Efficacy and safety of apitegromab in patients aged 13–21 years with Type 2 or 3 spinal muscular atrophy: outcomes from the SAPPHIRE Phase 3 trial

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Declaration of interests

Dr. Laurent Servais is a principal investigator of the SAPPHIRE trial

Grants:

- AveXis/Novartis Gene Therapies
- Biogen
- Roche

Personal fees:

- AveXis/Novartis Gene Therapies
- Biogen
- Biohaven
- Cytokinetics
- Roche
- Scholar Rock, Inc.

Study site investigator:

- Biohaven
- Scholar Rock, Inc.

SMA disease pathology: motor neuron degeneration and muscle atrophy

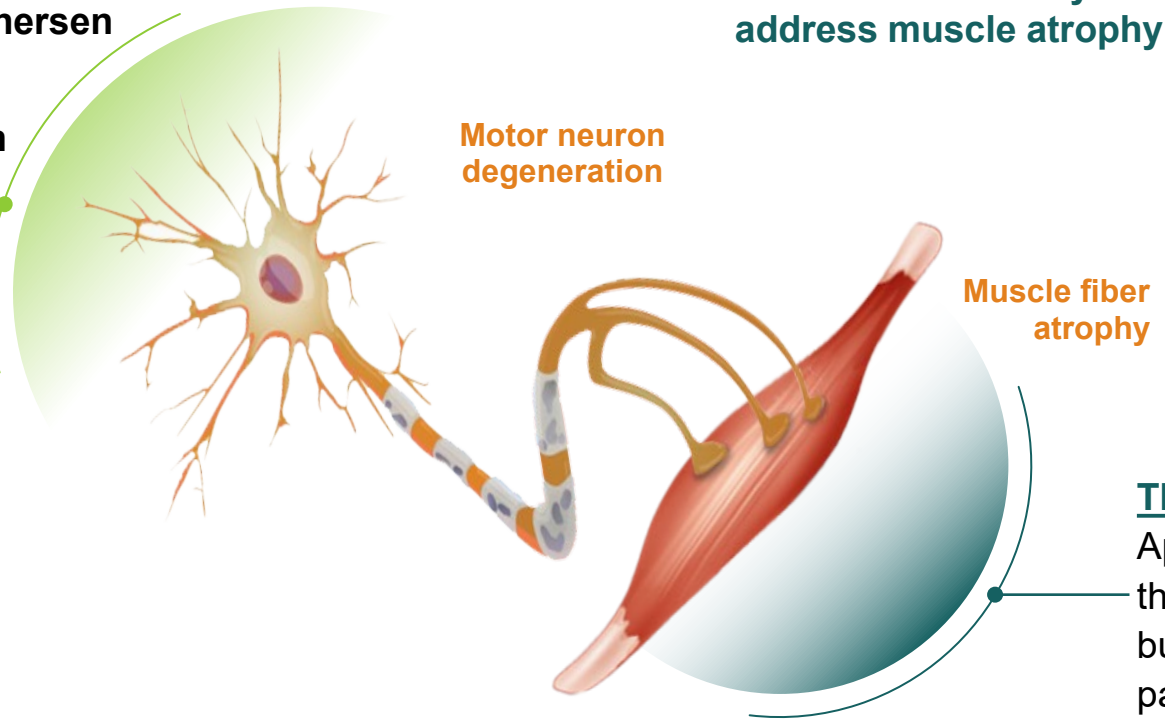
SMN-targeted treatments slow further degeneration of motor neurons[1]

