Apitegromab in SMA (TOPAZ Trial): Covariates of Multiple Efficacy Endpoints From 24 Month Data

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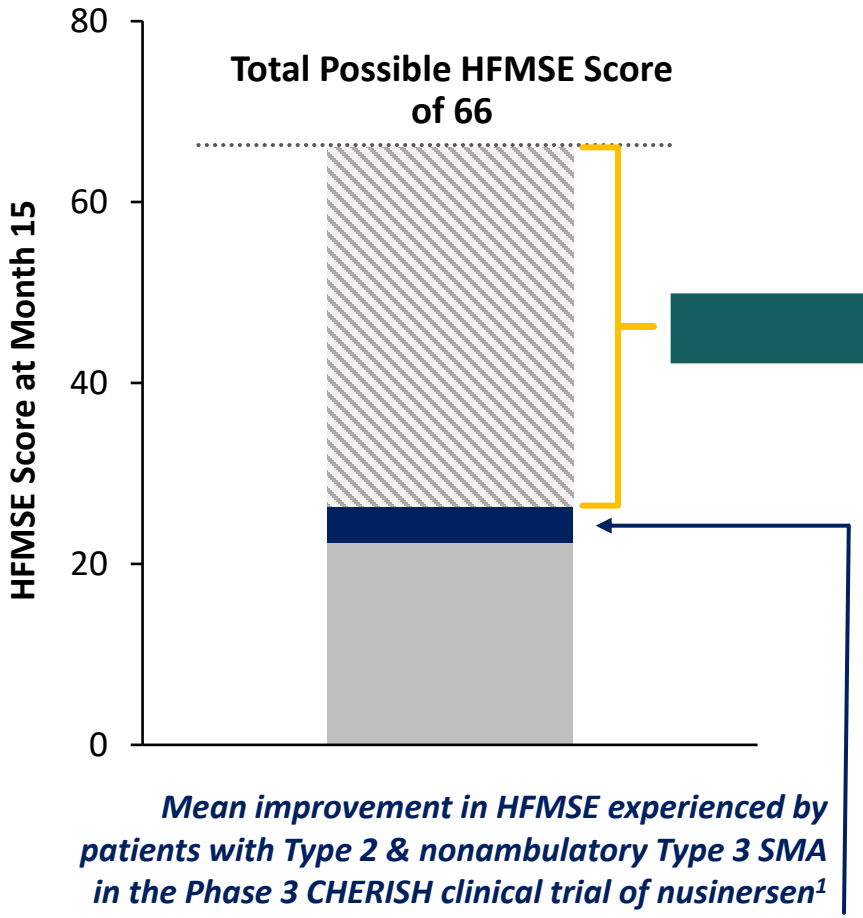
Declaration of Interests

Dr Thomas O. Crawford

- **Employment:** Professor of Neurology and Pediatrics; Johns Hopkins University
- **Consulting/Advisory Boards:** Biogen; Roche/Genentech; Avexis / Novartis; Pfizer
- **Research Funding/ Study Site Investigations:** Biogen; Avexis; Cytokinetics; Parexel; Catalyst
- **Patient Organizations:** CureSMA; SMA Foundation; Muscular Dystrophy Association; Ataxia Telangiectasia Children's Project

Disease Burden Persists Despite Current SMA Treatments



- Limitations in mobility and daily activities continue and are associated with a gradual deterioration in motor function[2,3]
- Fatigue and decreased QoL remain a burden on people living with SMA[2-4]

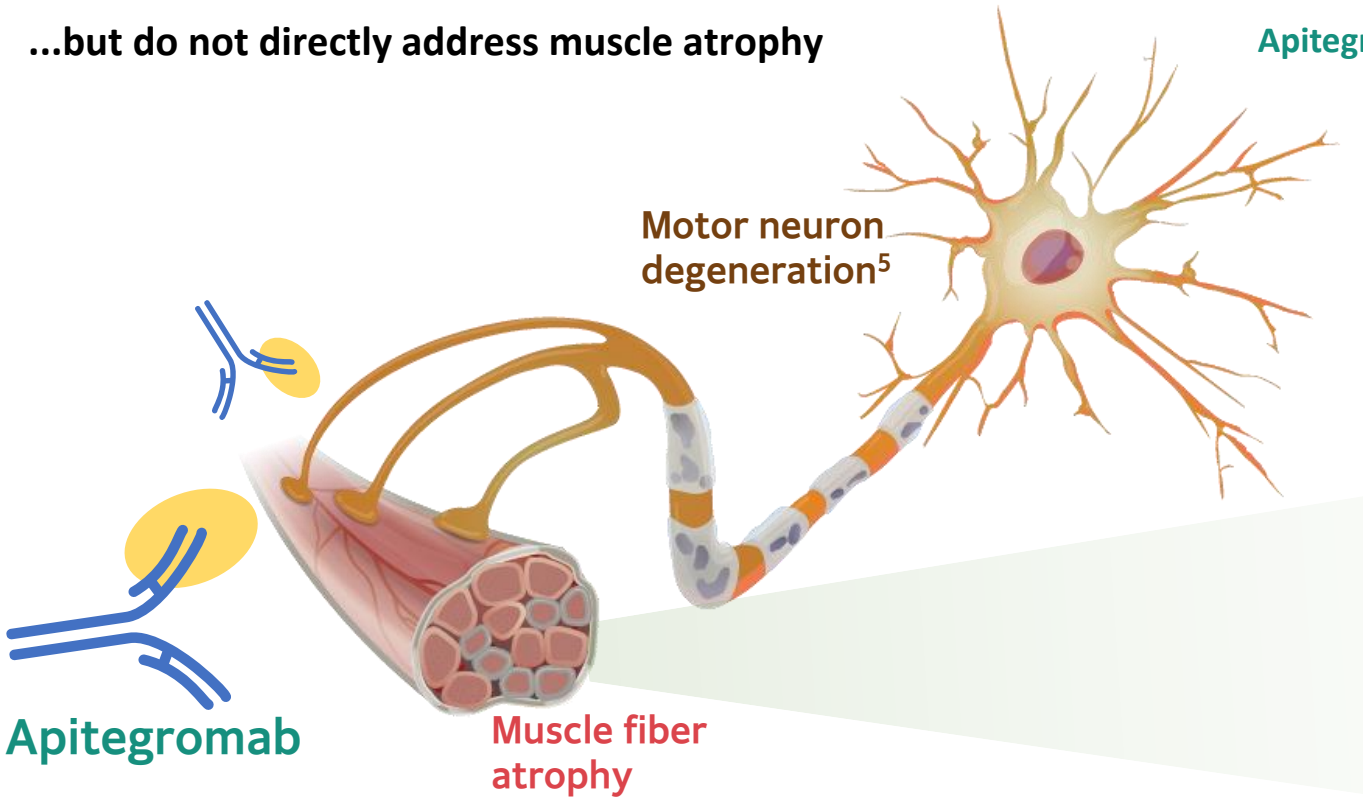
HFMSE, Hammersmith Functional Motor Scale Expanded; **QoL**, Quality of Life; **SMA**, Spinal Muscular Atrophy.

