Post hoc analyses from the Phase 3 SAPPHIRE study evaluating apitegromab in patients with nonambulatory Type 2 or 3 spinal muscular atrophy

Laurent Servais,[1] Andreea Seferian,[2] Jena M. Krueger,[3] Valeria A. Sansone,[4] Eugenio Mercuri,[5] Thomas Brown,[6] Crystal Watson,[6] Lian Lin,[6] Mouhamed Gueye,[6] Thomas O. Crawford[7]

[1]MDUK Oxford Neuromuscular Centre and NIHR Oxford Biomedical Research Centre, University of Oxford, Oxford, UK; Neuromuscular Reference Centre, University Hospital of Liège, Liège, Belgium; [2]Institut de Myologie, I-Motion Clinical Trials Platform, Paris, France; Hôpital Armand Trousseau, Paris, France; [3]Helen DeVos Children's Hospital Neurology-Grand Rapids, Grand Rapids, MI, USA; [4]NeMO Center in Milan, University of Milan, Milan, Italy; [5]Centro Clinico NeMo, UOC Neuropsichiatria Infantile Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy; Catholic University, Rome, Italy; [6]Scholar Rock, Cambridge, MA, USA; [7]Johns Hopkins Medicine, Baltimore, MD, USA

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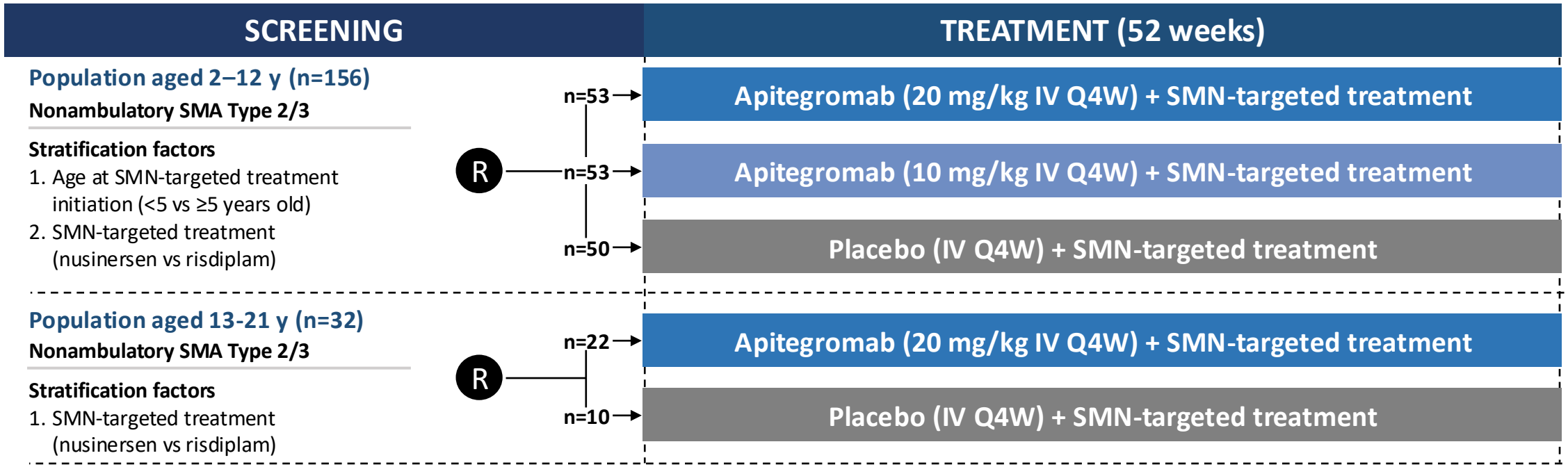
Declaration of interests

Dr. Jena M. Krueger has participated as the site principal investigator for clinical trials sponsored by Biohaven, FibroGen, Genentech, Novartis, Roche, and Scholar Rock, and has served as a consultant for Astellas as a member of an independent data monitoring committee.

