Efficacy and safety of apitegromab in individuals with type 2 and type 3 spinal muscular atrophy evaluated in the phase 3 SAPPHIRE trial

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Declaration of interests

Dr. Basil T. Darras is a principal investigator for the SAPPHIRE trial

Consulting/advisory boards:

- AveXis/Novartis Gene Therapies
- Biogen
- Merck
- Roche/Genentech
- Sarepta Therapeutics
- Scholar Rock, Inc.

Study site investigator:

- Steering Committee Member: Roche MANATEE study
- DSMB member: Argenx, Lexeo Therapeutics, and Vironexis

Institute/Patient organizations:

- Research Support: NIH/National Institute of Neurological Disorders and Stroke
- SMA Foundation
- CureSMA

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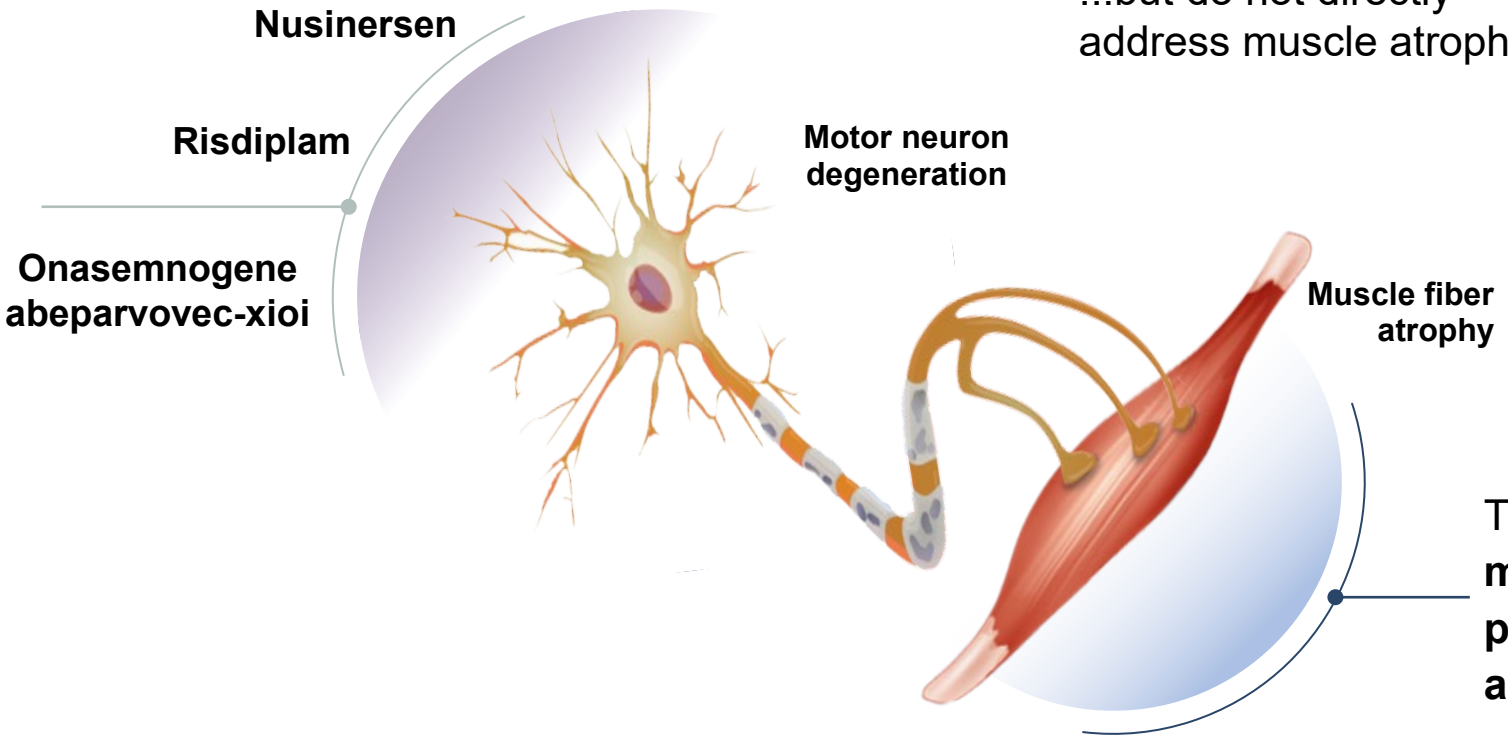
DSMB, Data and Safety Monitoring Board; NIH, National Institutes of Health; SMA, spinal muscular atrophy.

SMA disease pathology: motor neuron degeneration and muscle atrophy

SMN-targeted treatments
slow further degeneration of motor neurons[1]