1. Darras B, et al. *Neurology.* 2019;92:e2492-e2506. **2.** Yang M, et al. *Adv Ther*. 2022;39:1915-1958. **3.** Wan HWY, et al. *Orphanet J Rare Dis*. 2020;15:70. **4.** Thimm A, et al. *Front Neurol*. 2022;12:812063.

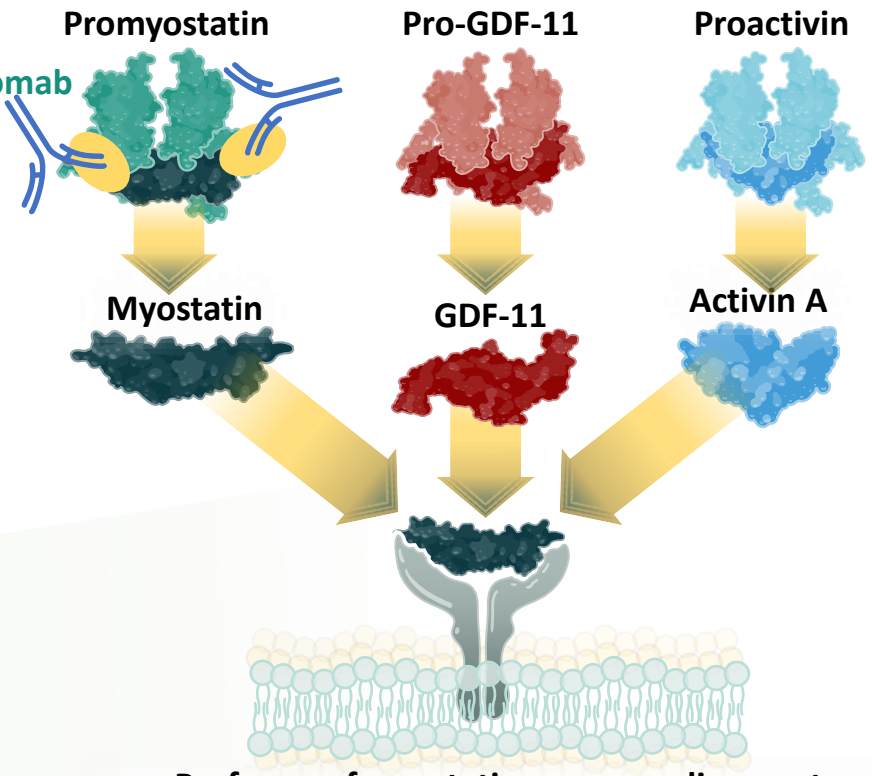
Apitegromab Is a Fully Human Monoclonal Antibody That Targets Muscle to Improve Motor Function in SMA[1-3]

SMN therapies prevent further degeneration of motor neurons[4]

...but do not directly address muscle atrophy



TGFβ ligands through ActRIIB signaling[1-3]