Nusinersen

Risdiplam

Onasemnogene abeparvovec-xioi

...but do not directly address muscle atrophy



Therapeutic hypothesis

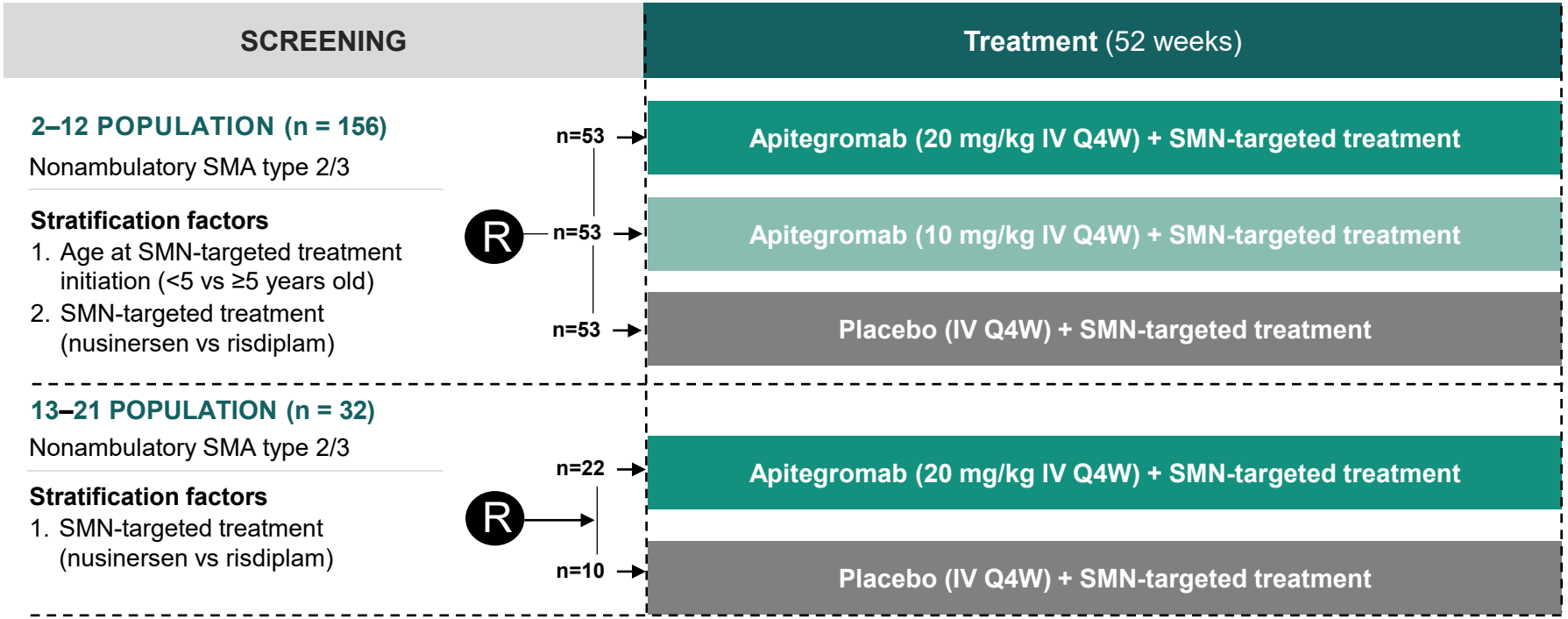
Apitegromab, an investigational treatment, has the potential to selectively inhibit myostatin and build muscle and strength to improve certain patient outcomes.

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.

Phase 3 SAPPHIRE trial design

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



KEY ELIGIBILITY CRITERIA

Inclusion criteria

- Aged ≥2 years
- Nonambulatory
- HFMSE score of ≥10 and ≤45
- Receiving SMN-targeted treatment (≥10 months nusinersen or ≥6 months risdiplam)

Exclusion criteria

- Previously treated with onasemnogene abeparvovec-xioi
- Severe scoliosis and/or contractures at screening

ENDPOINTS

Primary efficacy (aged 2-12 years)

- Change from baseline in HFMSE total score at 12 months

Secondary efficacy

- RULM, WHO, other outcome measures

Safety, PK/PD, ADA

LONG-TERM DATA OPPORTUNITIES (after SAPPHIRE completion)

ONYX open-label extension study

- Assessment of long-term safety and efficacy

Long-term safety follow-up

- Assessment of long-term safety for patients not enrolled in ONXY (20 weeks)

ClinicalTrials.gov Identifier: NCT05156320.

2–12, population aged 2 to 12 years; 13–21, population aged 13 to 21 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.