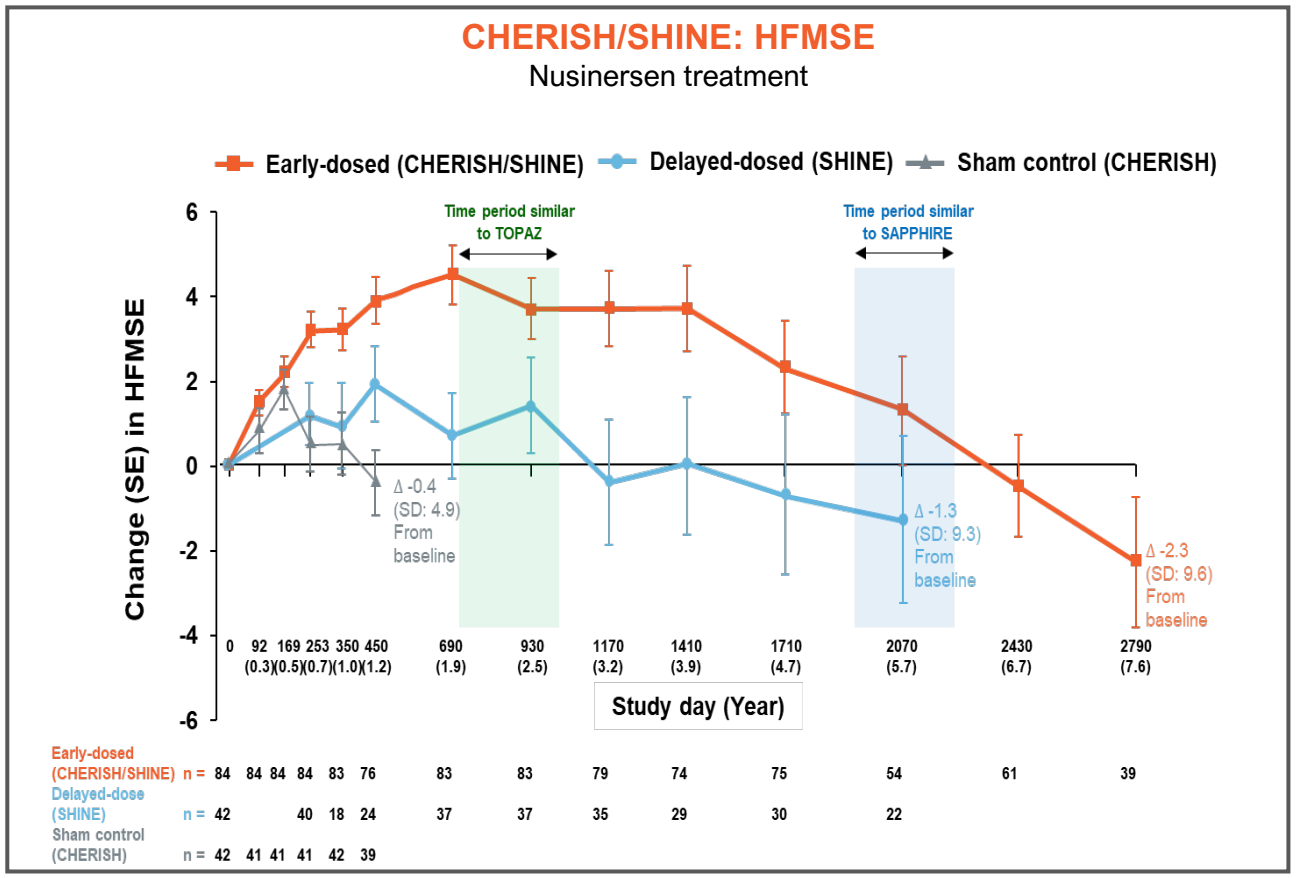


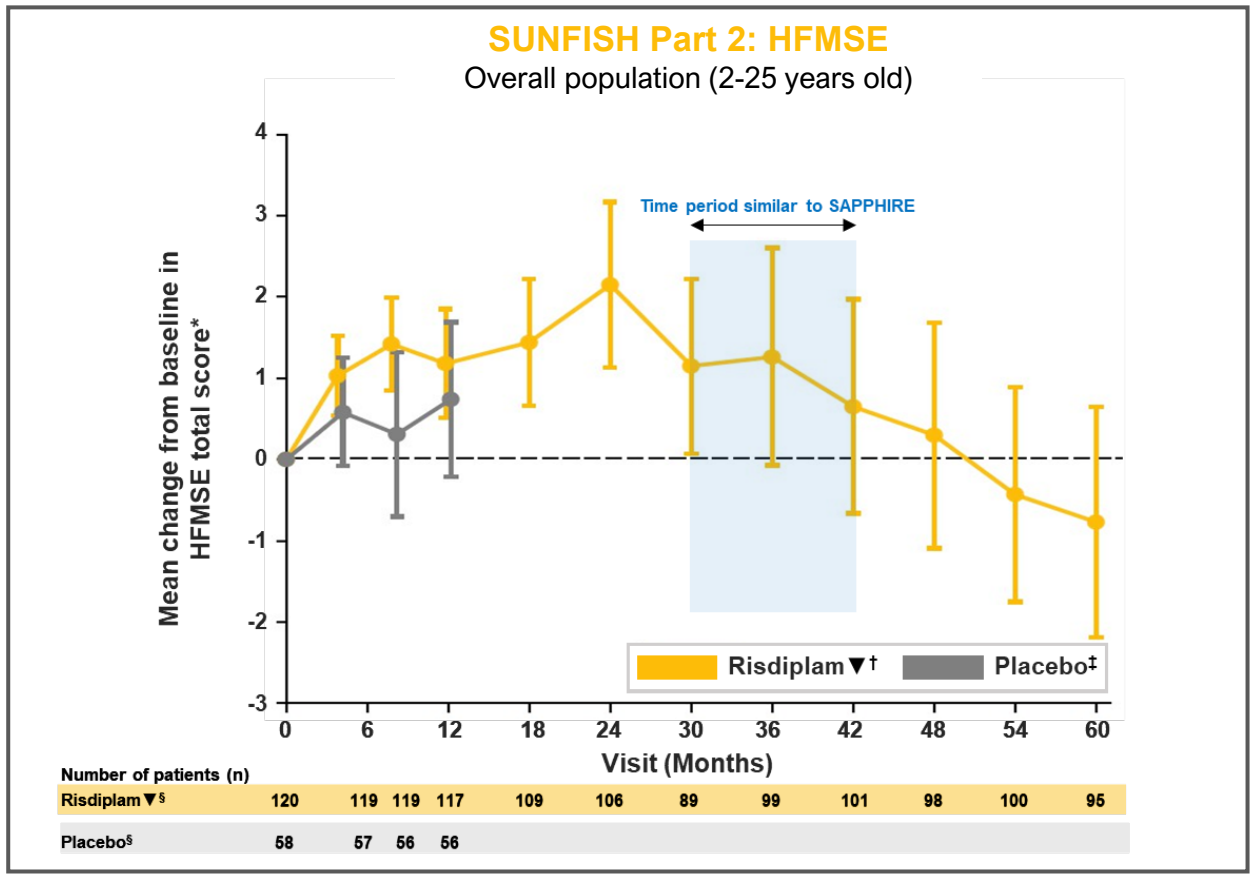
...but do not directly address muscle atrophy