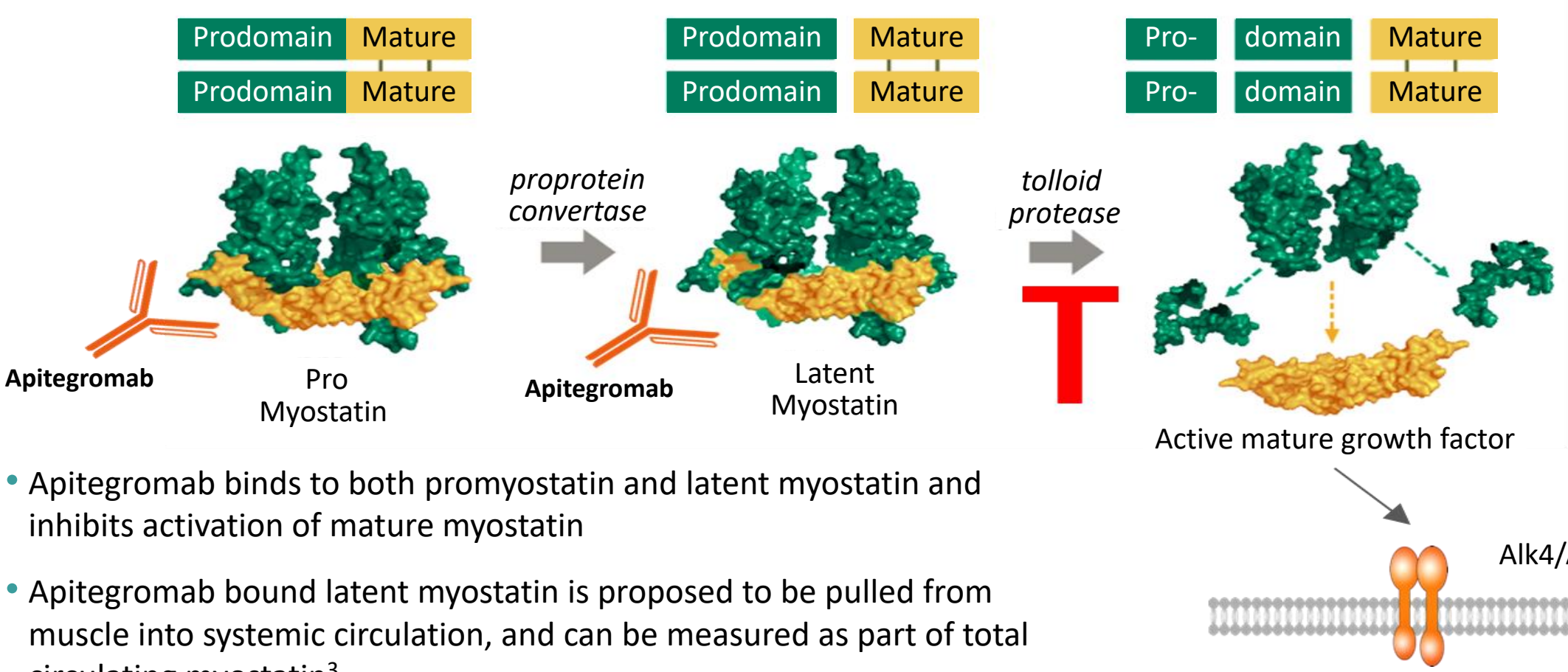


Proforms of myostatin are more divergent, thus inhibiting the activation of myostatin avoids unwanted off target effects of ActRIIB signaling[1]

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. **4.** Hua Y, et al. Nature. 2011;478(7367):123-6.
5. Figure adapted from: SMA Foundation Overview. http://www.smafoundation.org/wp-content/uploads/2012/03/SMA-Overview.pdf.; Accessed April 18, 2021.

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.

TOPAZ Phase 2 Trial Design[1,2]

Nonambulatory ≥ Age 2 Cohort

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

Nonambulatory Ages 5-21 Cohort

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

Ambulatory Ages 5-21 Cohort

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

24 months* → 36 months → 48 months

Three Successive 52-Week Extension Periods

ALL PATIENTS IN EXTENSION PERIODS RECEIVED 20 MG/KG APITEGROMAB

Primary Efficacy Endpoint at 12 months: Mean HFMSE Change from Baseline

All SMA Types 2/3, cohorts defined by age and present ambulatory status at time of enrollment.
*57/58 completed treatment period and enrolled in 1st extension period (24 months); 2 withdrew consent; 55 completed 1st extension period (24 months) and enrolled into 2nd extension period (36 months)

HFMSE, Hammersmith Functional Motor Scale Expanded; **IV**, intravenous; **q4w**, every 4 weeks**; SMA**, spinal muscular atrophy; **SMN**, survival motor neuron.

1. Place A, et al. *Eu J Neurol*. 2021;28(Suppl1):207-334 (EPR-184). **2.** Crawford T, et al. TOPAZ Extension: 24-month Efficacy and Safety of Apitegromab in Patients With Later-onset SMA (Type 2 and Type 3 SMA). Presented at CureSMA Annual Conference; June 16-19, 2022.

TOPAZ Phase 2 Trial Baseline Characteristics[1,2]

	Nonambulatory Age 2+ Cohort			Nonambulatory, Age 5-21 Cohort	Ambulatory Age 5-21 Cohort		
	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)			
Months Nusinersen Prior Therapy: 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
Discontinuation(s)	0	0	0	0	0	1†	1†

*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). *SMN2* copy numbers were not available for all patients. †12-month baseline characteristics recorded in the table, 1-cohort 1 patient and 1- cohort 2 patient discontinued during 24M Extension Period A. 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. TOPAZ Extension: 24-month Efficacy and Safety of Apitegromab in Patients With Later-onset Spinal Muscular Atrophy (Type 2 and Type 3 SMA). Presented at CureSMA Annual Conference; June 16-19, 2022.

Transformative Potential for Apitegromab as an Add-On

TOPAZ Age 2-12 Analysis* in Pooled Type 2 and Nonambulatory Type 3 Cohorts (20 mg/kg) (SAPPHIRE Main Cohort)

Nonambulatory Types 2/3 SMA (Apitegromab 20 mg/kg; Intent-to-Treat Population)	**Age 2-12 years** (n=16†)
Primary Efficacy Endpoint at 12 months: Mean HFMSE change from baseline, (95% CI)	**+4.4 (1.3, 7.4)**
Patients with ≥ 1-pt increase in HFMSE, n (%)	**13 (81%)**
Patients with ≥ 3-pt increase in HFMSE, n (%)	**9 (56%)**

