n=	28	31	31	27



n=	22	25	25	22

This analysis population included patients receiving either low dose (2 mg/kg) or high dose (20 mg/kg) apitegromab (inclusive of patients in Cohort 3 who transitioned from 2 mg/kg to 20 mg/kg in Year 2).
This analysis excludes data post scoliosis surgery from six patients. Error bars represent SE.
RULM, Revised Upper Limb Module; SE, standard error.

New WHO development milestones achieved



Proportion of patients gaining new milestones
Cohort 2: 12 months (20%), 24 months (7%), 36 months (0%)
Cohort 3: All doses: 12 months (24%), 24 months (26%), 36 months (30%)
Cohort 3: Randomized to 20mg/kg dose: 12 months (25%), 24 months (33%), 36 months (40%)
BL, baseline; M, month; WHO, World Health Organization

EFFECT OF APITEGROMAB ON PEDI-CAT AND PROMIS-FATIGUE QUESTIONNAIRE AT 36-MONTHS IN PATIENTS WITH TYPE 2 AND NONAMBULATORY TYPE 3 SPINAL MUSCULAR ATROPHY

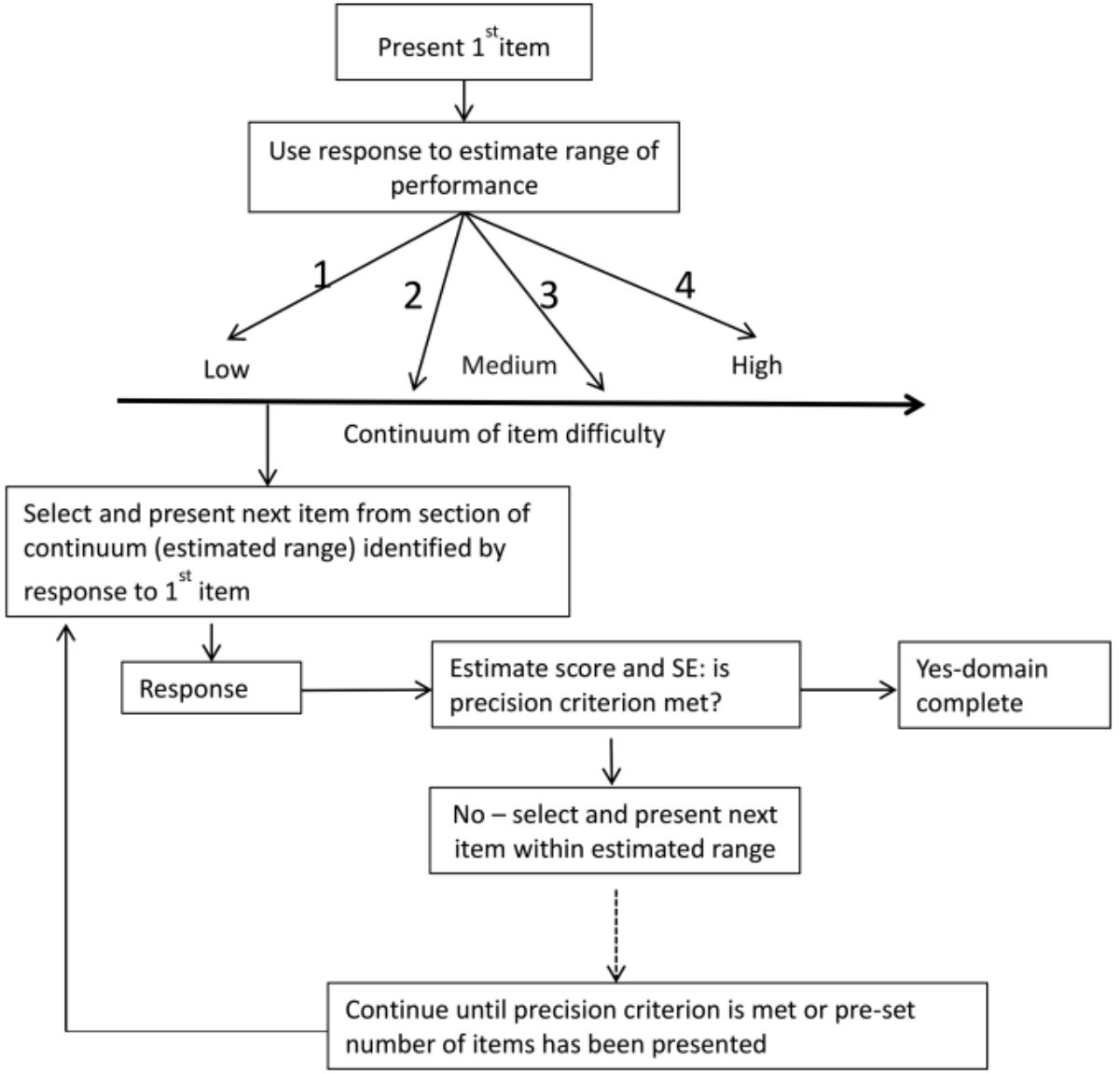
PEDI-CAT assessment: Description

The **PEDI-CAT** assesses four domains of function:

1. **Daily Activities**
2. **Mobility**
3. Social/Cognitive
4. Responsibility

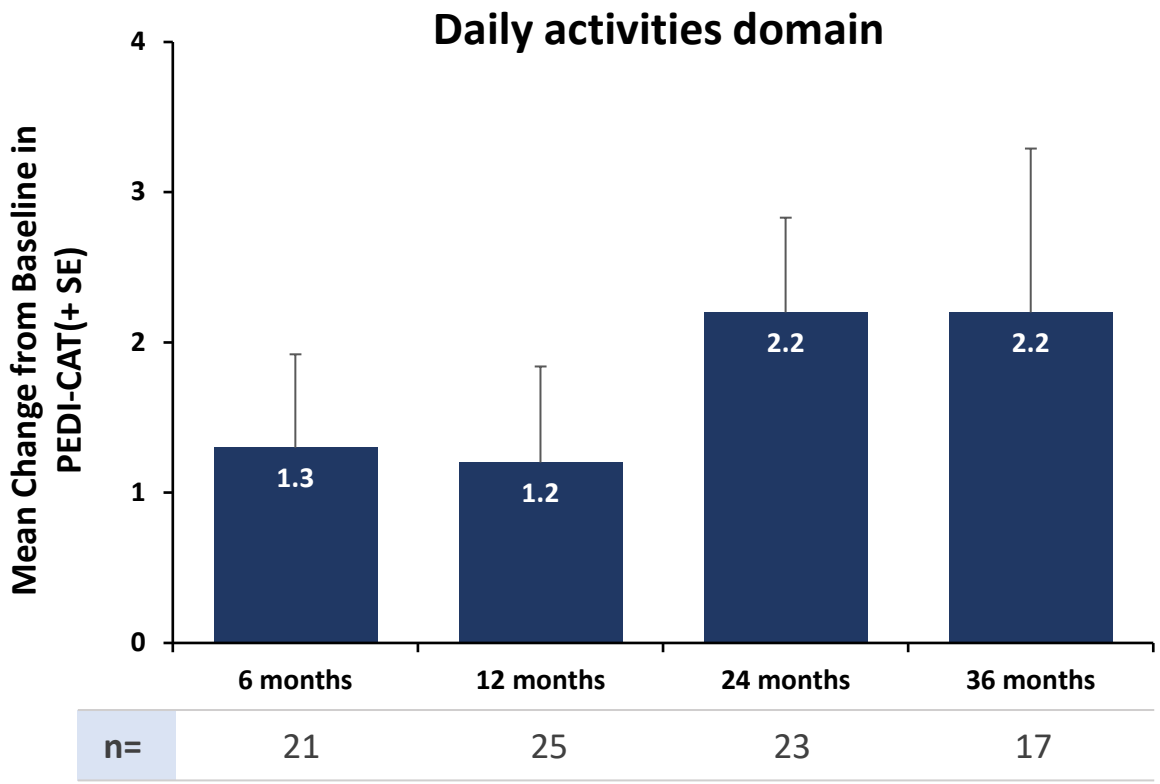
Possible daily activities questions:

