EFFECT OF APITEGROMAB ON MOTOR FUNCTION AND PATIENT-REPORTED OUTCOMES AT 36 MONTHS IN PATIENTS AGED 2–21 YEARS WITH SPINAL MUSCULAR ATROPHY

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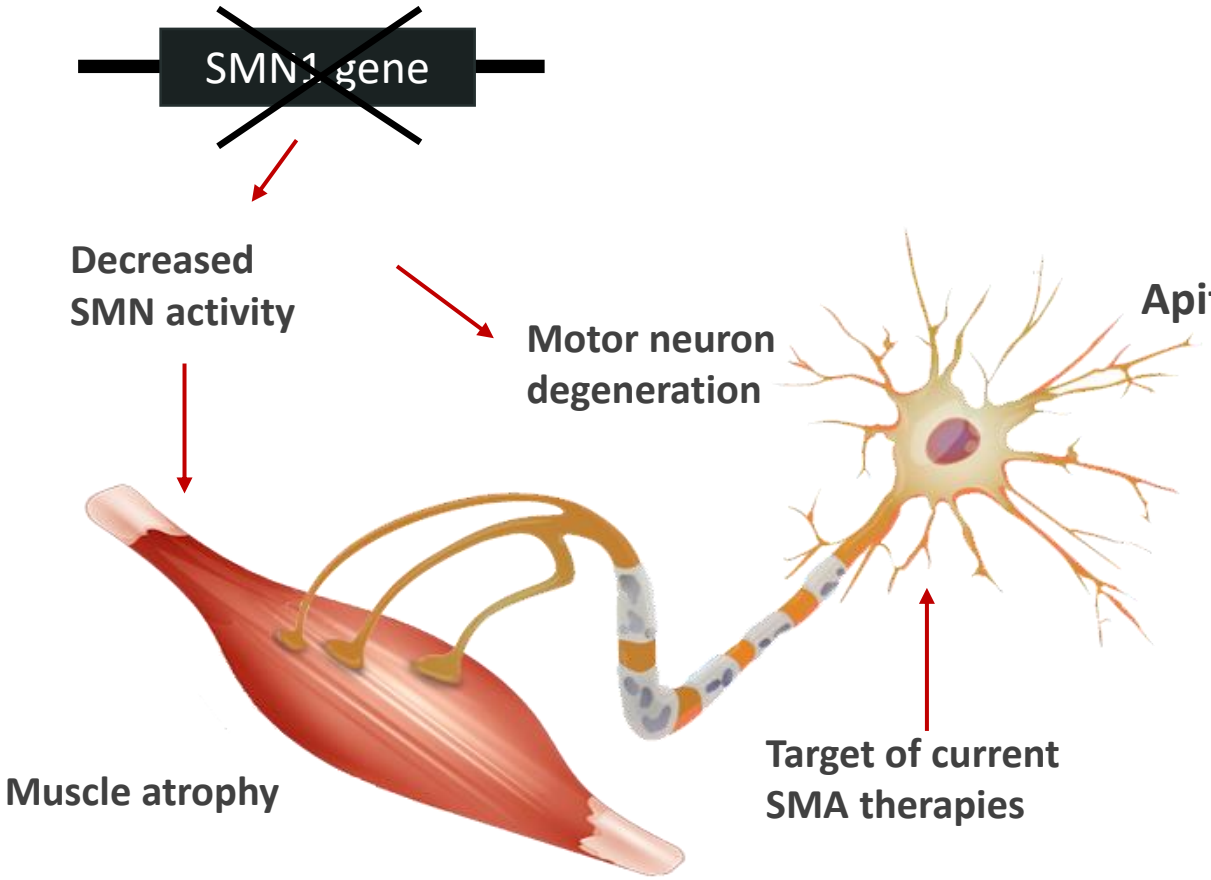
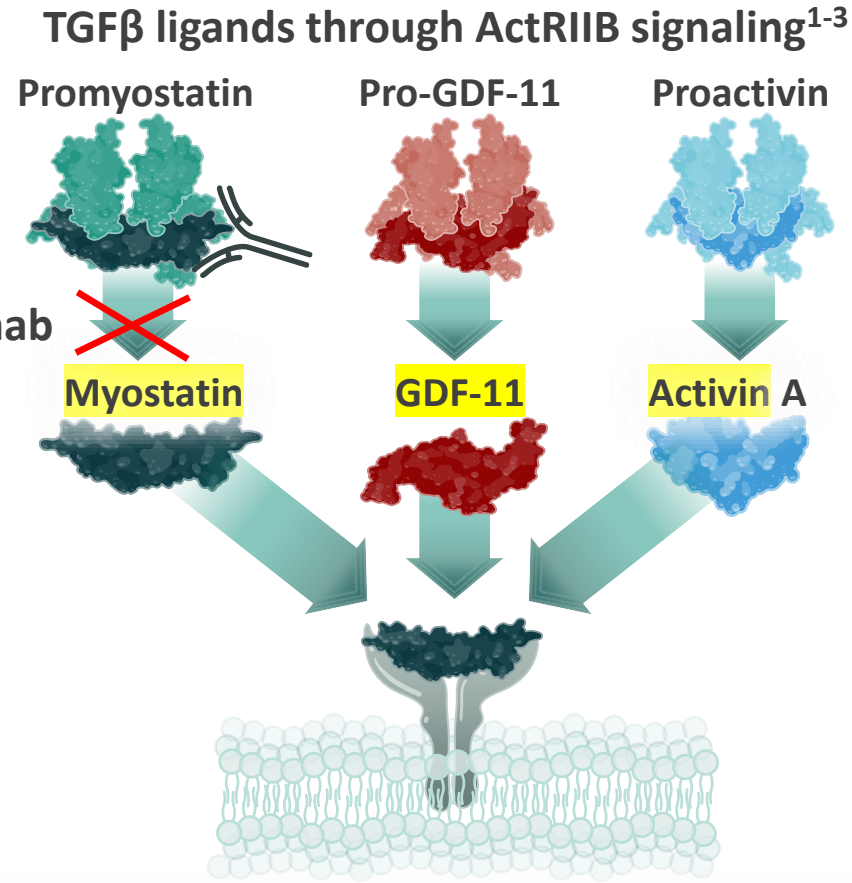
On behalf of the entire TOPAZ Study Team

AUTHOR DISCLOSURE

- Dr Baver is an employee of Scholar Rock and has no other industry-related activities to disclose.