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

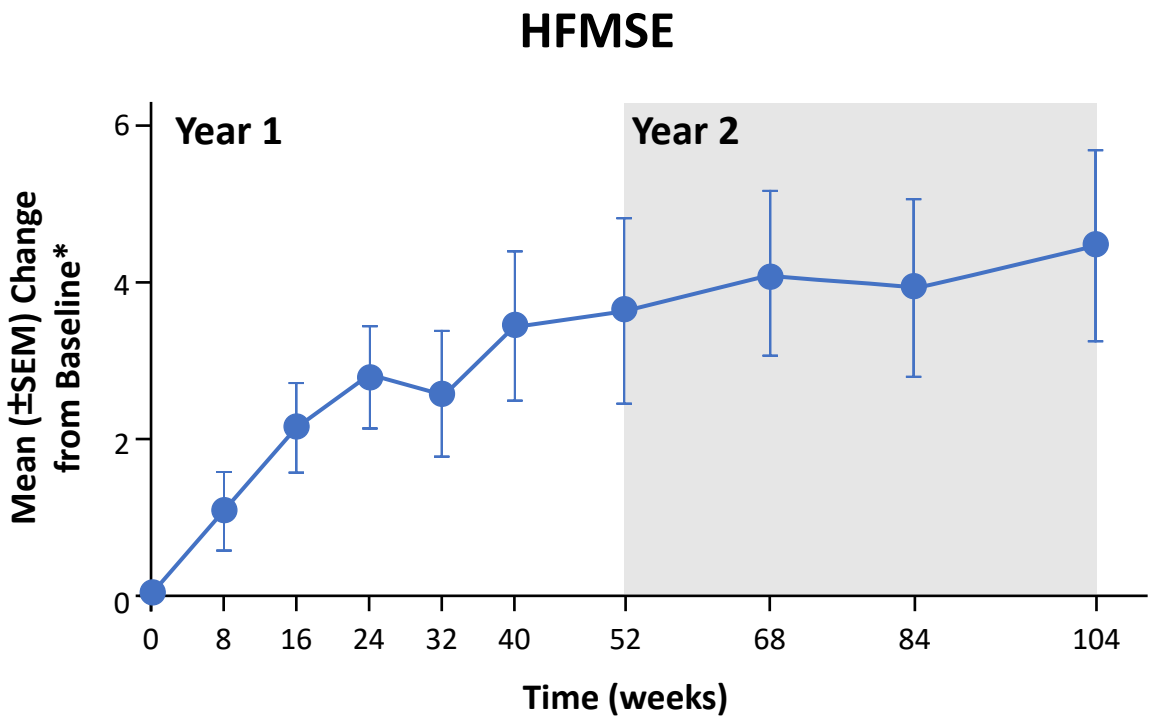
- 75% (6/8) with ≥ 1-point increase
- 50% (4/8) with ≥ 3-point increase

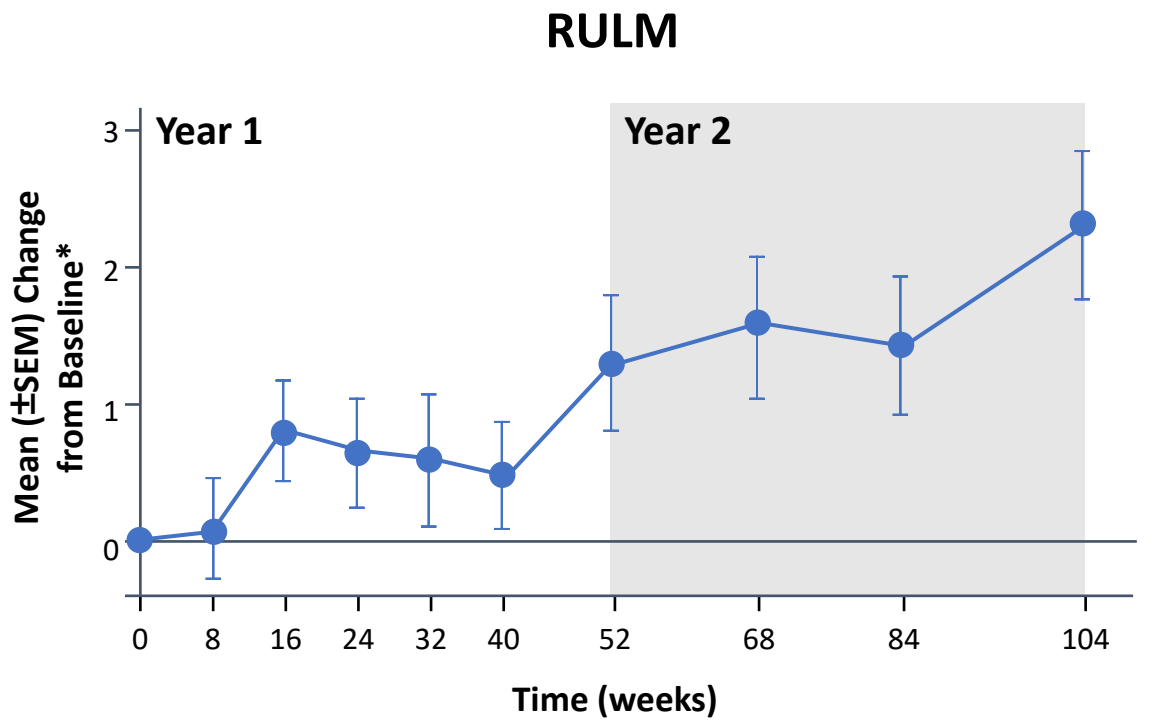
*Exploratory, post hoc analysis. †For 12-month endpoint, if patients skipped three consecutive doses due to site restrictions caused by COVID-19, records after dose skipping were excluded from analysis. The last observation carry forward was used for other missing data.

CI, confidence interval; **HFMSE**, Hammersmith functional motor scale expanded; **SMA**, spinal muscular atrophy.