There is further potential to **regain vital motor function** by addressing the **progressive muscle atrophy and associated weakness** of SMA

Figure adapted from: SMA Foundation Overview. Accessed February 11, 2025. http://www.smafoundation.org/wp-content/uploads/2012/03/SMA-Overview.pdf
SMA, spinal muscular atrophy; SMN, survival motor neuron.
1. Hua Y, et al. *Nature*. 2011;478(7367):123-6.

Patients treated chronically with an SMN-targeted treatment experience attenuation of motor function improvement over time





- On average, the TOPAZ study population is on the plateau phase of nusinersen treatment, and the SAPPHIRE study population is on the declining phase
- For risdiplam, the SAPPHIRE study population is on the declining phase of treatment; the TOPAZ study did not assess patients receiving risdiplam

Left) Data shown for visits with ≥ 10 participants. Right) *±95% CI. Baseline is the last measurement prior to the first dose of risdiplam▼or placebo. †Clinical cutoff date: Oct 2, 2023. ‡Clinical cutoff date: Sept 6, 2019. Patients in the placebo group received placebo for 12 months followed by risdiplam▼ treatment for 48 months. §Number of patients with valid results = number of patients with an available total score (result) at respective time points. Intent-to-treat patients.
HFMSE, Hammersmith Functional Motor Scale Expanded; SD, standard deviation; SE, standard error; SMN, survival motor neuron.

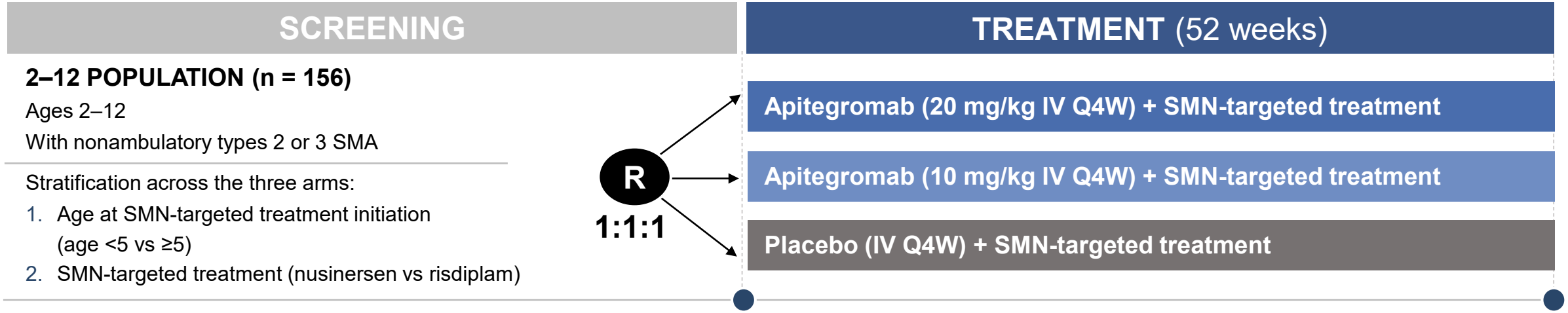
1. Finkel RS, et al. Poster at Annual SMA Research and Clinical Care Meeting; June 5-7, 2024. P95. **2.** Servais L, et al. Poster at the Muscular Dystrophy Association Clinical and Scientific Congress; March 16-19, 2025. P94.

Phase 3 SAPPHIRE trial design

Randomized, double-blind, placebo-controlled, parallel-arm design (n = 188)

Key Eligibility Criteria

- Patients with nonambulatory type 2 or 3 SMA, receiving an approved SMN-targeted treatment, ages 2–21
- Motor function score by HFMSE ≥10 and ≤45 at the screening visit



Primary efficacy population, ages 2–12 (n = 156)

Primary efficacy endpoint
Mean HFMSE change from baseline at 12 months (combined 20 and 10 mg/kg)

Additional efficacy: RULM, WHO, other outcome measures

Safety, PK/PD, ADA

Older subpopulation, ages 13–21 (n = 32)

Exploratory endpoints
Efficacy: mean HFMSE change from baseline at 12 months

Additional efficacy: RULM, WHO, other outcome measures

Safety, PK/PD, ADA

ClinicalTrials.gov Identifier: NCT05156320. The older subpopulation was stratified by SMN-targeted treatment, randomized 2:1 between apitegromab 20 mg/kg vs placebo.
2–12, population aged 2 to 12 years; ADA, antidrug antibody; HFMSE, Hammersmith Functional Motor Scale Expanded; IV, intravenous; PD, pharmacodynamics; PK pharmacokinetics; Q4W, every 4 weeks; R, randomization; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy; SMN, survival motor neuron; WHO, World Health Organization.