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 and avoiding unwanted off-target effects of ActRIIB signaling.[1]

ActRIIB, activin receptor type IIB; GDF, growth differentiation factor; SMA, spinal muscular atrophy; SMN, survival motor neuron; TGFß, transforming growth factor beta.

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.

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; 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.

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

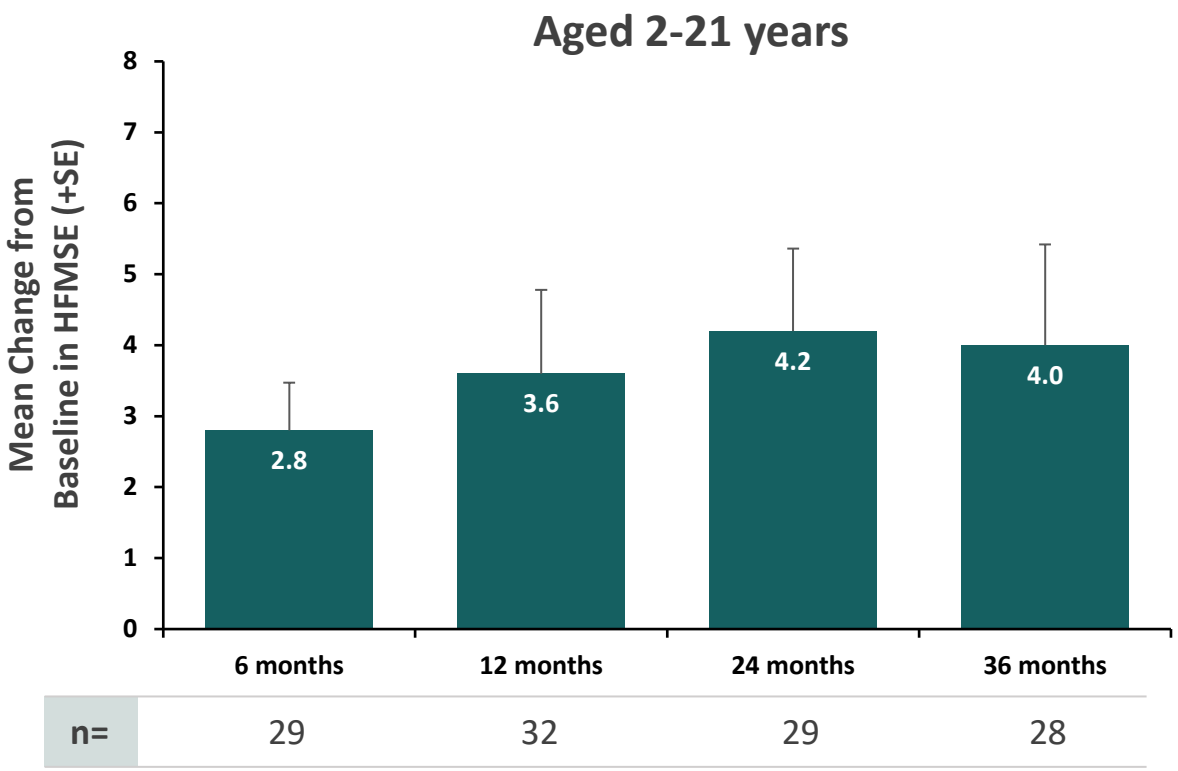
***For 12-month endpoint, if participants skipped 3 consecutive doses due to site restrictions caused by COVID-19, records after dose skipping were excluded from analysis. The last observation carried forward was used for other missing data.

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

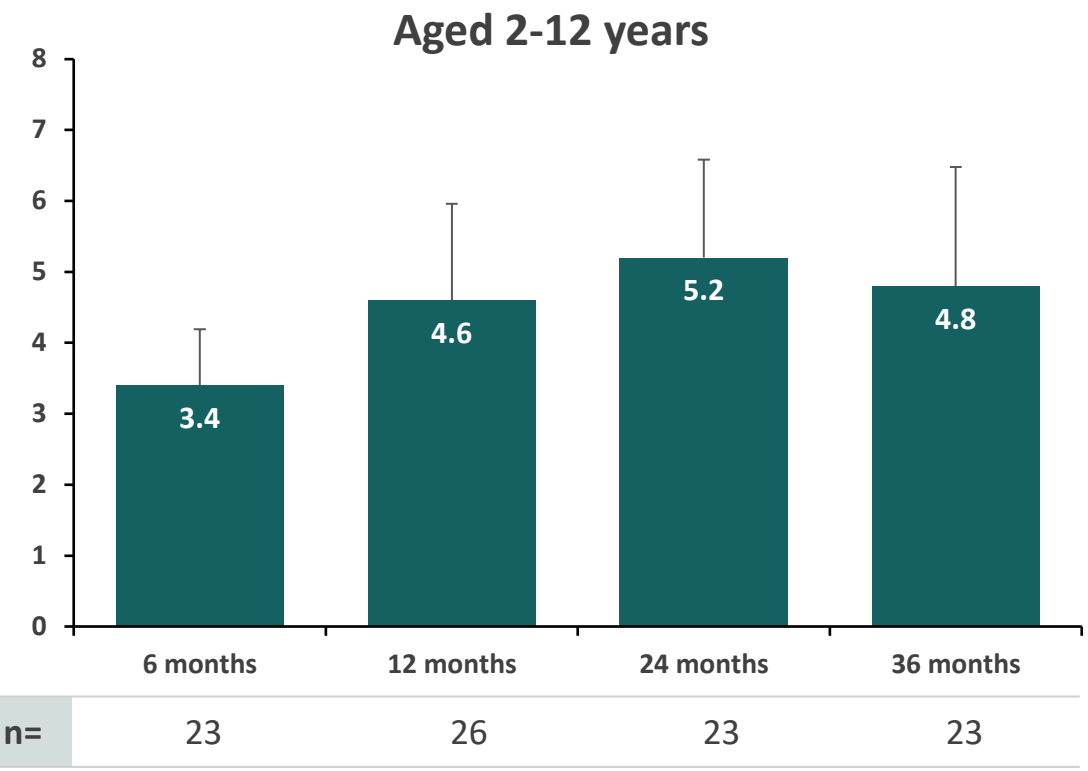
Crawford T et al. Presented at Muscular Dystrophy Association, 2021 Clinical & Scientific Conference; March 22, 2023.