1. Crawford TO, et al. *Lancet Neurol*; 2025;24:727-39.

SAPPHIRE participant demographics and disease characteristics were well-balanced

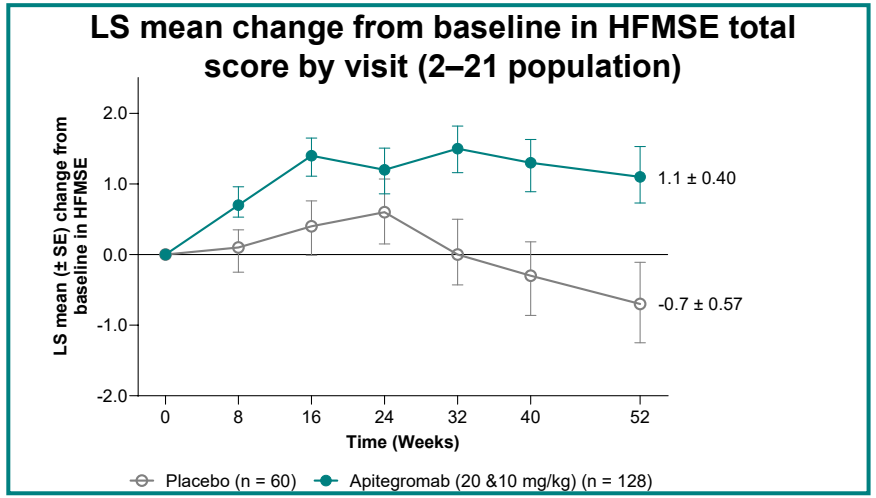
	2–21 pooled population		2–12 population			13–21 population	
	Placebo + SOC (n=60)	Apitegromab + SOC, combined (n=128)	Placebo + SOC (n=50)	Apitegromab 20 mg/kg + SOC (n=53)	Apitegromab 10 mg/kg + SOC (n=53)	Placebo + SOC (n=10)	Apitegromab 20 mg/kg + SOC (n=22)
Female sex, n (%)	30 (50.0)	64 (50.0)	25 (50.0)	26 (49.1)	23 (43.4)	5 (50.0)	15 (68.2)
Mean age at screening (min, max), y	9.3 (3, 18)	9.1 (2, 21)	8.1 (3, 12)	7.9 (2, 12)	7.4 (2, 12)	15.2 (13, 18)	16.1 (13, 21)
SMN-targeted treatment at randomization							
Nusinersen/risdiplam, %	76.7/23.3	72.7/27.3	80.0/20.0	77.4/22.6	75.5/24.5	60/40	54.5/45.5
Mean duration of nusinersen/risdiplam, y	5.7/2.9	5.0/3.4	5.5/2.7	5.3/3.5	4.4/3.0	6.7/3.3	5.9/3.8
SMN-targeted treatment initiation age,[a,b] <5/≥5 y, %	73.3/10.0	71.1/11.7	88.0/12.0	84.9/15.1	86.8/13.2	N/A	N/A
Number of SMN-targeted treatments, 1/2, %	85.0/15.0	86.7/13.3	86.0/14.0	84.9/15.1	86.8/13.2	80.0/20.0	90.9/9.1
SMA type, type 2/3, %	88.3/11.7	78.9/21.1	94.0/6.0	90.6/9.4	83.0/17.0	60.0/40.0	40.9/59.1
SMN2 copy number, 2/3/4, %	3.3/88.3/3.3	8.6/78.1/8.6	4.0/90.0/2.0	7.5/86.8/5.7	11.3/77.4/7.5	0/80.0/10.0	4.5/59.1/18.2
Mean baseline HFMSE score (min, max)	27.0 (9, 46)	24.7 (8, 48)	27.8 (9, 46)	25.5 (10, 43)	25.5 (9, 48)	22.8 (10, 45)	20.6 (8, 43)
History of scoliosis, %	73.3	74.2	70.0	71.7	71.7	90.0	86.4

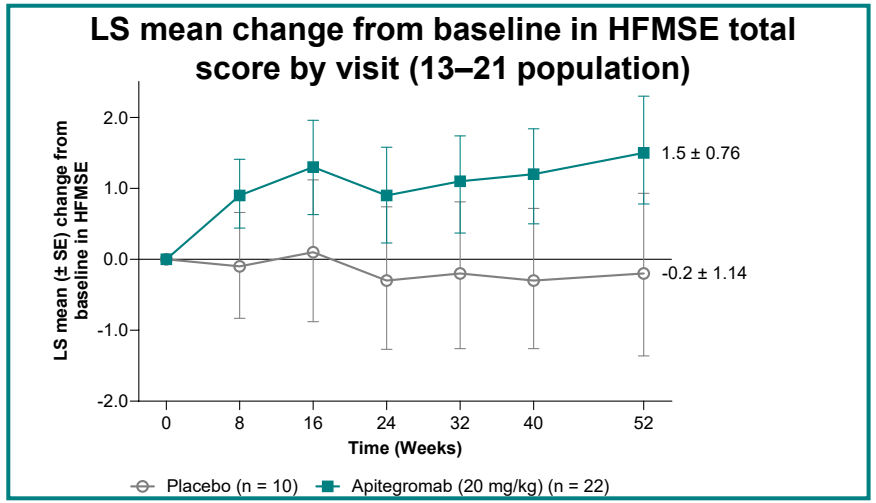
- Study population was broadly representative of SMA population
- Baseline demographics and disease characteristics were well balanced across arms
- Patients were in the advanced phase of their SMN-targeted treatment journey