SAPPHIRE study design

SAPPHIRE was a Phase 3 randomized, double-blind, placebo-controlled, parallel-arm study of apitegromab in participants with nonambulatory Type 2 or Type 3 SMA receiving SMN-targeted treatment (nusinersen or risdiplam)



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

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

Primary efficacy endpoint

Mean HFMSE change from baseline at 12 months

Additional efficacy: RULM, WHO, other outcome measures

Safety, PK/PD, ADA

Full analysis set, ages 2–21 (n = 188)

Exploratory endpoints

Mean HFMSE change from baseline at 12 months

Additional efficacy: RULM, WHO, other outcome measures

Safety, PK/PD, ADA

2–12, population aged 2 to 12 years; 2–21, population aged 2 to 21 years; ADA, antidrug antibodies; 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.

Crawford TO, et al. *Lancet Neurol*. 2025;24(9):727-739.

Baseline demographics and disease characteristics

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

	2–21 population (full analysis set)	
	SMN-targeted treatment alone (placebo) n=60	Apitegromab (10 and 20 mg/kg) + SMN-targeted treatment n=128
Female sex, n (%)	30 (50)	64 (50)
Age at screening, mean (min, max), years	9 (3, 18)	9 (2, 21)
SMN-targeted treatment at randomization		
Nusinersen/risdiplam, %	77/23	73/27
Duration of nusinersen/risdiplam, mean, years	6/3	5/3
Age at SMN-targeted treatment initiation, %		
<5 years	77	73
≥5 years	23	27
Number of SMN-targeted therapies, 1/2, %	85/15	87/13
SMA type, Type 2/3, %	88/12	79/21
SMN2 copy number, 2/3/≥4, %	3/88/3	9/78/9
Baseline HFMSE total score, mean (min, max)	27.0 (9, 46)	24.7 (8, 48)
History of scoliosis, %	73	74

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.
2–21, population aged 2 to 21 years; HFMSE, Hammersmith Functional Motor Scale–Expanded; SMA, spinal muscular atrophy; SMN, survival motor neuron.
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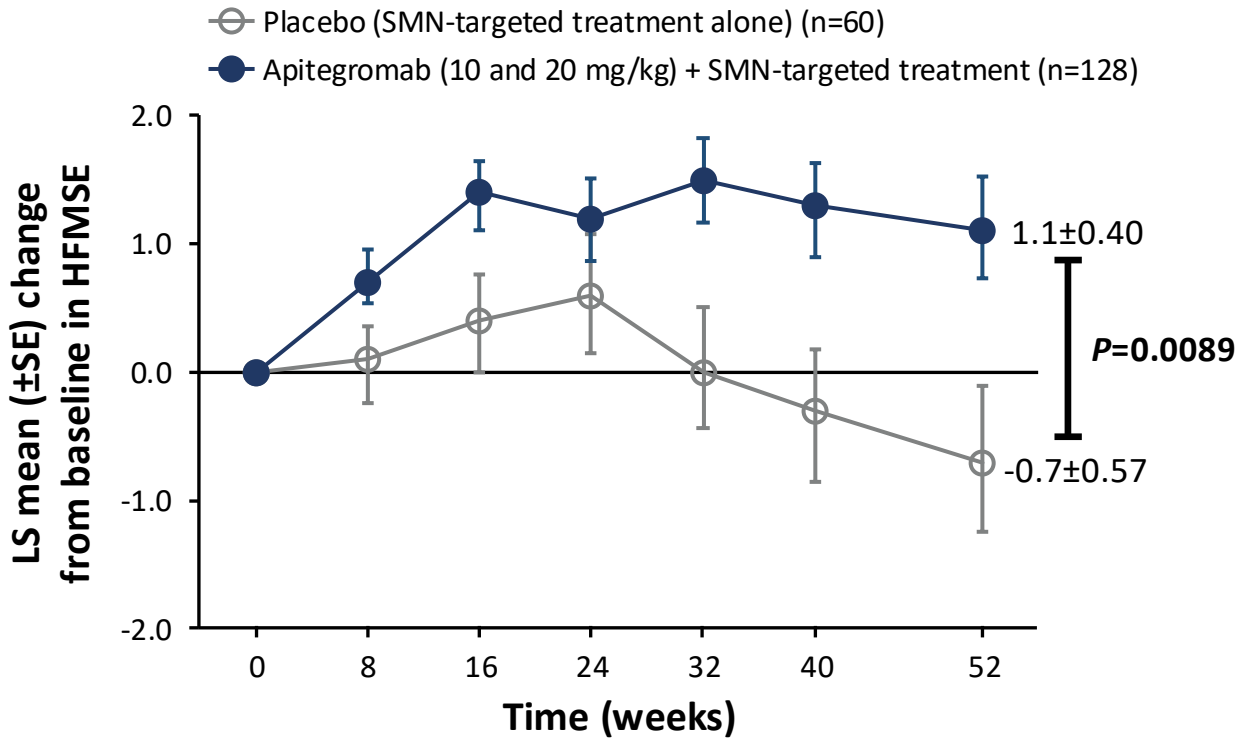
Prespecified efficacy analysis: overall study population