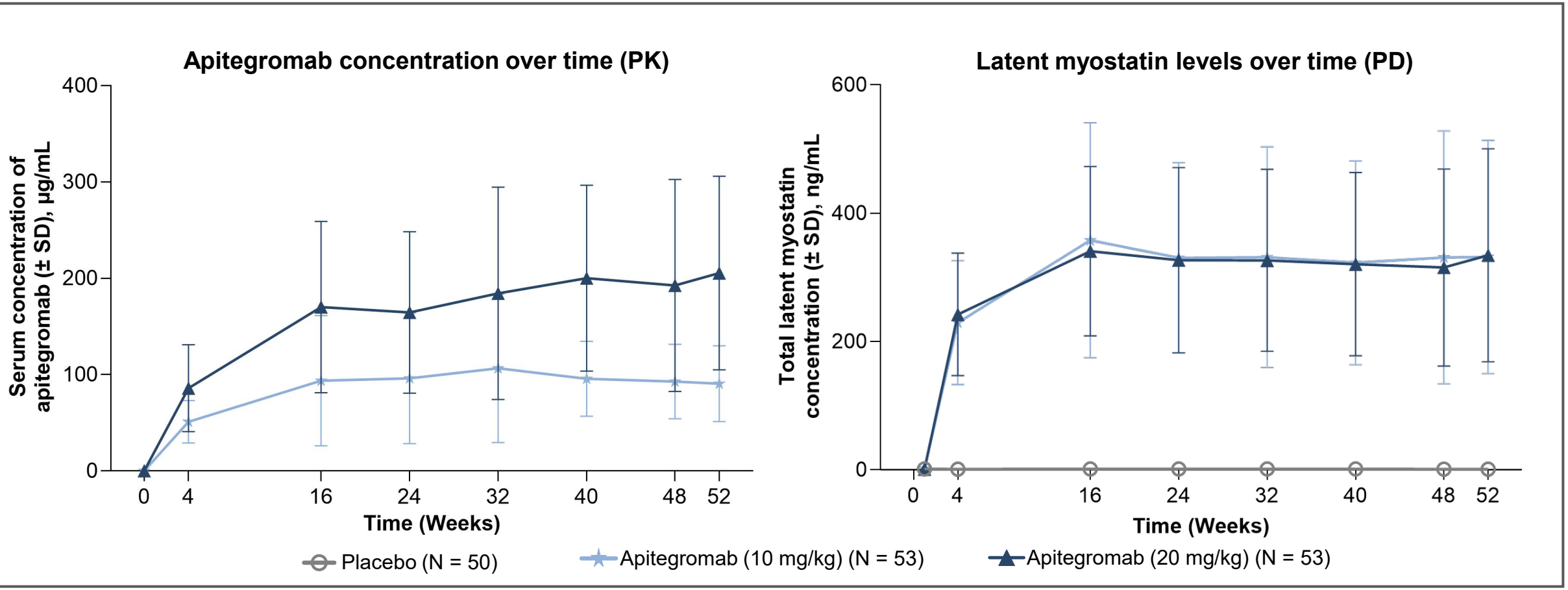
SAPPHIRE participant demographics and disease characteristics were well-balanced

	2–12 population				13–21 population	
	Placebo + SOC (N = 50)	Apitegromab 20 mg/kg + SOC (N = 53)	Apitegromab 10 mg/kg + SOC (N = 53)	Apitegromab 20 & 10 mg/kg + SOC (N = 106)	Placebo + SOC (N = 10)	Apitegromab 20 mg/kg + SOC (N = 22)
Female sex, n (%)	25 (50.0)	26 (49.1)	23 (43.4)	49 (46.2)	5 (50.0)	15 (68.2)
Mean age at screening, years (min, max)	8.1 (3, 12)	7.9 (2, 12)	7.4 (2, 12)	7.6 (2, 12)	15.2 (13, 18)	16.1 (13, 21)
SMN-targeted treatment at randomization						
Nusinersen/risdiplam, %	80/20	77.4/22.6	75.5/24.5	76.4/23.6	60/40	54.5/45.5
Mean duration of nusinersen/risdiplam, years	5.5/2.7	5.3/3.5	4.4/3.0	4.8/3.2	6.7/3.3	5.9/3.8
SMN-targeted treatment initiation age, <5/≥5 years, %	88/12	84.9/15.1	86.8/13.2	85.8/14.2	N/A	N/A
Number of SMN-targeted treatments, 1/2, %	86/14	84.9/15.1	86.8/13.2	85.8/14.2	80/20	90.9/9.1
SMA type, type 2/3, %	94/6	90.6/9.4	83/17	86.8/13.2	60/40	40.9/59.1
SMN2 copy number, 2/3/4, %	4/90/2	7.5/86.8/5.7	11.3/77.4/7.5	9.4/82.1/6.6	0/80/10	4.5/59.1/18.2
Mean baseline HFMSE score (min, max)	27.8 (9, 46)	25.5 (10, 43)	25.5 (9, 48)	25.5 (9, 48)	22.8 (10, 45)	20.6 (8, 43)
History of scoliosis, %	70	71.7	71.7	71.7	90	86.4

- Study population was broadly representative of SMA population
- Baseline demographics and disease characteristics were well balanced across arms
- Patients were in the advanced phase of their SMN-targeted treatment journey

Baseline demographics and clinical characteristics are presented for all randomized participants. Baseline HFMSE total score was defined as the last nonmissing measurement prior to or on the day of the first dosing.
"SOC" represents treatment with either nusinersen or risdiplam.
2–12, population aged 2 to 12 years; 13–21, population aged 13 to 21 years; HFMSE, Hammersmith Functional Motor Scale Expanded; max, maximum; min, minimum; N/A, not applicable; SD, standard deviation; SMA, spinal muscular atrophy; SMN, survival motor neuron; SOC, standard of care.