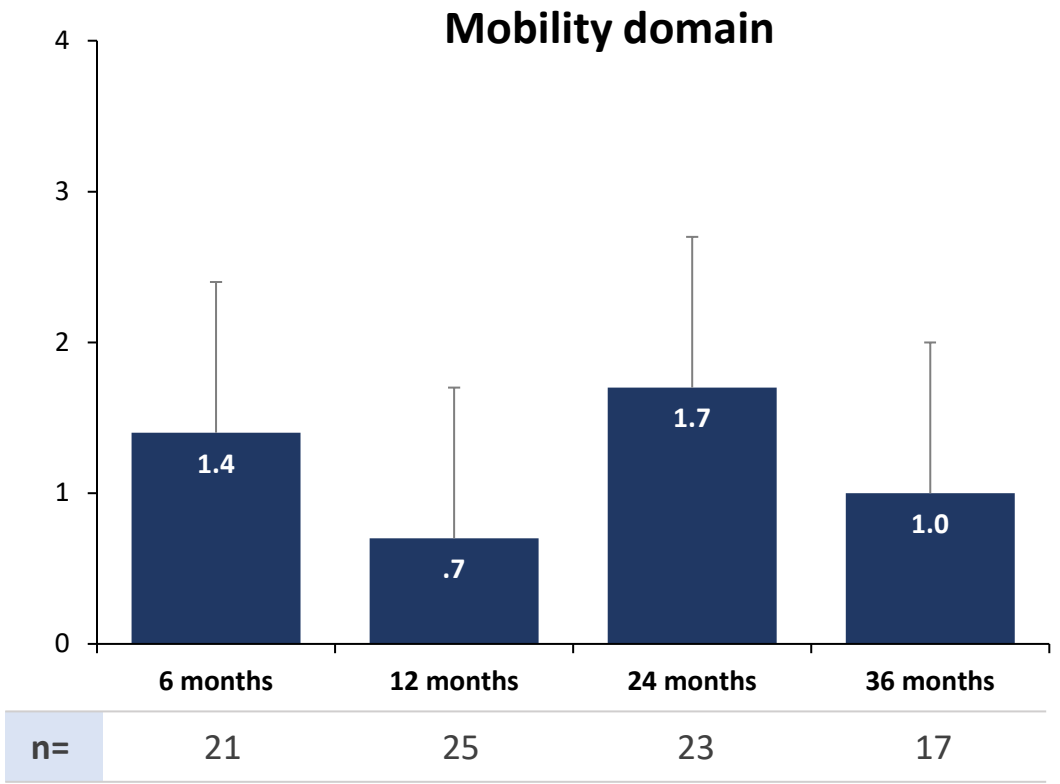
- "Tucks in shirt or blouse"
- "Dries hair with a towel"



Coster WJ, et al. *Autism*. 2016;20(1):14-25. doi:10.1177/1362361314564473
PEDI-CAT, Pediatric Evaluation Of Disability Inventory-computer Adaptive Test; SE, standard error.

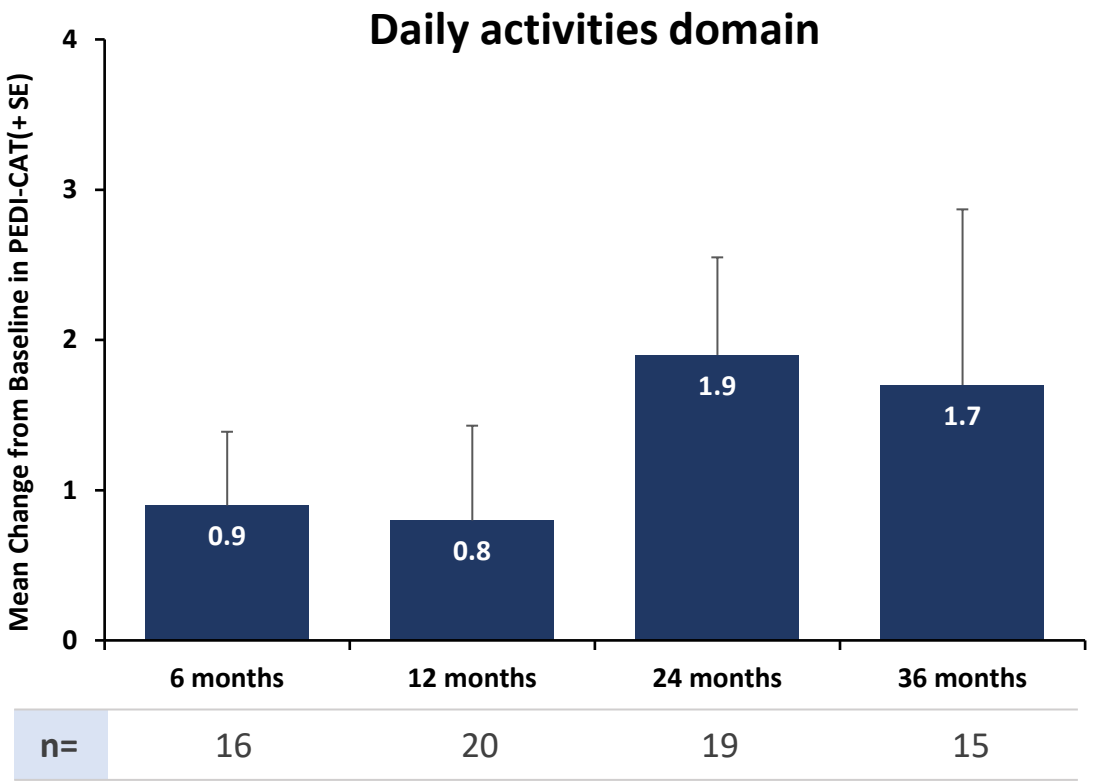
Mean changes in PEDI-CAT daily activities and mobility scaled scores over 36 months in patients aged 2-21 years