- SAPPHIRE outcomes showed that 12 months of two-part apitegromab + SMN-targeted treatment significantly improved or stabilized motor function outcomes vs SMN-targeted treatment alone (placebo)[1,2]
- In a prespecified analysis of the overall study population (full analysis set; aged 2–21 years), apitegromab 10 and 20 mg/kg was associated with a 1.8-point change from baseline to Month 12 vs placebo in HFMSE score (nominal *P*=0.0089)[1]
- Post hoc analyses of SAPPHIRE data were conducted to assess the impact of several baseline characteristics on HFMSE outcomes following 12 months of apitegromab

Least squares mean change from baseline in HFMSE total score by visit (full analysis set; aged 2–21 years)



HFMSE, Hammersmith Functional Motor Scale–Expanded; LS, least squares; SE, standard error; SMN, survival motor neuron.

1. Crawford TO, et al. *Lancet Neurol*. 2025;24(9):727-739. 2. Seferian A, et al. Presented at: World Muscle Society; Oct 7-11, 2025; Vienna, Austria. Poster 426P.

Methods

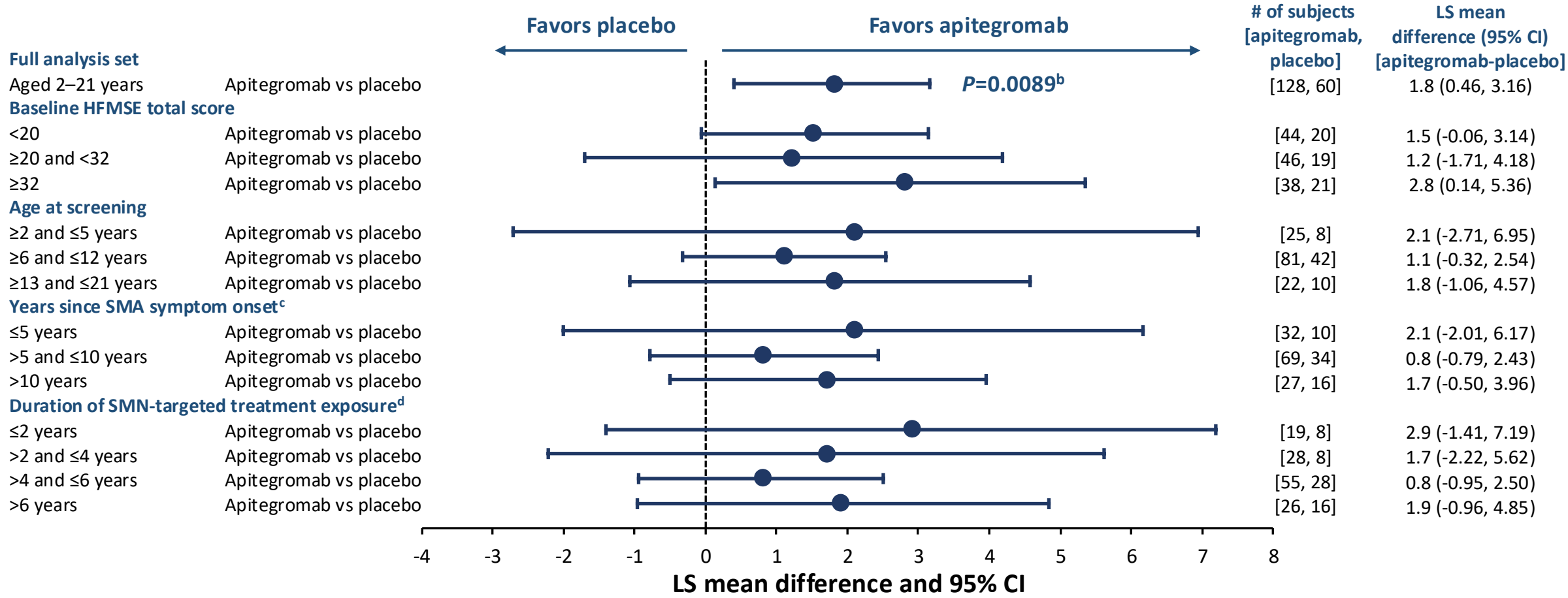
- Overall trends for the baseline characteristics were evaluated
- Subgroups were defined as those having a similar pattern, being clinically plausible, and those that allow sufficient representation across subgroups