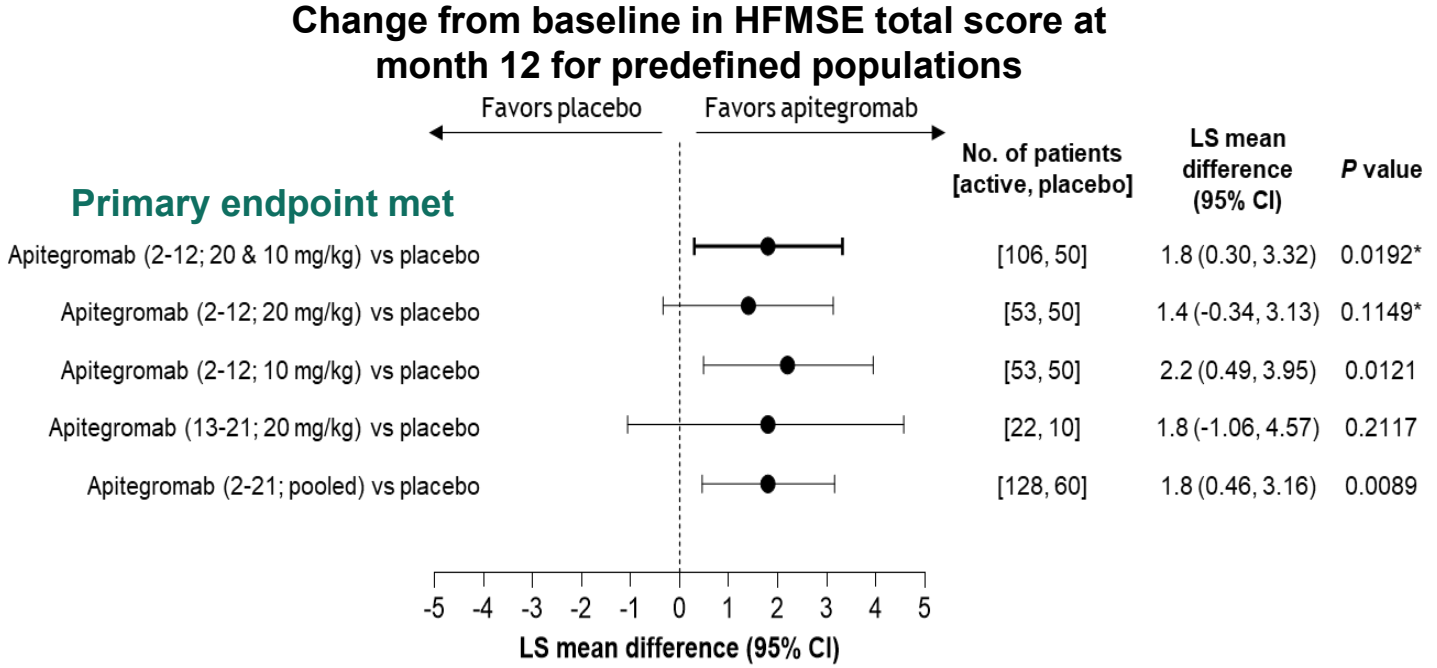
Baseline demographics and clinical characteristics are presented for all randomized participants. Baseline HFMSE total score was defined as the last nonmissing measurement prior to or on the day of the first dosing. "SOC" represents treatment with either nusinersen or risdiplam. [a]In the 2-12 population, 3 participants were mis-stratified for age at initiation of SMN-targeted treatment at randomization. [b]The 13-21 population was stratified by type of SMN-targeted treatment only; age at initiation of SMN-targeted treatment at randomization is not applicable as the randomization stratification.