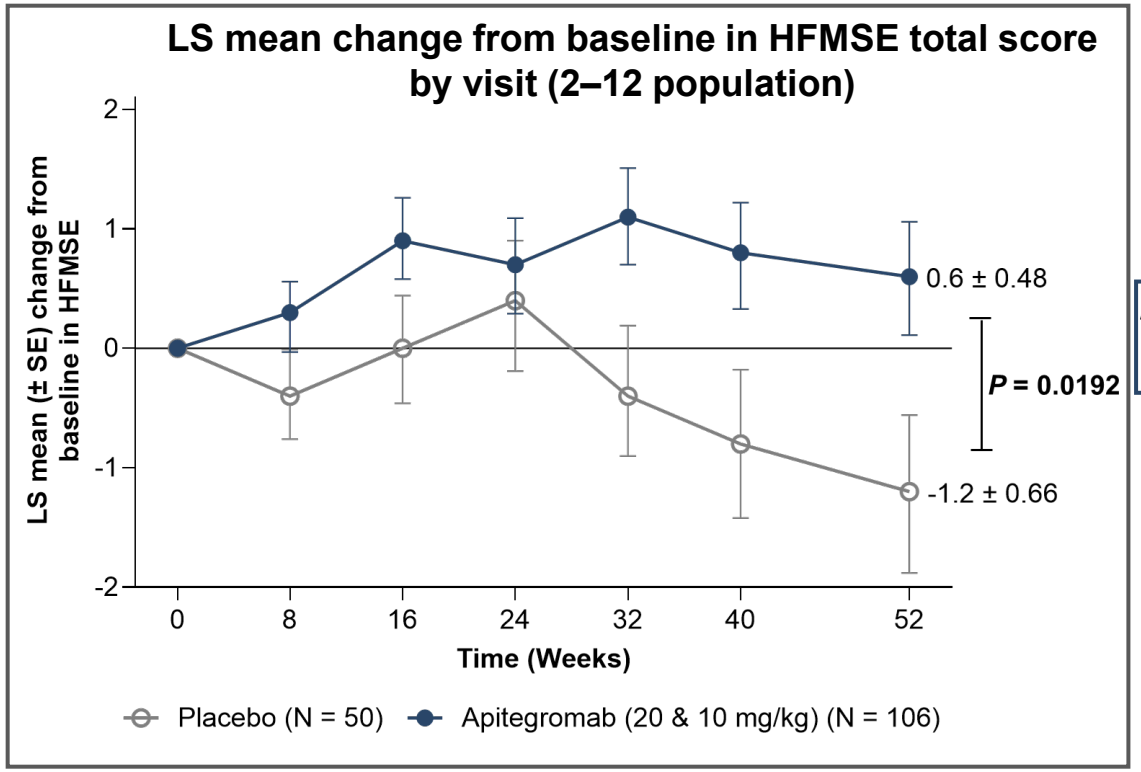
SAPPHIRE PK and PD vs time

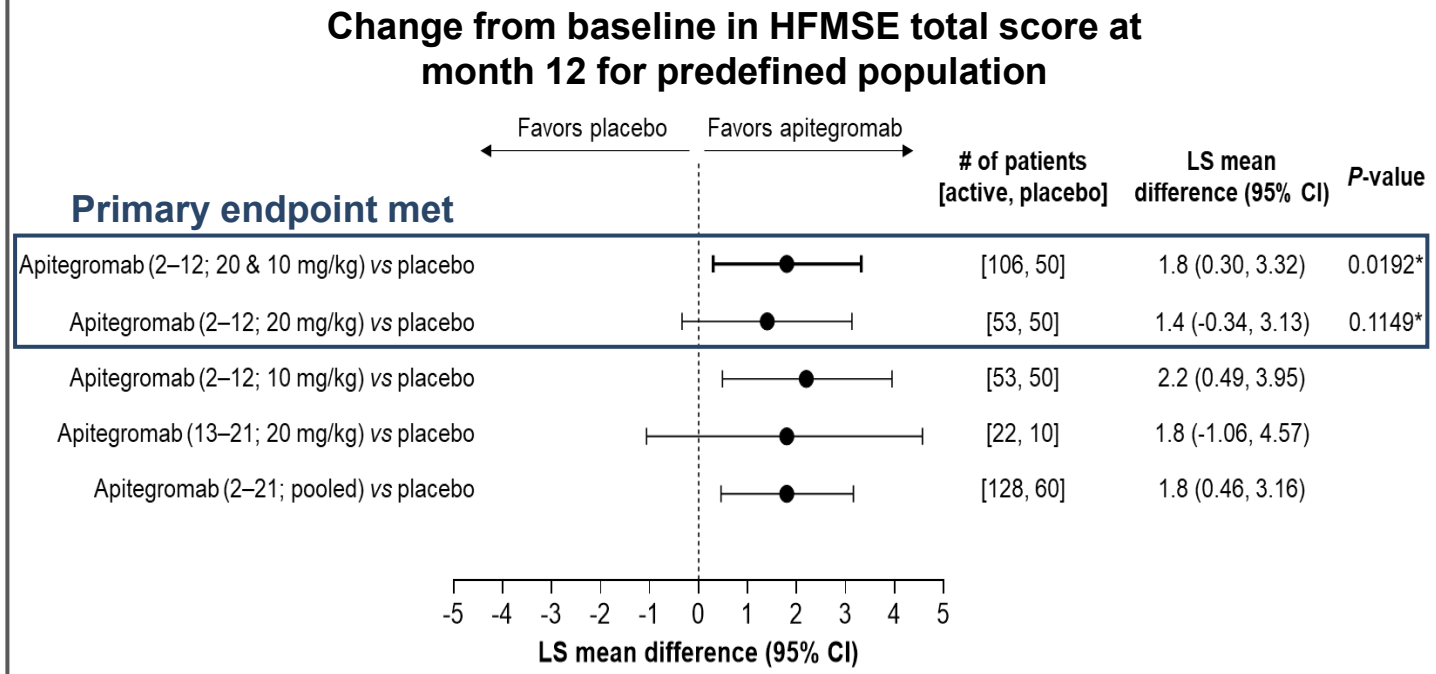


- Increase in exposure of apitegromab (PK) was generally dose-proportional
- Robust and sustained target engagement (PD) was observed following apitegromab dosing
- Similar levels of target engagement were observed for 10 mg/kg and 20 mg/kg