Subgroup characteristic	Subgroup categories and rationale
Baseline HFMSE score	• <20 (high risk of complications and functional declines) • ≥20 and <32 • ≥32 (likely to be a strong sitter/early stander)
Age at enrollment	• 2–5 years (complex movement skills are typically developed and refined around age 5 years) • 6–12 years • 13–21 years (distinct SAPPHIRE cohort)
Duration of current SMN-targeted treatment	2-year intervals
Time since SMA symptom onset	5-year intervals

HFMSE, Hammersmith Functional Motor Scale–Expanded; SMA, spinal muscular atrophy; SMN, survival motor neuron.

Post hoc subgroup analysis: SAPPHIRE[a]

In the full analysis set, all post hoc subgroup analyses showed improvements in mean HFMSE scores favoring apitegromab over placebo (SMN-targeted treatment alone)



		# of subjects [apitegromab, placebo]	LS mean difference (95% CI) [apitegromab-placebo]
Full analysis set			
Aged 2–21 years	Apitegromab vs placebo	[128, 60]	1.8 (0.46, 3.16)
Baseline HFMSE total score			
<20	Apitegromab vs placebo	[44, 20]	1.5 (-0.06, 3.14)
≥20 and <32	Apitegromab vs placebo	[46, 19]	1.2 (-1.71, 4.18)
≥32	Apitegromab vs placebo	[38, 21]	2.8 (0.14, 5.36)
Age at screening			
≥2 and ≤5 years	Apitegromab vs placebo	[25, 8]	2.1 (-2.71, 6.95)
≥6 and ≤12 years	Apitegromab vs placebo	[81, 42]	1.1 (-0.32, 2.54)
≥13 and ≤21 years	Apitegromab vs placebo	[22, 10]	1.8 (-1.06, 4.57)
Years since SMA symptom onset[c]			
≤5 years	Apitegromab vs placebo	[32, 10]	2.1 (-2.01, 6.17)
>5 and ≤10 years	Apitegromab vs placebo	[69, 34]	0.8 (-0.79, 2.43)
>10 years	Apitegromab vs placebo	[27, 16]	1.7 (-0.50, 3.96)
Duration of SMN-targeted treatment exposure[d]			
≤2 years	Apitegromab vs placebo	[19, 8]	2.9 (-1.41, 7.19)
>2 and ≤4 years	Apitegromab vs placebo	[28, 8]	1.7 (-2.22, 5.62)
>4 and ≤6 years	Apitegromab vs placebo	[55, 28]	0.8 (-0.95, 2.50)
>6 years	Apitegromab vs placebo	[26, 16]	1.9 (-0.96, 4.85)