Crawford T et al. TOPAZ topline results. Presented at CureSMA, 2021 Virtual SMA Research & Clinical Care Meeting; June 9-11, 2021.

Over 24 Months, Effect of Apitegromab in Type 2 and Nonambulatory Type 3 SMA Continues*



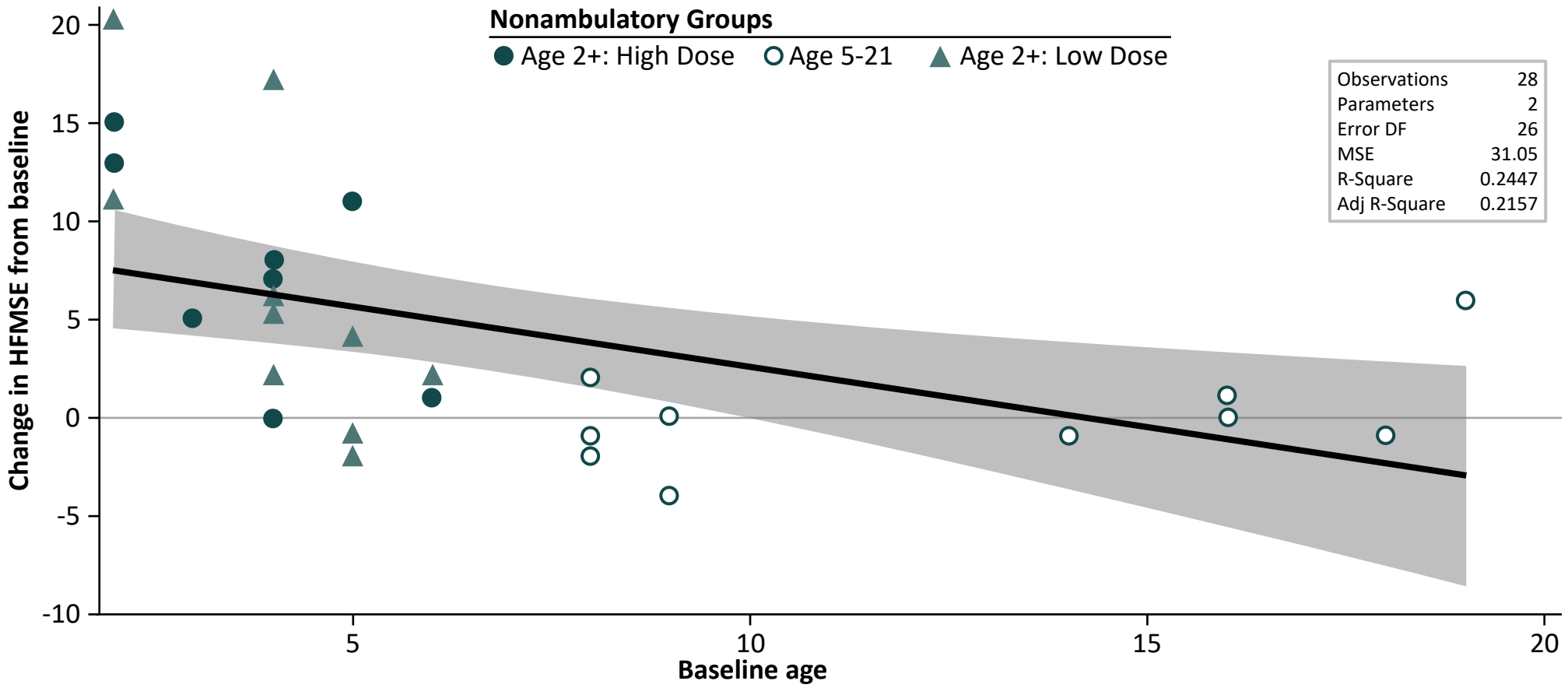


*24-month Sensitivity Analysis excludes from the Observed Case Analysis any data following scoliosis surgery in TOPAZ. Of the three nonambulatory patients who had scoliosis surgery, data from one was excluded and the other two did not have valid HFMSE assessments. Observed Case Analysis includes all patients who had a valid measurement at Day 728; and included patients treated with 2 as well as 20 mg/kg of apitegromab. This analysis does not exclude any patients who missed doses due to COVID-19 related site access restrictions.

HFMSE, Hammersmith functional motor scale expanded; **No**., number; **RULM**, refined upper limb module; **SEM**, standard error of the mean; **SMA**, spinal muscular atrophy.

Crawford T, et al. TOPAZ Extension: 24-month Efficacy and Safety of Apitegromab in Patients With Later-onset Spinal Muscular Atrophy (Type 2 and Type 3 SMA). Presented at CureSMA Annual Conference; June 16-19, 2022.

Over 24 Months, Correlation of the Change of HFMSE to Age in Type 2 and Nonambulatory Type 3 SMA*