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

Primary endpoint met with consistency across doses and age groups





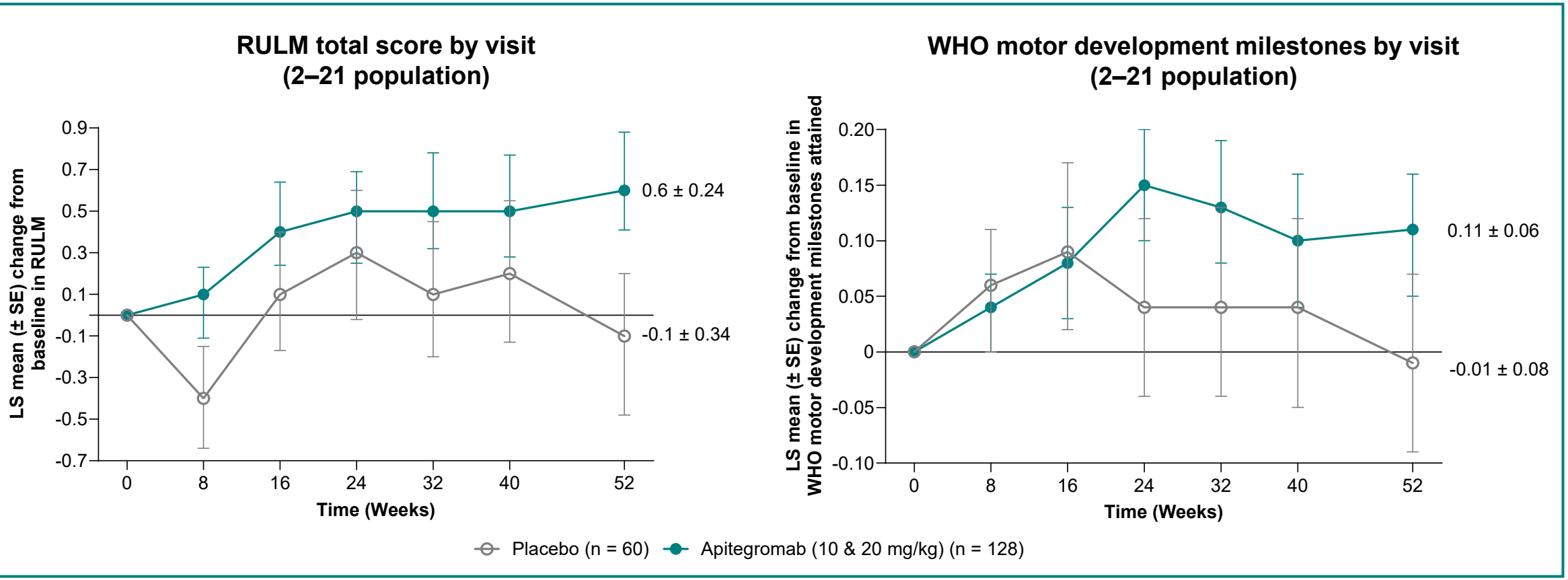


- Primary endpoint met based on the comparison of apitegromab (2–12; 20 mg/kg and 10 mg/kg) vs placebo with $P \leq 0.025$ ($P = 0.0192$*)
- Consistent improvements in HFMSE total score across the pooled 2–21 ($P = 0.0089$, nominal) and 13–21 ($P = 0.2117$, nominal) populations, favoring apitegromab vs placebo

*P-values controlled for multiplicity. All P-values not controlled for multiplicity are nominal.
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; SE, standard error.

1. Crawford TO, et al. *Lancet Neurol*; 2025;24:727-39.

Secondary endpoint outcomes associated with positive trends in patients receiving apitegromab