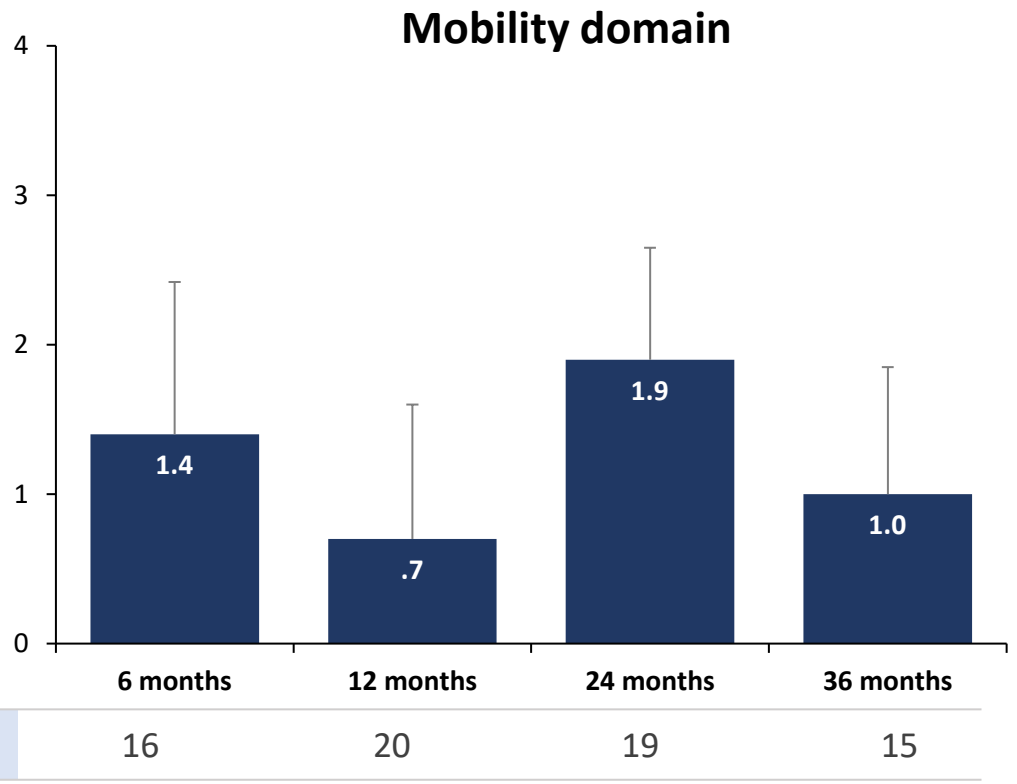


This analysis population included patients receiving either low dose (2 mg/kg) or high dose (20 mg/kg) apitegromab (inclusive of patients in Cohort 3 who transitioned from 2 mg/kg to 20 mg/kg in Year 2).
Error bars represent SE.
PEDI-CAT, Pediatric Evaluation of Disability Inventory-computer Adaptive Test; SE, standard error.