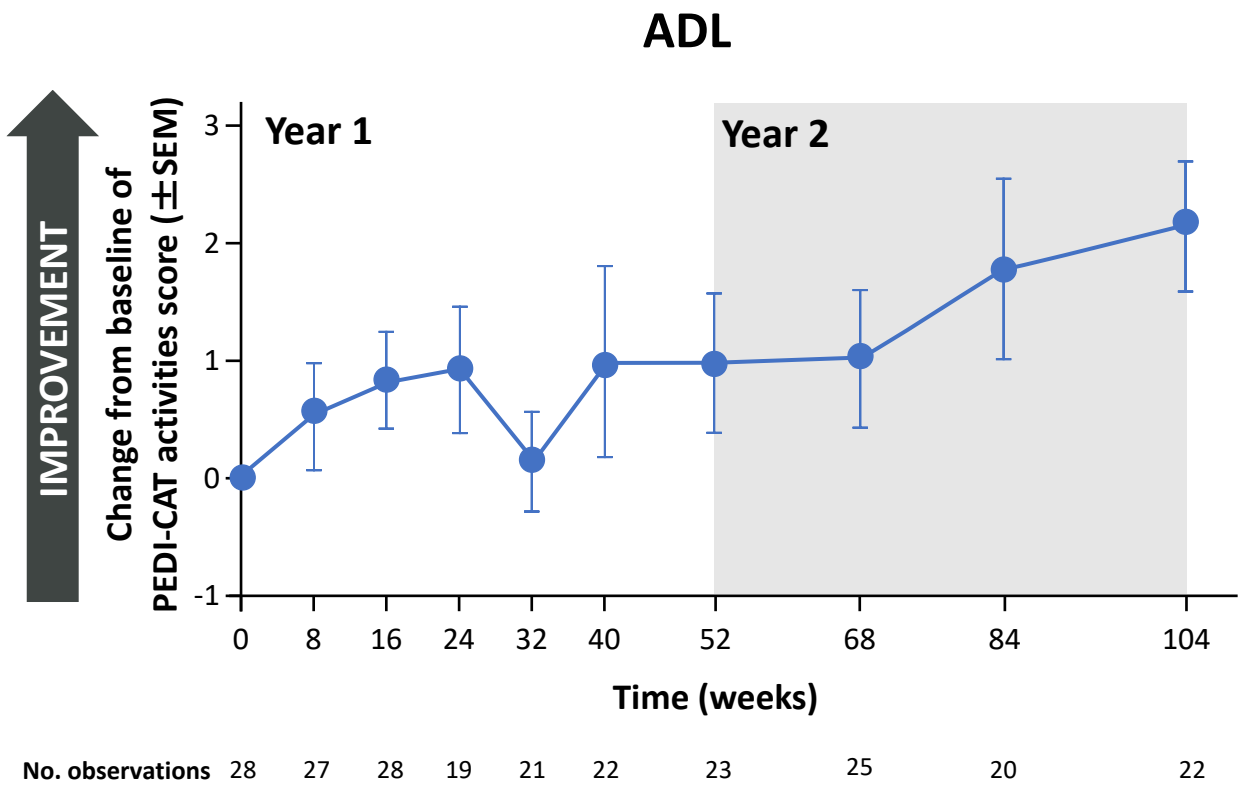


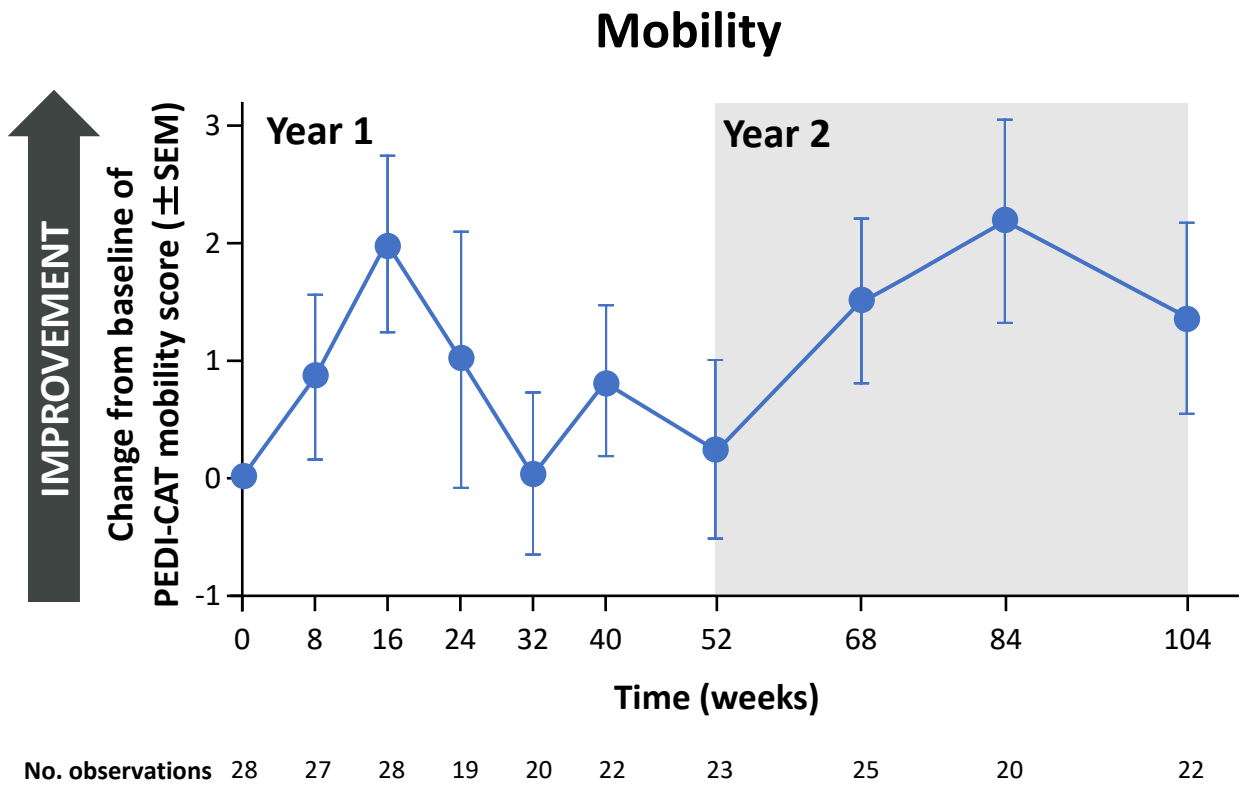
Note: After adjusting age, baseline weight is not correlated with change in HFMSE, Data not Shown

*24-month Sensitivity Analysis excludes from the Observed Case Analysis any HFMSE data following scoliosis surgery in TOPAZ. Of the three nonambulatory patients who had scoliosis surgery, data from one was excluded and the other two did not have valid HFMSE assessments.