PK data are shown as geometric mean (± SD) µg/mL, and PD data are shown as mean (± SD) ng/mL. PK samples from patients receiving placebo were not tested and therefore not included in PK assessments.
2–12, population aged 2 to 12 years; PD, pharmacodynamics; PK, pharmacokinetics; SD, standard deviation.

Primary endpoint met with consistency across doses and age groups



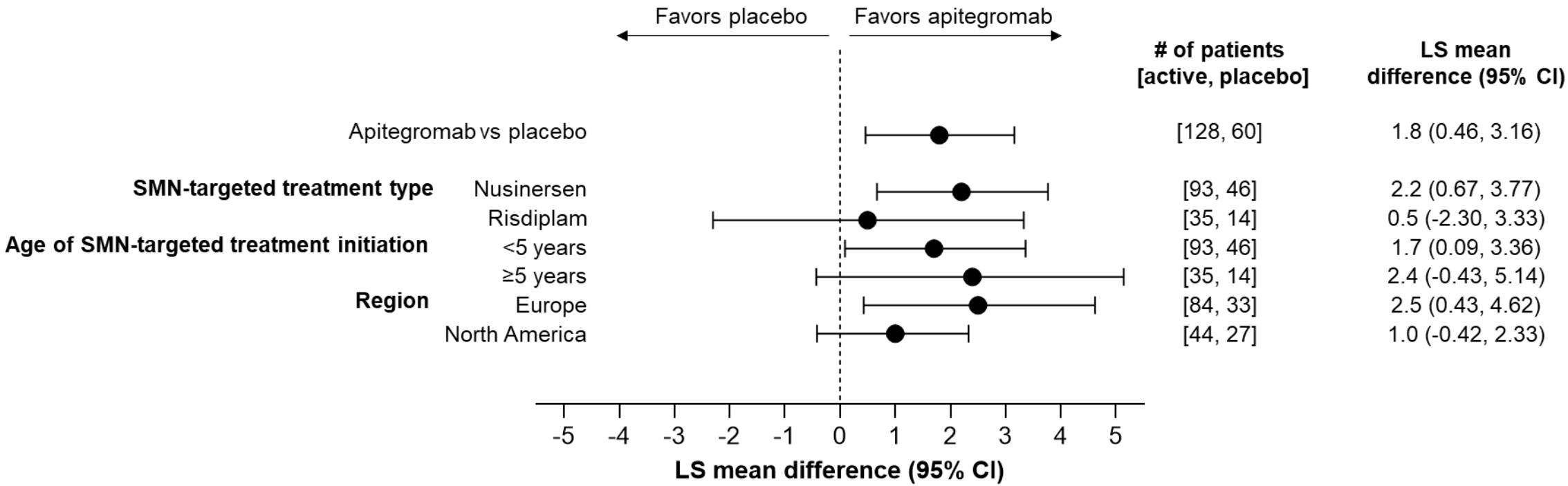


- Primary endpoint met based on the comparison of apitegromab (20 and 10 mg/kg) vs placebo with $P \leq 0.025$
- Motor function outcomes were consistent across 2–12 and 13–21 SAPPHIRE populations, favoring apitegromab vs placebo
- Patients treated with apitegromab demonstrated improved motor function while those on placebo lost function over time

*P-values controlled for multiplicity.
2–12, population aged 2 to 12 years; 13–21, population aged 13 to 21 years; 2–21, pooled population aged 2 to 21 years; CI, confidence interval; HFMSE, Hammersmith Functional Motor Scale Expanded; LS, least squares.

Efficacy was consistent across subgroups in pooled 2–21 population

Change from baseline in HFMSE total score at month 12 – subgroup analyses for pooled population