Mean changes in PEDI-CAT daily activities and mobility scaled scores over 36 months in patients aged 2-12 years



n=	16	20	19	15



n=	16	20	19	15

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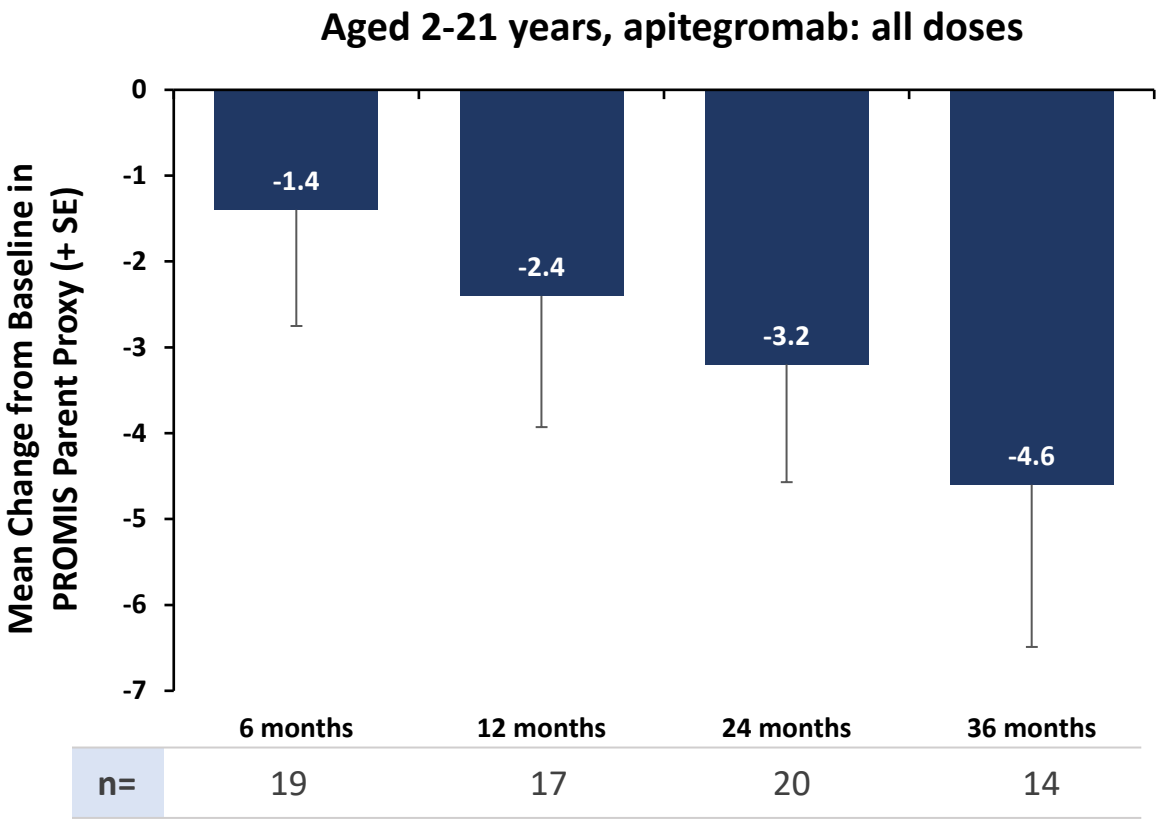
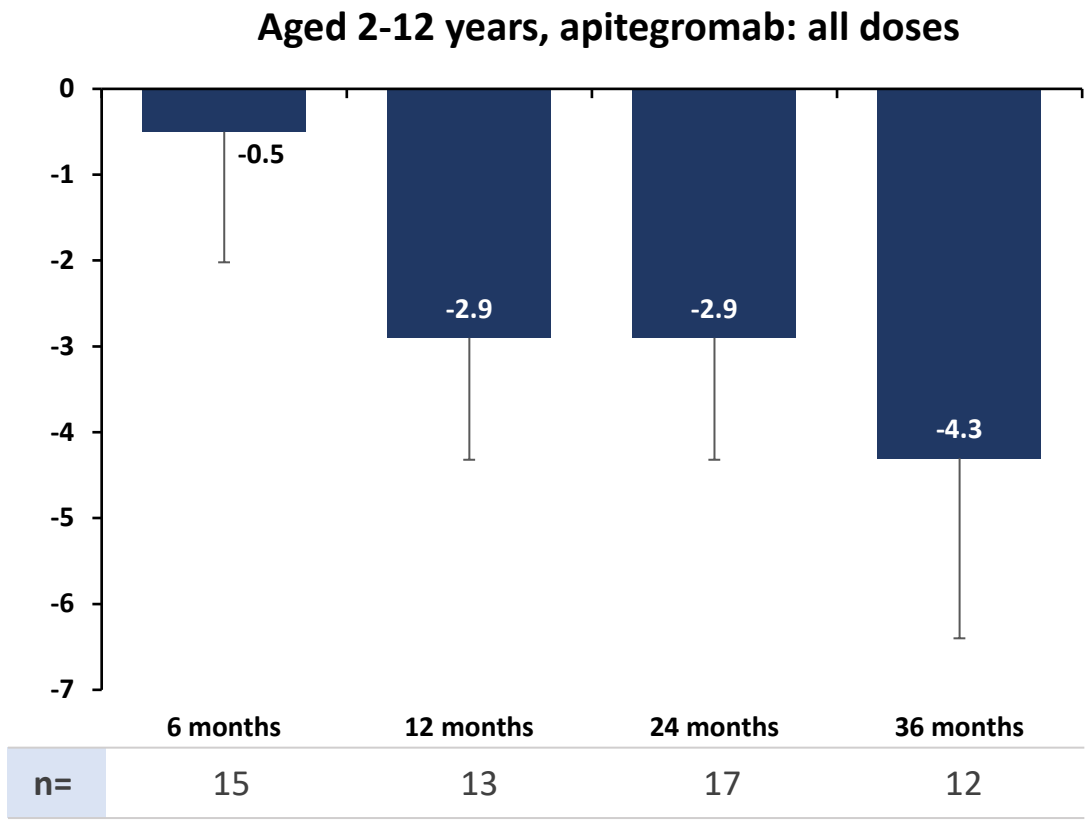
Error bars represent SE.
PEDI-CAT, Pediatric Evaluation of Disability Inventory-computer Adaptive Test; SE, standard error.