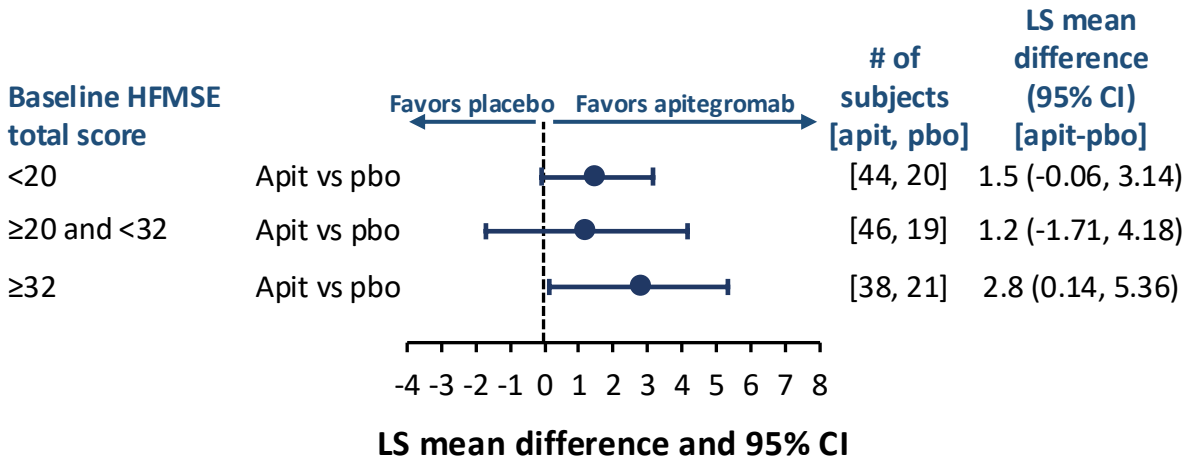
[a]Subgroup analyses were performed on the full analysis set (population aged 2–21 years) using the MMRM approach, which included fixed effects of treatment group, visit, treatment group-by-visit interaction, baseline HFMSE total score, baseline HFMSE total score-by-visit interaction, and type of SMN-targeted treatment (nusinersen/risdiplam). An unstructured covariance structure was used. [b]*P* value is nominal. [c]Years since SMA symptom onset was calculated as age at screening (years) - age at SMA symptom onset (years). [d]Years on current SMN-targeted treatment were calculated as (date of first study drug - current SMN-targeted treatment start date)/(365.25).