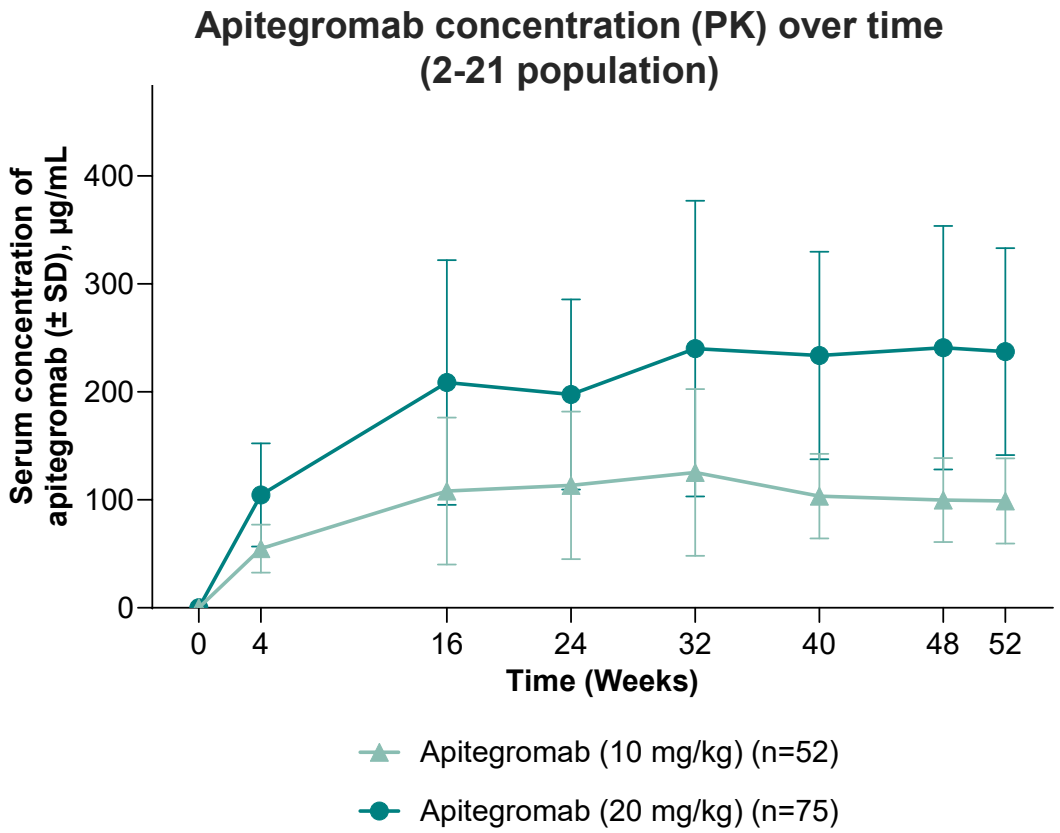


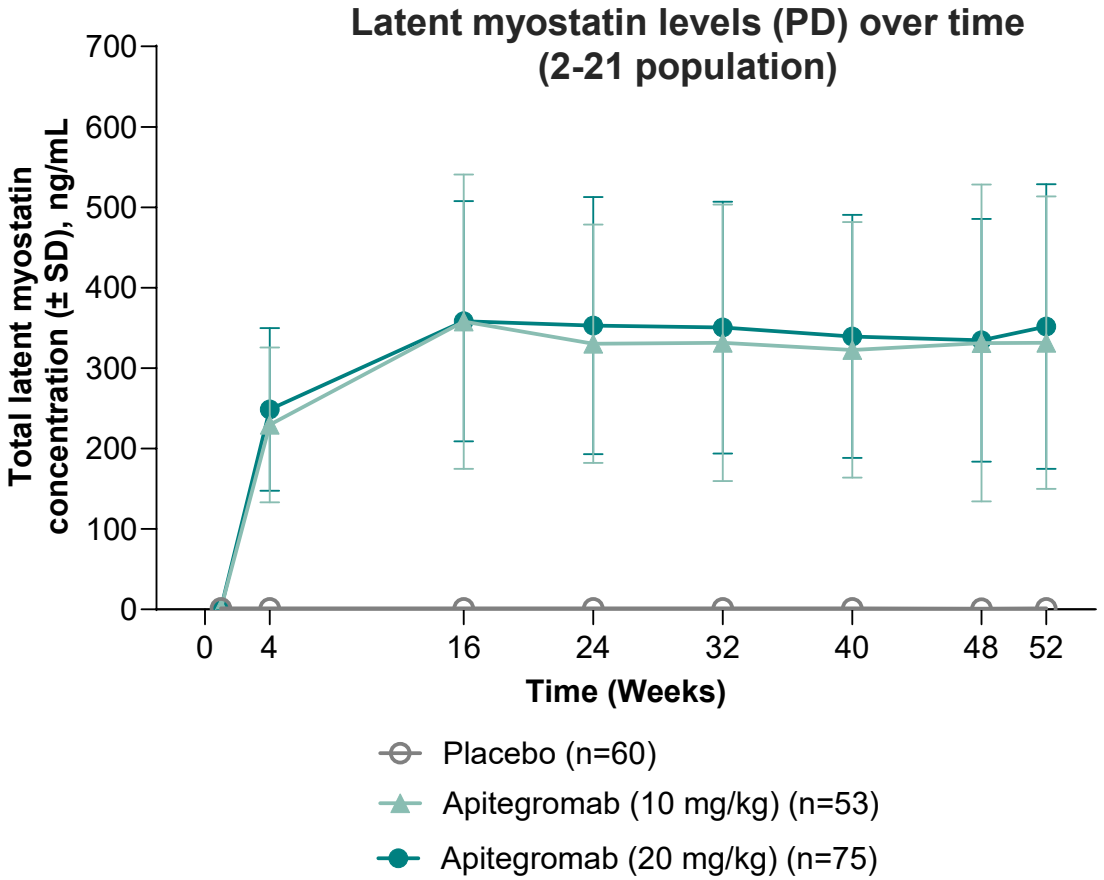
- Patients treated with apitegromab demonstrated improved motor function vs placebo
- Efficacy was consistent across outcome measures, including RULM and WHO motor developmental milestones