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 were sustained over 36 months



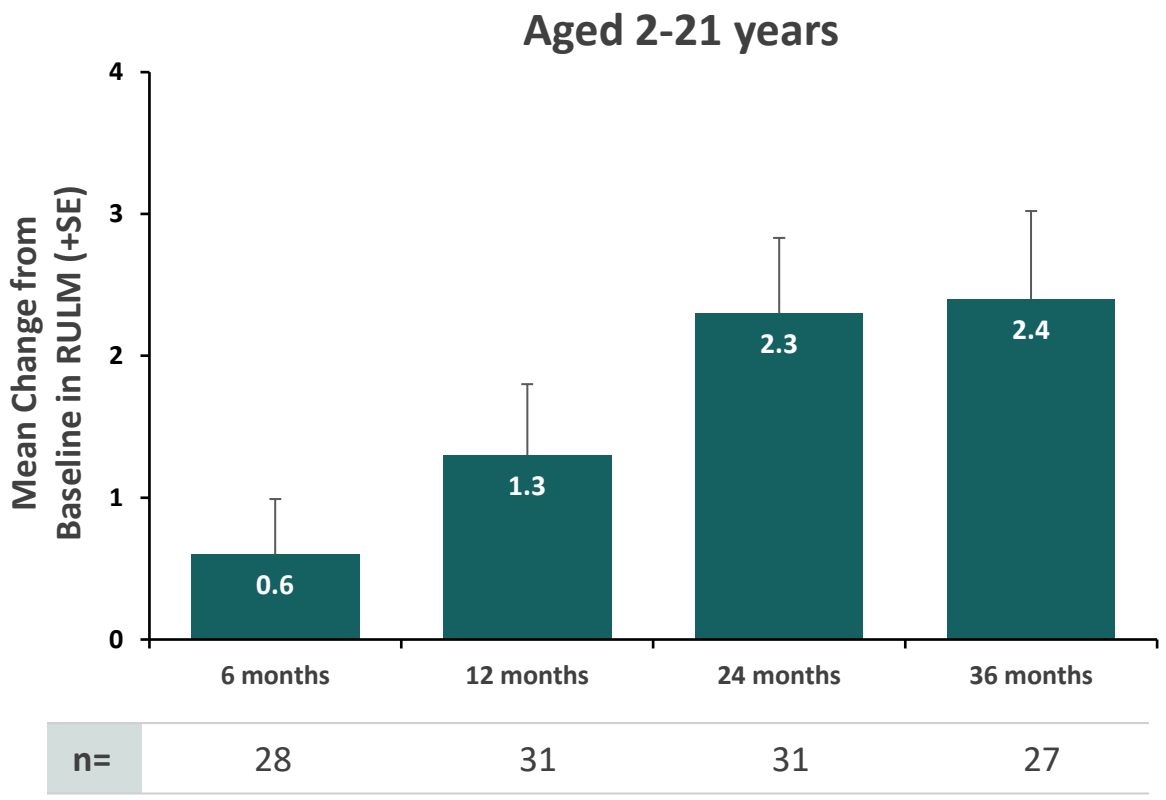
n=	29	32	29	28

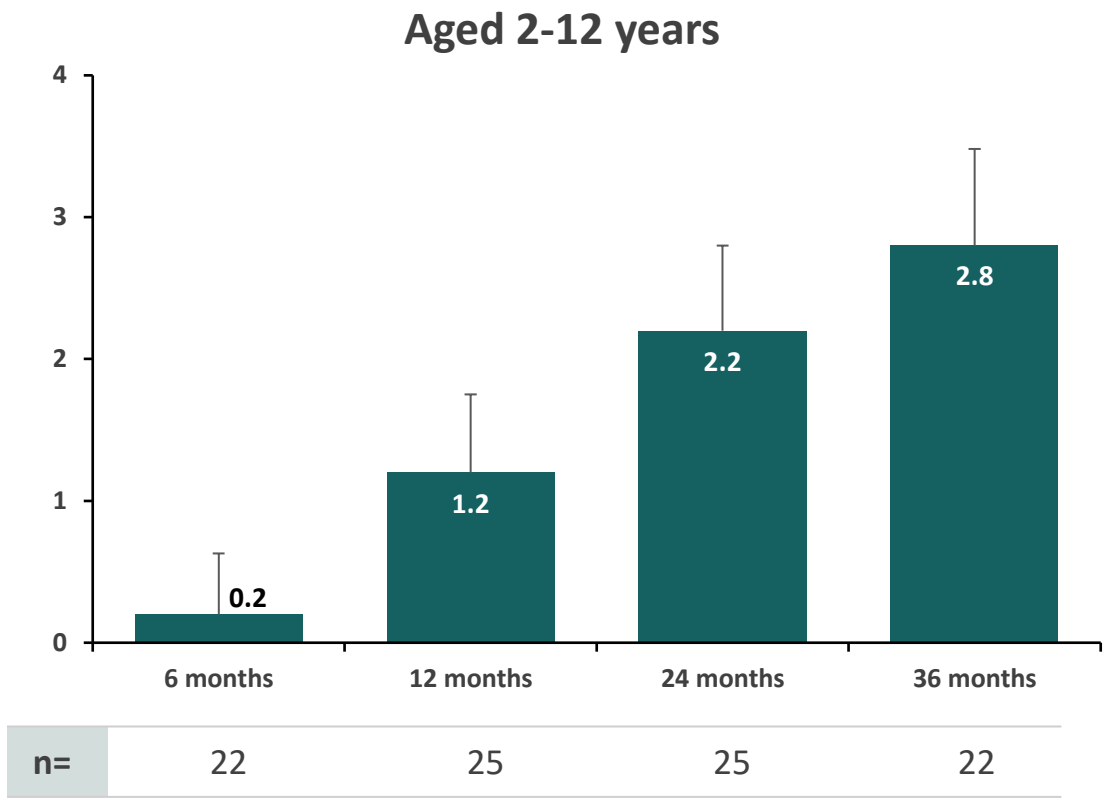


n=	23	26	23	23

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.
HFMSE, Hammersmith Functional Motor Scale–Expanded; SE, standard error.

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





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RULM, Revised Upper Limb Module; SE, standard error.