Improvement in PROMIS fatigue scores (caregiver proxy) over 36 months





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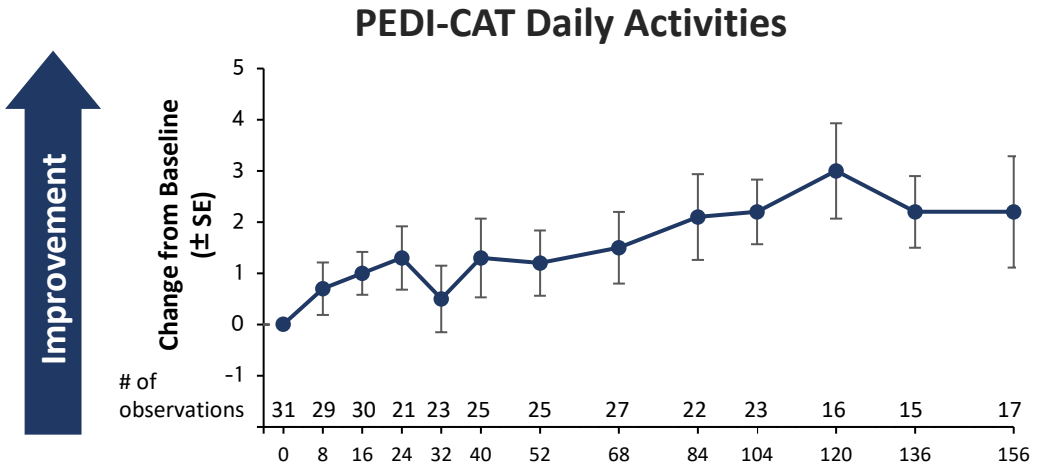
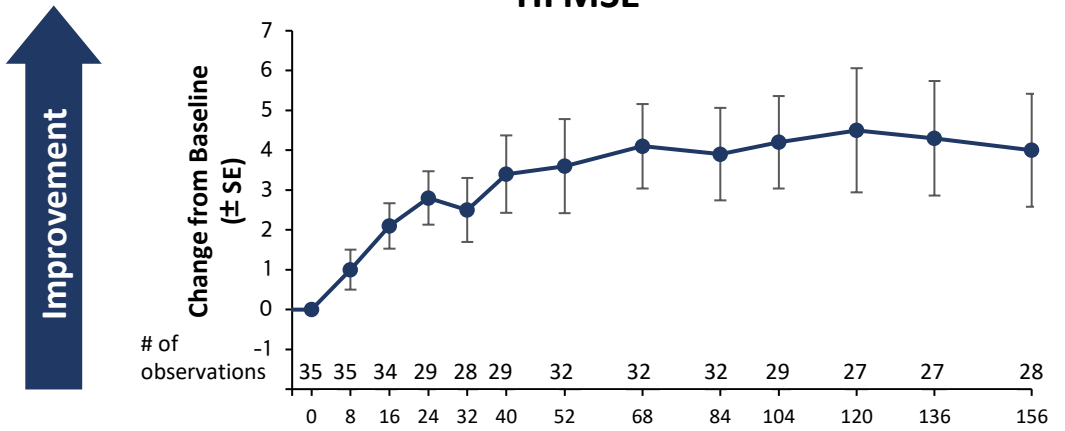