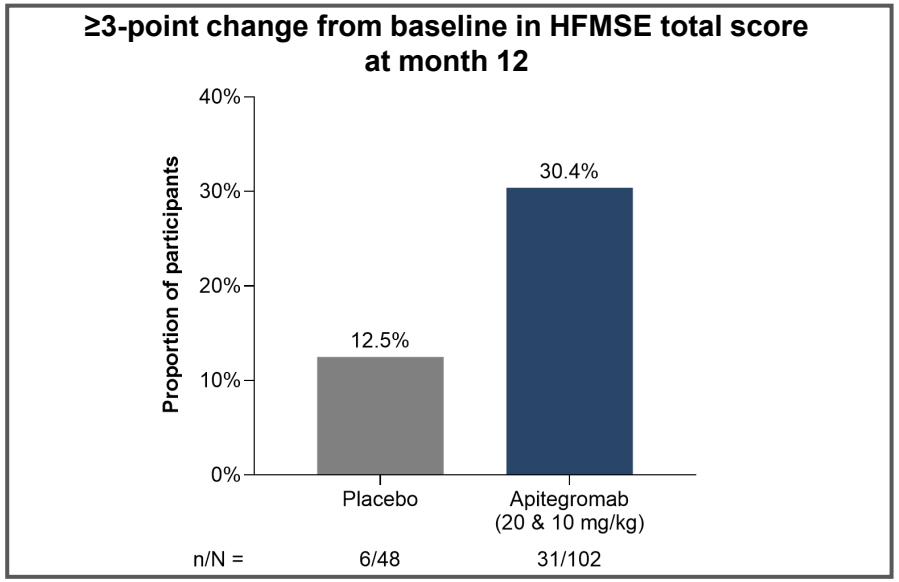


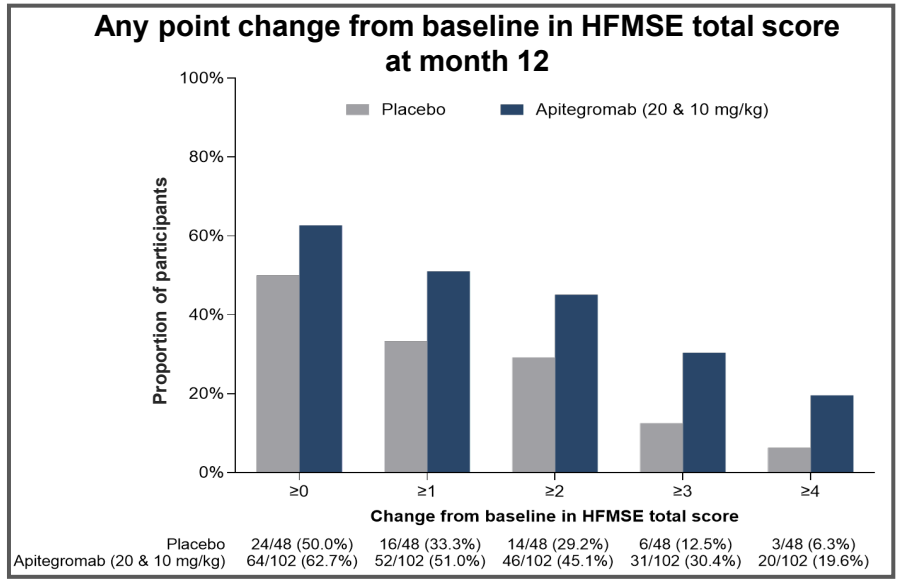
- Efficacy was consistent across prespecified subgroups (type of SMN-targeted treatment, age of SMN-targeted treatment initiation) and region

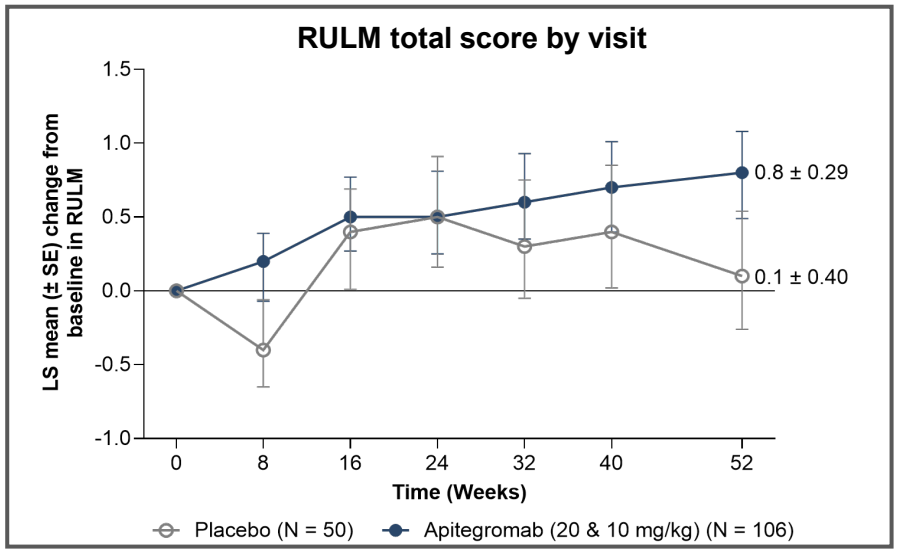
SMN-targeted treatment type was a randomization stratification factor for both the 2–12 population and 13–21 population. Age at initiation of SMN-targeted treatment (<5 years or ≥5 years) is derived from the age the participant received the first dose of SMN-targeted treatment in months.

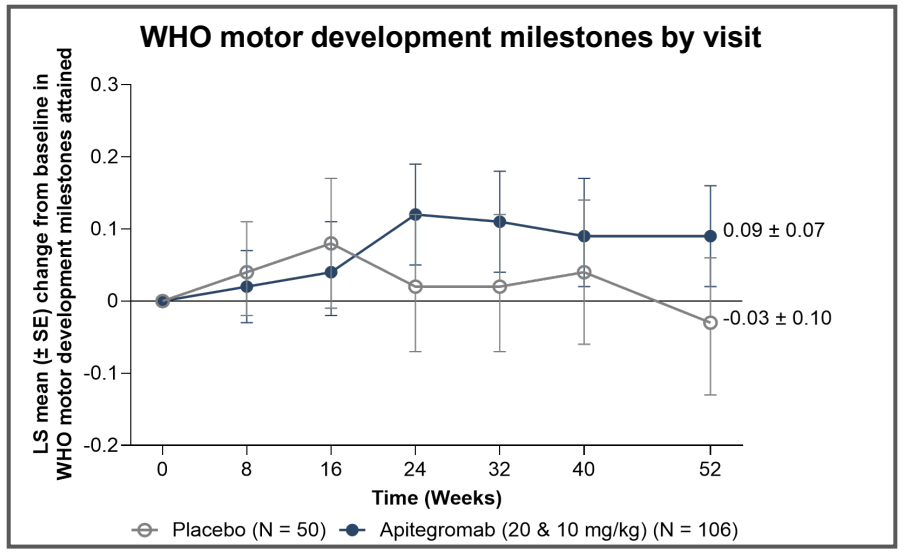
2–21, population aged 2 to 21 years; CI, confidence interval; HFMSE, Hammersmith Functional Motor Scale Expanded; LS, least squares; SMN, survival motor neuron.