New WHO development milestones achieved

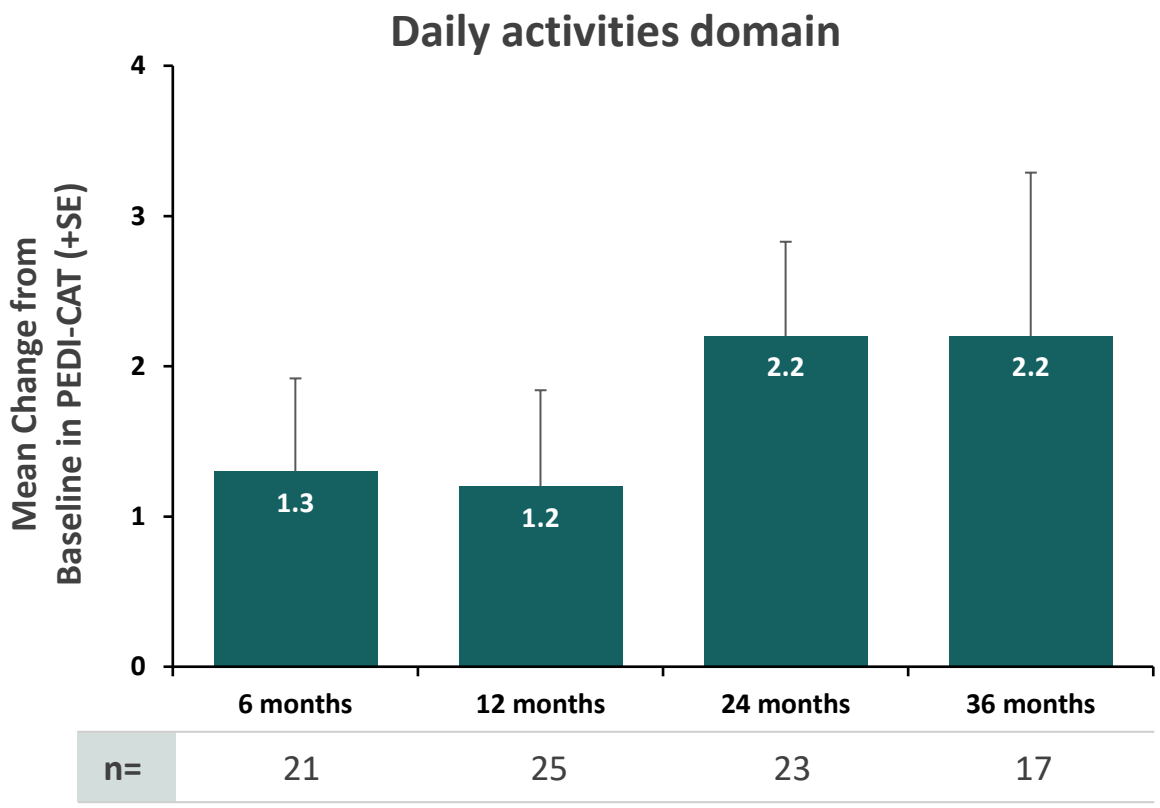
WHO Development Milestones

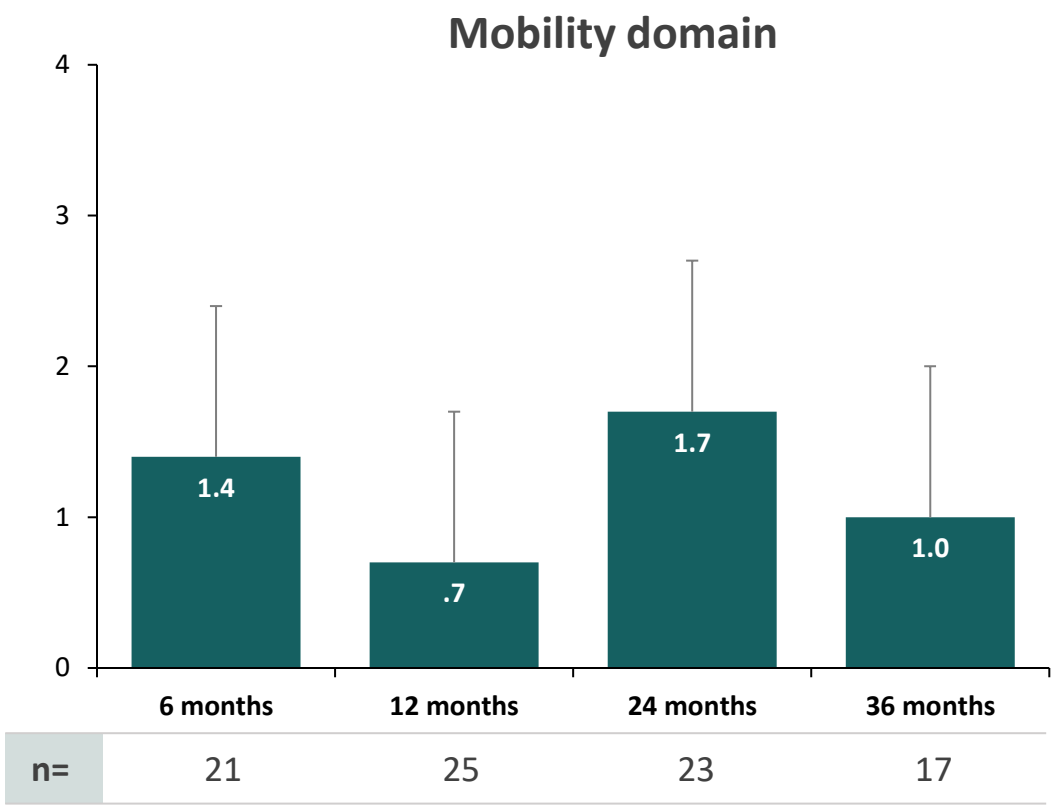
- Over 36 months, 86% (30/35) of patients improved or maintained WHO motor milestones that they had achieved at baseline
- Excluding those who had scoliosis surgery, 93% (27/29) of participants improved or maintained baseline WHO motor milestones
  - Of 20 patients receiving nusinersen earlier than 5 years of age, 6 gained new WHO motor milestones, including 2 who were able to walk independently

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 20 mg/kg dose: 12 months (25%), 24 months (33%), 36 months (40%).
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 of daily activities and mobility domains showed sustained improvement over 36 months in patients aged 2-21 years