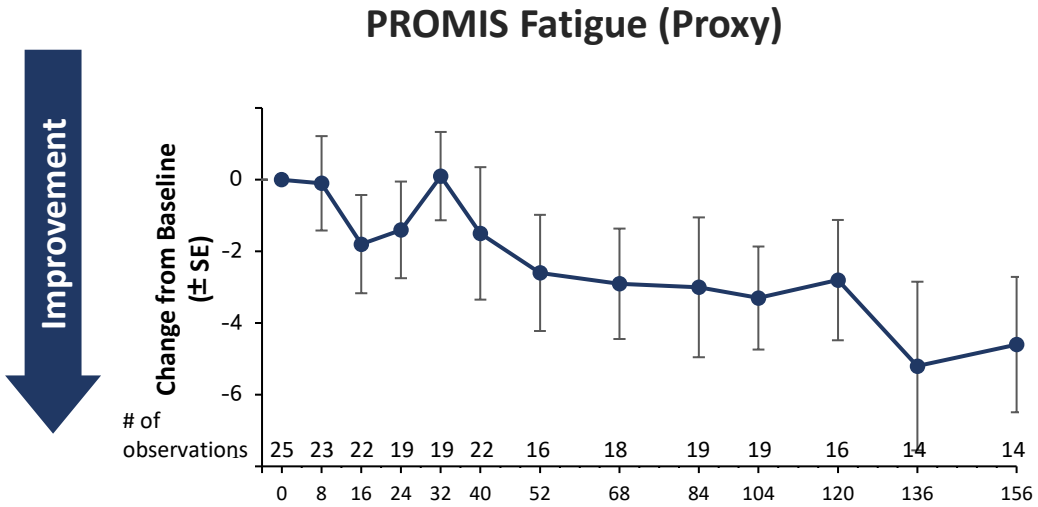
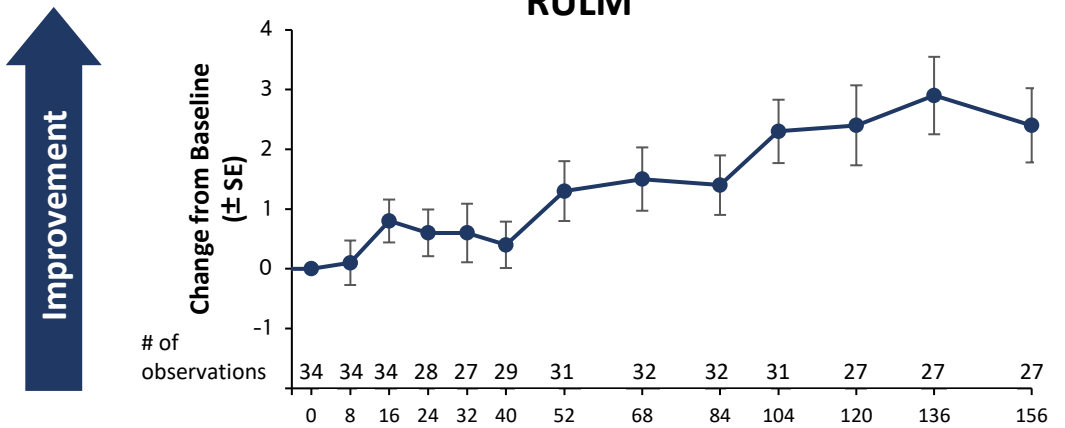
Error bars represent SE.
PROMIS, Patient-reported Outcomes Measurement Information System; SE, standard error.