2–21, pooled population aged 2 to 21 years; LS, least squares; RULM, Revised Upper Limb Module; SE, standard error; WHO, World Health Organization.

1. Crawford TO, et al. *Lancet Neurol*; 2025;24:727-39.

Apitegromab pharmacokinetics and pharmacodynamics 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 apitegromab 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.
2–21, pooled population aged 2 to 21 years; PD, pharmacodynamics; PK, pharmacokinetics; SD, standard deviation.

Well-tolerated safety consistent with established profile

	2–21 pooled population		13–21 population	
Summary of AEs, n (%)	**Placebo + SOC** (n = 60)	**Apitegromab + SOC, combined** (n = 128)	**Placebo + SOC** (n = 10)	**Apitegromab 20 mg/kg + SOC** (n = 22)
AE	52 (87)	116 (91)	9 (90)	19 (86)
SAE	6 (10)	21 (16)	1 (10)	0
AE grade ≥3	6 (10)	21 (16)	1 (10)	1 (5)
AE leading to treatment discontinuation	0	0	0	0
AE leading to study withdrawal	0	0	0	0
AE with highest incidence				
Pyrexia	17 (28)	33 (26)	1 (10)	2 (9)
Nasopharyngitis	14 (23)	32 (25)	4 (40)	6 (27)
Cough	12 (20)	30 (23)	1 (10)	4 (18)
Treatment-emergent SAE with highest incidence				
Pneumonia	0	7 (5)	0	0

- Treatment with apitegromab was well-tolerated across age, consistent with established safety profile[1]
- SAEs were consistent with underlying disease and SMN-targeted treatment[2,3]; no SAEs were assessed as related to apitegromab
- There were no deaths or study-drug discontinuations due to AEs

All participants within the safety set received at least 1 dose of apitegromab or placebo. All AEs were coded using the MedDRA version 26.1. “SOC” represents treatment with either nusinersen or risdiplam.
13–21, population aged 13 to 21 years; 2–21, pooled population aged 2 to 21 years; AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities Terminology; SAE, serious AE; SMN, survival motor neuron.

1. Crawford TO, et al. *Lancet Neurol*; 2025;24:727-39. **2.** Spinraza. Package insert. Biogen; 2024. **3.** Evrysdi. Package insert. Genentech; 2024.

Conclusions

- Apitegromab, an investigational, muscle-targeted treatment, resulted in clinically meaningful improvements[1-3] in motor function in the 2–21 pooled and 13–21 SAPPHIRE populations[4]
  - Efficacy results were consistent across outcome measures (ie, HFMSE, RULM, and WHO)
  - The PD profile was similar between the apitegromab 20 mg/kg and 10 mg/kg doses, and target engagement was sustained for the duration of the treatment period
- The safety profile of apitegromab was consistent with the overall patient population with SMA and a background SMN-targeted treatment[4-6]
- SAPPHIRE results represent the first time a myostatin-targeting agent has demonstrated improved function in any disease in a placebo-controlled clinical setting

Acknowledgments

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13–21, population aged 13 to 21 years; 2–21, pooled population aged 2 to 21 years; 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. *Lancet Neurol*; 2025;24:727-39. **5.** Spinraza. Package insert. Biogen; 2024. **6.** Evrysdi. Package insert. Genentech; 2024.