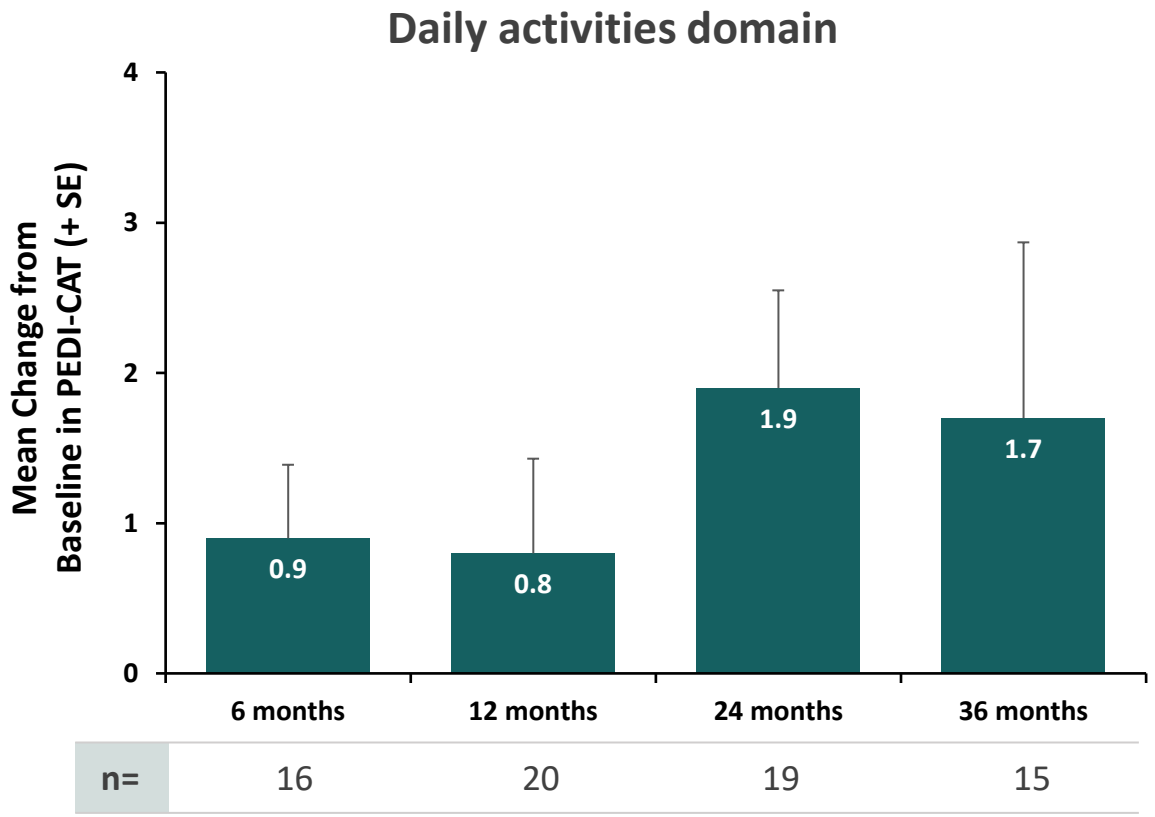


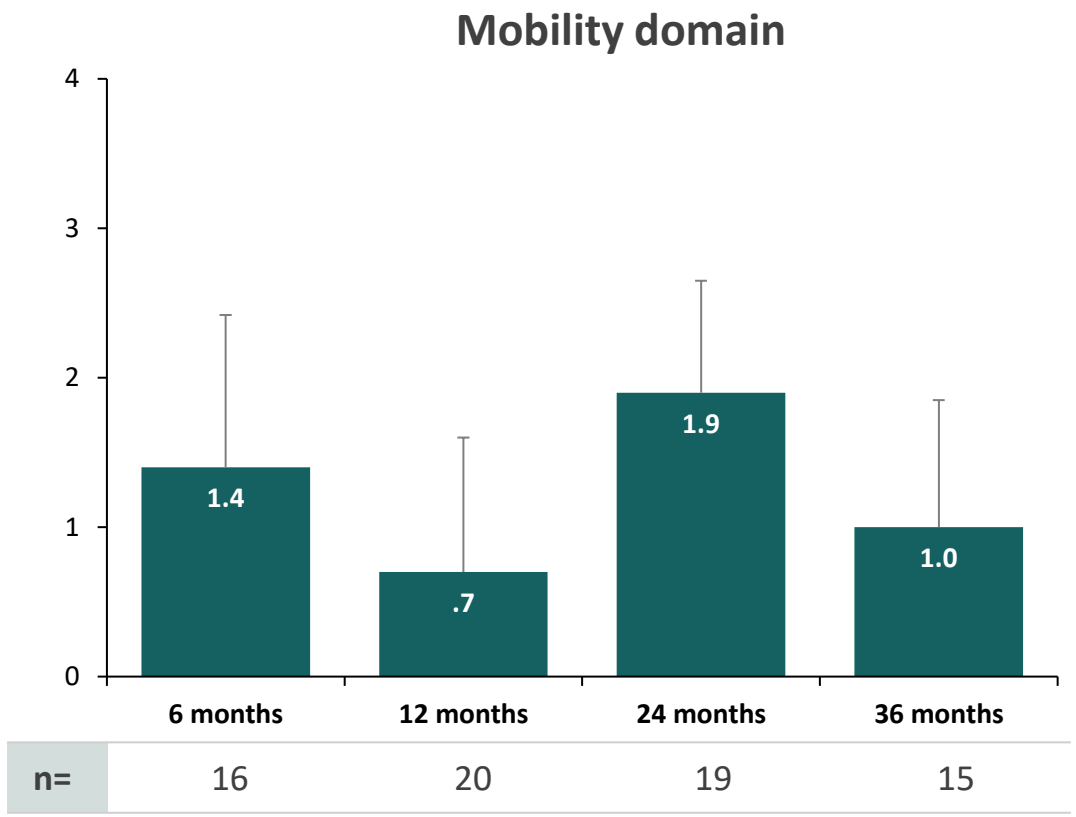


This analysis population included patients receiving either low dose (2 mg/kg) or high dose (20 mg/kg) apitegromab (inclusive of patients in Cohort 3 who transitioned from 2 mg/kg to 20 mg/kg in Year 2). Error bars represent SE.

PEDI-CAT, Pediatric Evaluation of Disability Inventory-Computer Adaptive Test; SE, standard error.

PEDI-CAT assessment of daily activities and mobility domains showed sustained improvement over 36 months in patients aged 2-12 years