Patient-reported outcomes and motor function measures over 36 months in patients aged 2-21 years









HFMSE, Hammersmith Functional Motor Scale–Expanded; SE, standard error; RULM, Revised Upper Limb Module; PEDI-CAT, Pediatric Evaluation of Disability Inventory-computer Adaptive Test; PROMIS, Patient-reported Outcomes Measurement Information System.

TOPAZ safety summary over 36 months

TEAEs*	Apitegromab 2 mg/kg N=10 n (%)	Apitegromab 20 mg/kg N=48 n (%)	Total N=58 n (%)
Any TEAE	10 (100)	46 (95.8)	56 (96.6)
Any serious TEAE	5 (50)	16 (33.3)	21 (36.2)
Any TEAE leading to study drug discontinuation	0	1 (2.1)	1 (1.7)
Any grade 3 (severe) or higher TEAE	4 (40)	16 (33.3)	20 (34.5)

- TEAEs were consistent with previous reports with no new findings after 198 patient-years of exposure
  - Most frequently reported TEAEs*: headache (38%), pyrexia (38%), COVID-19 (36%), nasopharyngitis (36%), and upper respiratory tract infection (33%)
  - TEAEs were mostly mild to moderate in severity and generally consistent with the underlying patient population and nusinersen therapy
- No deaths or suspected unexpected serious adverse reactions or hypersensitivity reactions to apitegromab were reported
- Three patients tested positive for the presence of anti-apitegromab antibodies (ADA), but confirmatory test showed titers were below the level of sensitivity, therefore interpreted as negative

*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. % = 100 x n/N; % at 12 months.

ADA, anti-drug antibody; TEAE, treatment emergent adverse event; COVID-19, coronavirus disease 2019.

Summary

- Improvements in motor function outcomes are sustained over 36 months with apitegromab treatment in Type 2 and nonambulatory Type 3 SMA
- Results on caregiver-reported outcomes are consistent with improvements in motor function as assessed by the HFMSE and RULM
- New WHO development milestones were achieved in patients from both nonambulatory groups and maintained in patients receiving prior SMN treatment before 5 years old
- The safety profile was consistent with previous reports
- A randomized, double-blind, placebo-controlled, phase 3 clinical trial, assessing the efficacy and safety of apitegromab is ongoing

HFMSE, Hammersmith Functional Motor Scale–Expanded; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy.

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- Lexa Enterprises Inc.
- ChilliPharm
- BBK
- CRECare
- Immunologix
- Charles River Labs
- Sephirus Inc.

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Scholar Rock Research and Development Team

TOPAZ sponsorship and funding provided by Scholar Rock, Inc.

Many thanks to the patients who participate in these studies, caregivers/families, healthcare professionals, & patient advocacy groups.

*TOPAZ *Patient Advisory Board*

CRO, contract research organization; PI, principal investigator.

1. Johns Hopkins; Baltimore, MD; **2.** Oregon Health & Science University; Portland, OR; **3.** Columbia University Pediatric Neuromuscular Center; NY, NY; **4.** Children's Hospital of the King's Daughters; Norfolk, Virginia; **5.** Stanford University Medical Center; Palo Alto, CA; **6.** Children's Hospital Colorado; Aurora, CO; **7.** Boston Children's Hospital; Boston, MA; **8.** Children's Medical Center Dallas; Dallas, TX; **9.** Wake Forest Baptist Health; Winston-Salem, NC; **10.** Phoenix Children's Hospital; Phoenix, AZ; **11.** Helen DeVos Children's Hospital at Spectrum Health; Grand Rapids, MI; **12.** Fondazione Policlinico Universitario A. Gemelli IRCCS - Universita Cattolica del Sacro Cuore for the institution; Rome, Italy; **13.** ASST Grande Ospedale Metropolitano Niguarda; Milan, Italy; **14**. University Medical Center Utrecht; Netherlands; **15**. Hospital Sant Joan de Deu; Barcelona, Spain; **16**. Hospital Universitari i Politecnic La Fe; Valencia, Spain; **17**. Stanford Neuroscience Health Center; Palo Alto, CA.