Secondary endpoint outcomes for the 2–12 population









- Patients treated with apitegromab demonstrated improved motor function vs placebo
- Efficacy was consistent across outcome measures, including HFMSE, RULM, and WHO motor developmental milestones
- A greater proportion of participants treated with apitegromab had ≥3-point improvements in their HFMSE scores vs placebo (odds ratio 3.0, nominal $P = 0.0256$)
- Higher proportions of patients on apitegromab achieved HFMSE improvements vs placebo across all point thresholds

Proportionality data are based on the observed data for the placebo and apitegromab treatment groups. One participant from the apitegromab 10 mg/kg dose group was too young at baseline to conduct the RULM and therefore was not included in RULM analyses.
2–12, population aged 2 to 12 years; HFMSE, Hammersmith Functional Motor Scale Expanded; LS, least squares; RULM, Revised Upper Limb Module; SE, standard error; WHO, World Health Organization.

Well-tolerated safety consistent with established profile

Summary of AEs n (%)	2–12 population				13–21 population	
	Placebo + SOC (N = 50)	Apitegromab 20 mg/kg + SOC (N = 53)	Apitegromab 10 mg/kg + SOC (N = 53)	Apitegromab 20 & 10 mg/kg + SOC (N = 106)	Placebo + SOC (N = 10)	Apitegromab 20 mg/kg + SOC (N = 22)
AE	43 (86.0)	46 (86.8)	51 (96.2)	97 (91.5)	9 (90.0)	19 (86.4)
SAE	5 (10.0)	12 (22.6)	9 (17.0)	21 (19.8)	1 (10.0)	0
AE grade ≥3	5 (10.0)	11 (20.8)	9 (17.0)	20 (18.9)	1 (10.0)	1 (4.5)
AE leading to treatment discontinuation	0	0	0	0	0	0
AE leading to study withdrawal	0	0	0	0	0	0
AE with highest incidence						
Pyrexia	16 (32.0)	13 (24.5)	18 (34.0)	31 (29.2)	1 (10.0)	2 (9.1)
Nasopharyngitis	10 (20.0)	11 (20.8)	15 (28.3)	26 (24.5)	4 (40.0)	6 (27.3)
Cough	11 (22.0)	11 (20.8)	15 (28.3)	26 (24.5)	1 (10.0)	4 (18.2)
SAE with highest incidence						
Pneumonia	0	4 (7.5)	3 (5.7)	7 (6.6)	0	0
Dehydration	0	1 (1.9)	2 (3.8)	3 (2.8)	0	0

- Treatment with apitegromab was well-tolerated across all age groups, consistent with established safety profile[1,2]
- There were no clinically relevant differences in the AE profile by dose (10 mg/kg vs 20 mg/kg)
- SAEs were consistent with underlying disease and SMN-targeted treatment[3,4]; no SAEs were assessed as related to apitegromab
- There were no deaths or study-drug discontinuations due to AEs
- One patient tested positive for ADA; the samples were further assessed and determined to be below the sensitivity cutoff point

All AEs were coded using the MedDRA version 26.1. “SOC” represents treatment with either nusinersen or risdiplam.
2–12, population aged 2 to 12 years; 13–21, population aged 13 to 21 years; ADA, antidrug antibody; AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities Terminology; SAE, serious AE; SOC, standard of care; SMN, survival motor neuron.

1. Crawford TO, et al. *Neurology*. 2024;102:e209151. **2.** Crawford TO, et al. *Front Neurol.* 2024;15:1419791. **3.** Spinraza. Package insert. Biogen; 2024. **4.** Evrysdi. Package insert. Genentech; 2024.

Conclusions

- Apitegromab treatment resulted in statistically significant and clinically meaningful[1-3] improvements in motor function
  - Efficacy results were consistent across outcomes measures (HFMSE, RULM, and WHO)
  - Efficacy results were consistent across age, background SMN-targeted treatment, age of SMN-targeted treatment initiation, and region
  - Based on similar PD, efficacy, and safety, the benefit-risk profile was optimized at the apitegromab 10 mg/kg dose
- Safety profile was consistent with the underlying SMA patient population and background SMN-targeted treatment[4-7]
- SAPPHIRE results represent the first time a myostatin-targeting agent has demonstrated improved function in any disease in a placebo-controlled clinical setting

Acknowledgments

- We are grateful to all the patients who participated in the study and to their families, caregivers, health care professionals, and patient advocacy groups for their dedication and support.
- Medical writing support was provided by Taryn Bosquez-Berger, PhD, of Scholar Rock, Inc., and was in accordance with Good Publication Practice. Funding for this trial is provided by Scholar Rock, Inc.

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HFMSE, Hammersmith Functional Motor Scale Expanded; PD, pharmacodynamics; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy; SMN, survival motor neuron; WHO, World Health Organization.

1. Pera MC, et al. *BMN Neurol.* 2017;17:39. **2.** Stolte B, et al. *Eur J Neurol.* 2020;27:2586-94. **3.** Wu JW, et al. *Am J Phys Med Rehabil.* 2022;101:590-608. **4**. Crawford TO, et al. *Neurology.* 2024;102:e209151. **5.** Crawford TO, et al. *Front Neurol.* 2024;15:1419791. **6.** Spinraza. Package insert. Biogen; 2024. **7.** Evrysdi. Package insert. Genentech; 2024.