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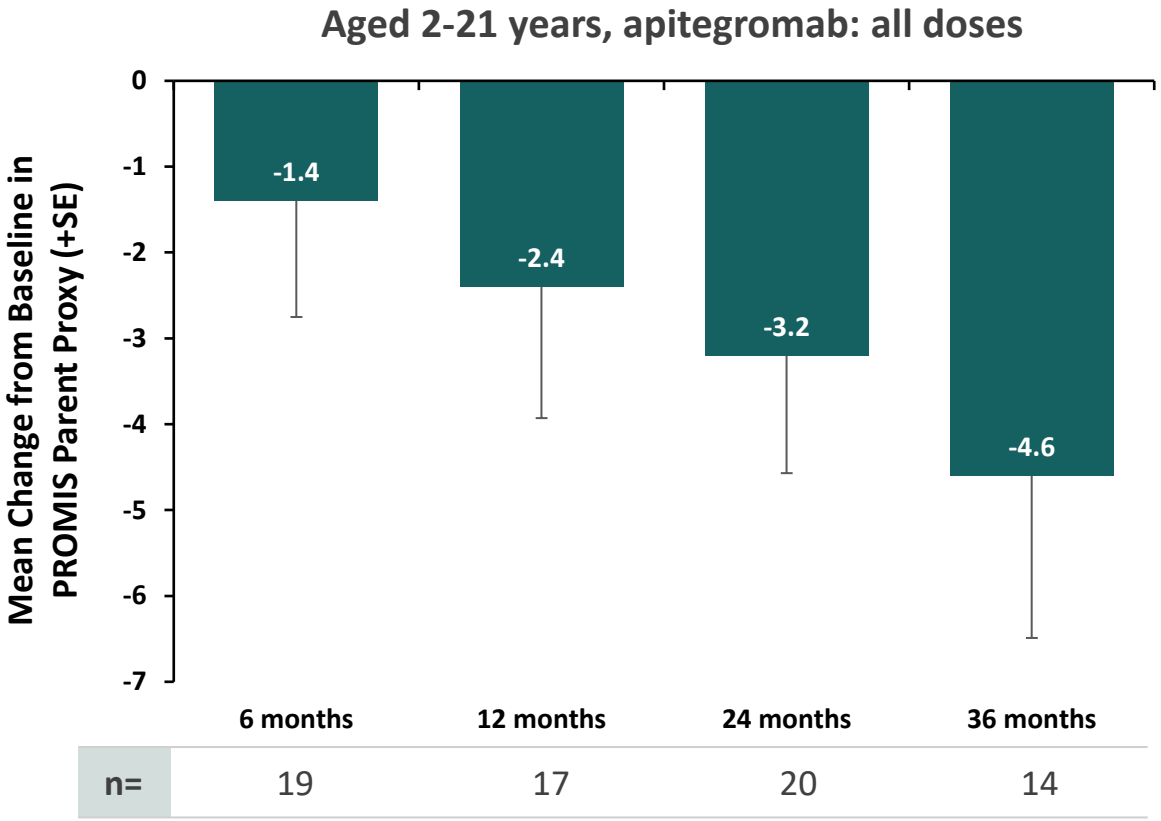
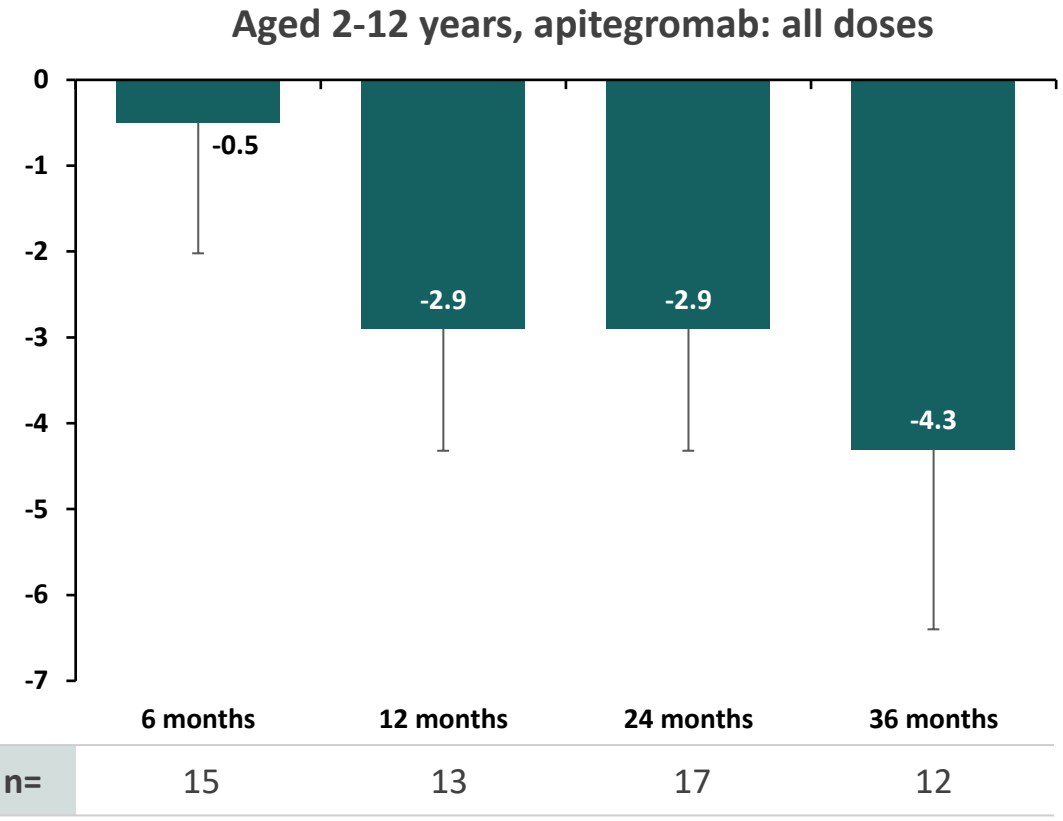
PEDI-CAT, Pediatric Evaluation of Disability Inventory-Computer Adaptive Test; SE, standard error.