Adj, adjusted; **DF**, degree of freedom; **HFMSE**, Hammersmith Functional Motor Scale Expanded; **MSE**, mean squared error; **SMA**, spinal muscular atrophy.

Over 24 Months, Effect of Apitegromab on ADL and Mobility Domains of PEDI-CAT in Type 2 and Nonambulatory Type 3 SMA

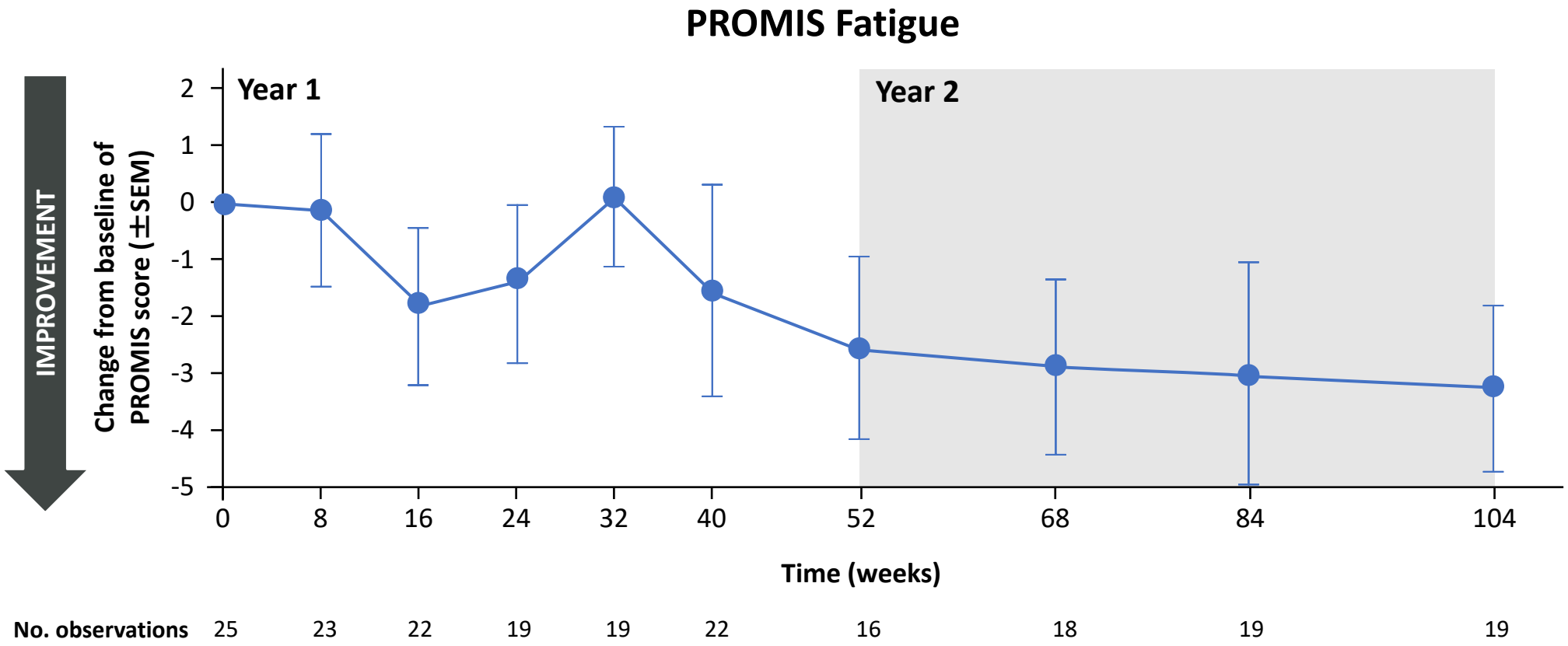




Observed Case Analysis includes all patients who had a valid measurement at Day 728 and included patients treated with 2 as well as 20 mg/kg of apitegromab. This analysis does not exclude any patients who missed doses due to COVID-19 related site access restrictions.

ADL, activities of daily living; **No.,** number; **PEDI-CAT**, Pediatric Evaluation of Disability Inventory computer adaptive test; **SEM**, standard error of the mean