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



	6 months	12 months	24 months	36 months
n=	19	17	20	14

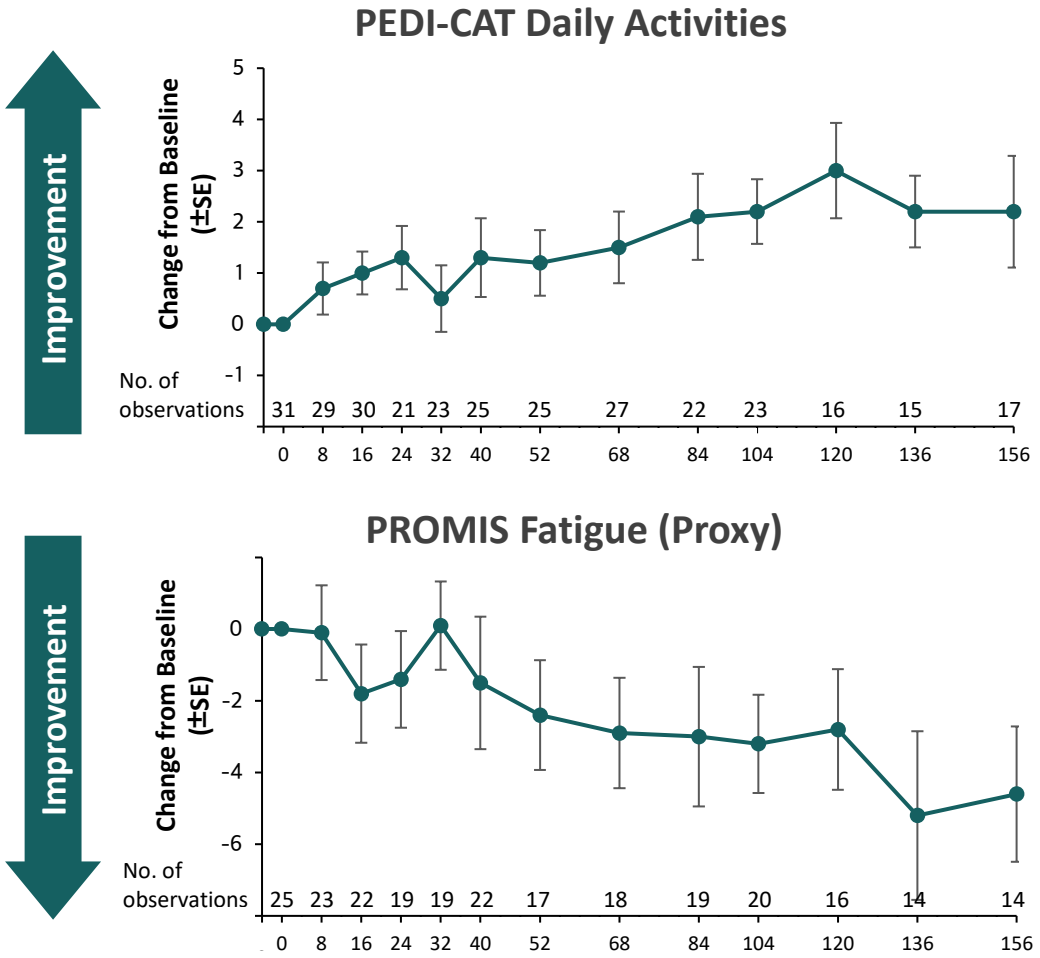


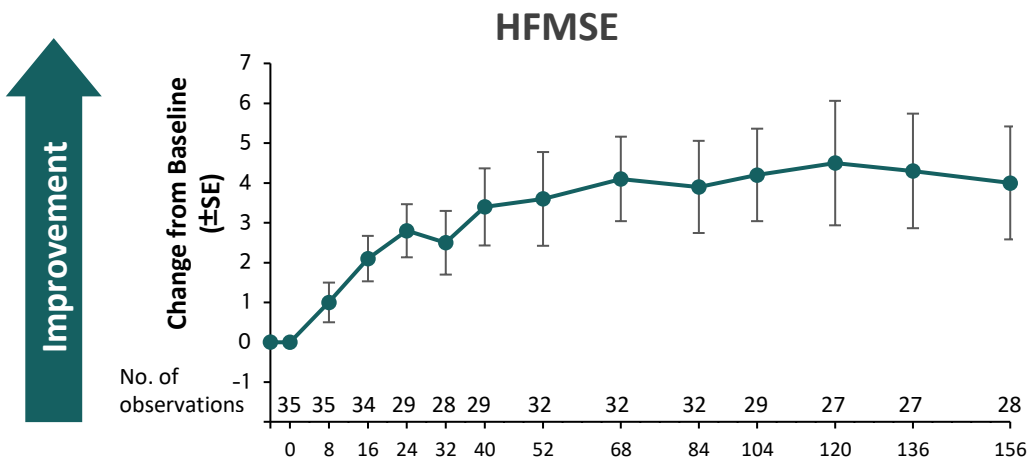
	6 months	12 months	24 months	36 months
n=	15	13	17	12

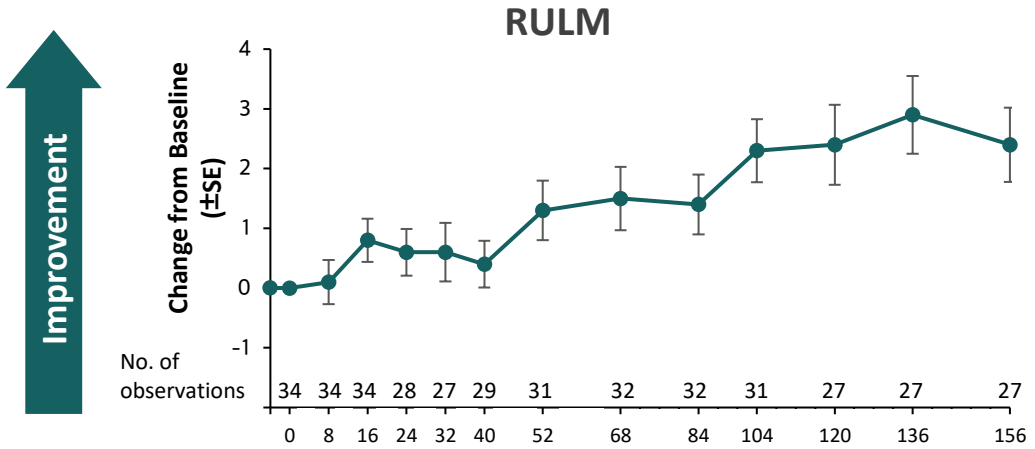
This analysis population included patients receiving either low dose (2 mg/kg) or high dose (20 mg/kg) apitegromab (inclusive of patients in Cohort 3 who transitioned from 2 mg/kg to 20 mg/kg in Year 2). Error bars represent SE.

PROMIS, Patient-Reported Outcomes Measurement Information System; SE, standard error.

Change in PEDI-CAT and PROMIS outcomes were consistent with change in motor function measures over 36 months in patients aged 2-21 years







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

TOPAZ safety summary over 36 months

Treatment-emergent adverse events (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 (50.0)	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 (40.0)	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; AE, adverse event; COVID-19, coronavirus disease 2019.

Summary

- Improvements in motor function outcomes were 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
- Majority of patients improved or maintained WHO motor milestones that they had achieved at baseline
- 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; WHO, World Health Organization.

Concluding lay slide

Apitegromab was studied in patients 2–21 years old for the treatment of SMA.

Treatment with apitegromab was shown to be safe for over 3 years and patients showed improvement in movement, daily tasks, and fatigue.

SMA EUROPE

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

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*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.