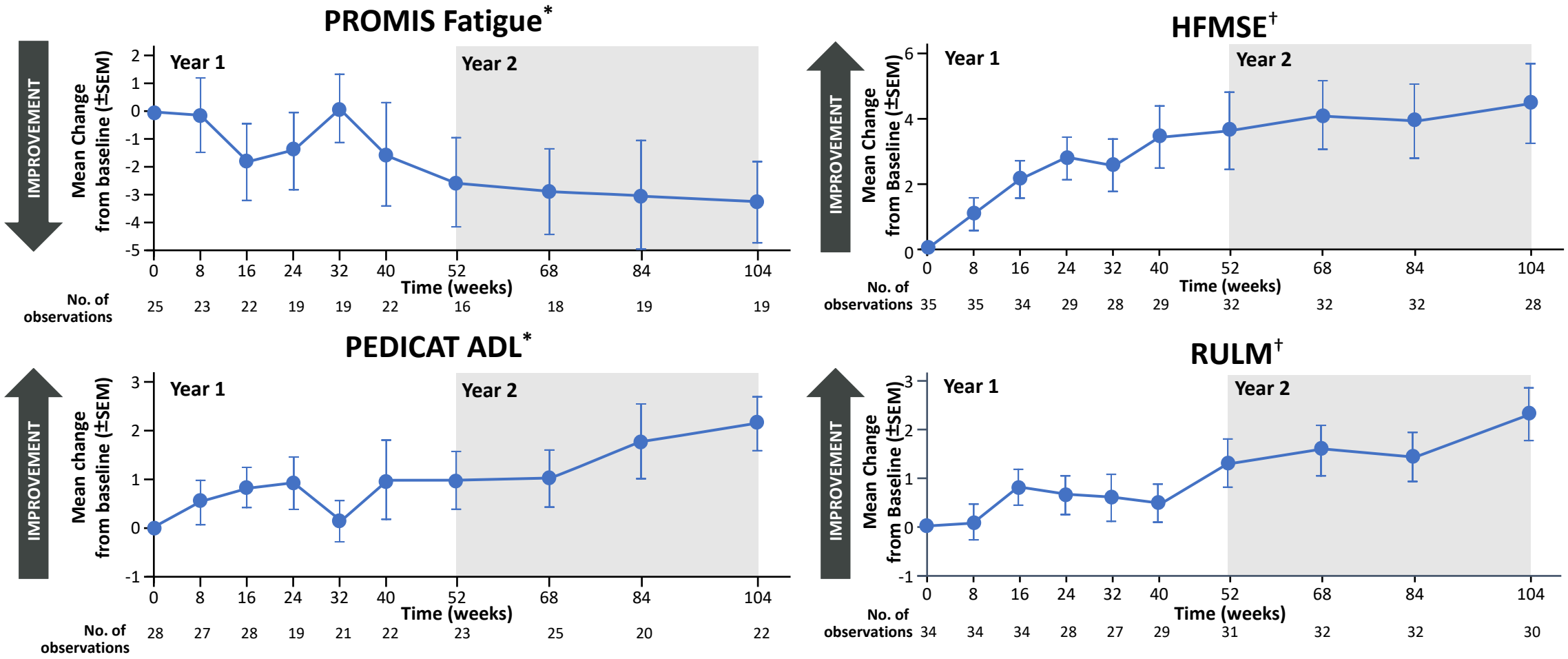
Over 24 Months, Effect of Apitegromab on PROMIS Fatigue in Type 2 and Nonambulatory Type 3 SMA*



*Parent Proxy Measure: Observed Case Analysis includes all patients who had a valid measurement at Day 728 and included patients treated with 2 as well as 20 mg/kg of apitegromab. This analysis does not exclude any patients who missed doses due to COVID-19 related site access restrictions.

No., number; **PROMIS**, Patient-Reported Outcome Measurement Information System; **SEM**, standard error of the mean; **SMA**, spinal muscular atrophy

Over 24 Months, Improvements in PRO Measures are Consistent With Motor Function



*Observed Case Analysis includes all patients who had a valid measurement at Day 728.; OC analysis included patients treated with 2 mg/kg as well as 20 mg/kg of apitegromab. This analysis does not exclude any patients who missed doses due to COVID-19 related site access restrictions. †24-month Sensitivity Analysis excludes from the OC Analysis any HFMSE data following scoliosis surgery in TOPAZ. Of the three nonambulatory patients who had scoliosis surgery, data from one was excluded and the other two did not have valid HFMSE assessments.

ADL, activities of daily living; **HFMSE**, Hammersmith Functional Motor Scale Expanded; **OC**, observed case; **PRO**, patient reported outcomes; **RULM**, Revised upper limb module; **SEM**, standard error of the mean

Safety Over 24 Months in TOPAZ

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)	45 (93.8)	55 (94.8)
Any serious TEAE	3 (30)	11 (22.9)	14 (24.1)
Any TEAE leading to study drug discontinuation	0	1 (2.1)	1 (1.7)
Any grade 3 (severe) or higher TEAE	2 (20)	9 (18.8)	11 (19)

- Reported TEAEs and incidence of TEAEs were consistent with the underlying patient population and nusinersen therapy
- Most frequently reported TEAEs*: headache (24%), upper respiratory tract infection (22%), pyrexia (22%), cough (22%), and nasopharyngitis (21%)
- No deaths or suspected unexpected serious adverse reactions reported
- Treatment emergent adverse events reported at 24 months were mostly mild to moderate in severity, as observed during the 12-month analysis
- All patients tested negative for the presence of anti-apitegromab antibodies
- No hypersensitivity reactions were identified

*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 month.

AE, adverse event; **TEAE**, treatment emergent adverse events.

Crawford T et al. TOPAZ Extension: 24-month Efficacy and Safety of Apitegromab in Patients With Later-onset Spinal Muscular Atrophy (Type 2 and Type 3 SMA). Presented at CureSMA Annual Conference; June 16-19, 2022.

Summary

- Improvements in measures of motor function (HFMSE and RULM) and caregiver/patient reported outcomes are consistent and maintained over 24 months with apitegromab
- Greater improvements are observed in younger patients over 24 months
- The efficacy and safety profile of apitegromab in TOPAZ suggests that targeting muscle in SMA is important to reducing overall disease burden

HFMSE, Hammersmith Functional Motor Scale expanded; **RULM**, revised upper limb module; **SMA**, spinal muscular atrophy

Crawford T et al. TOPAZ Extension: 24-month Efficacy and Safety of Apitegromab in Patients With Later-onset Spinal Muscular Atrophy (Type 2 and Type 3 SMA). Presented at CureSMA Annual Conference; June 16-19, 2022.

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

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Scholar Rock Research and Development Team

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*TOPAZ *PT Advisory Board*

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