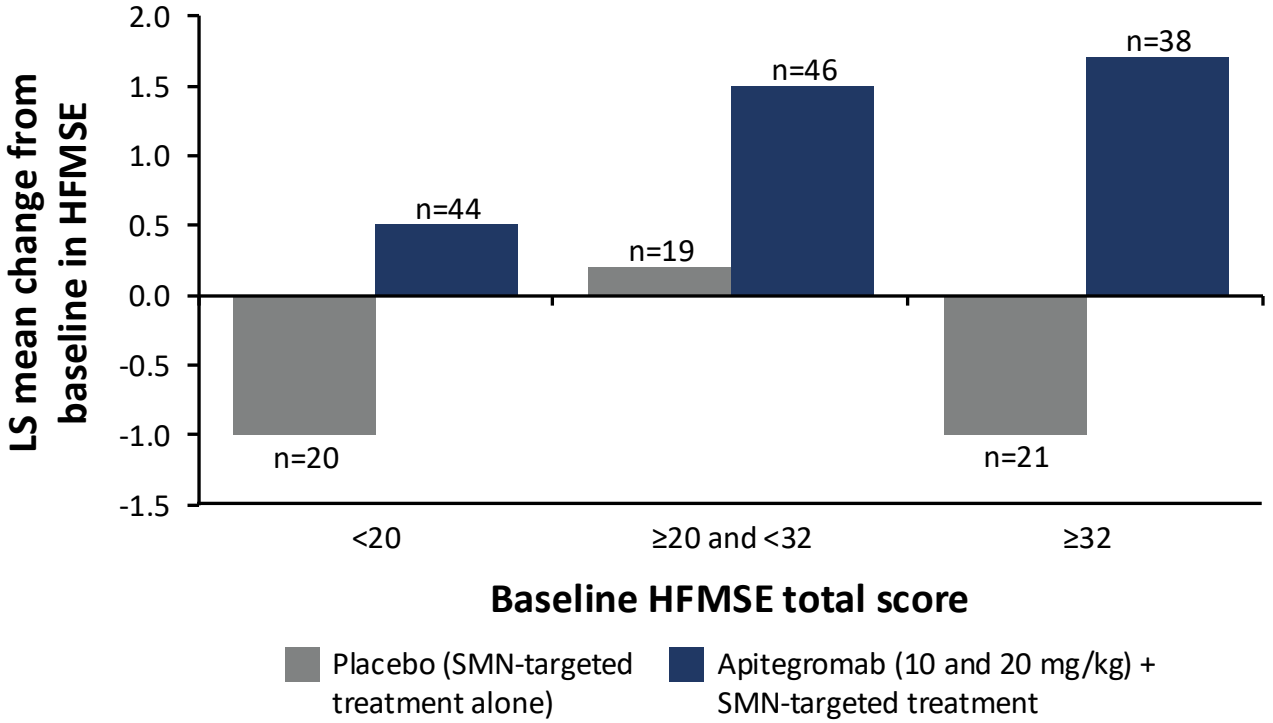
CI, confidence interval; HFMSE, Hammersmith Functional Motor Scale–Expanded; LS, least squares; MMRM, mixed model for repeated measures; SMA, spinal muscular atrophy; SMN, survival motor neuron.

Post hoc subgroup analysis: SAPPHIRE[a]

Baseline HFMSE total score

Apitegromab was associated with motor function benefits over SMN-targeted treatment alone across all baseline HFMSE strata





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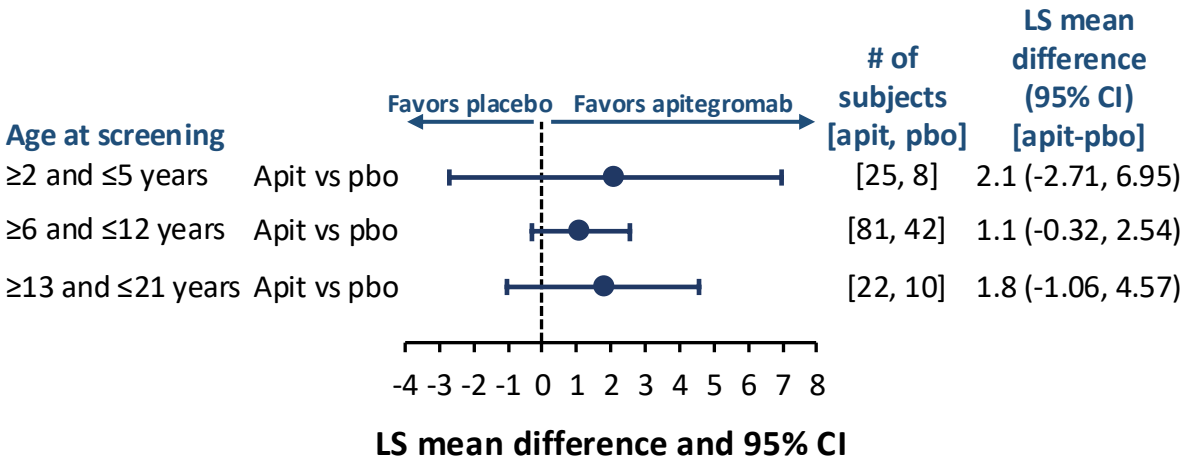
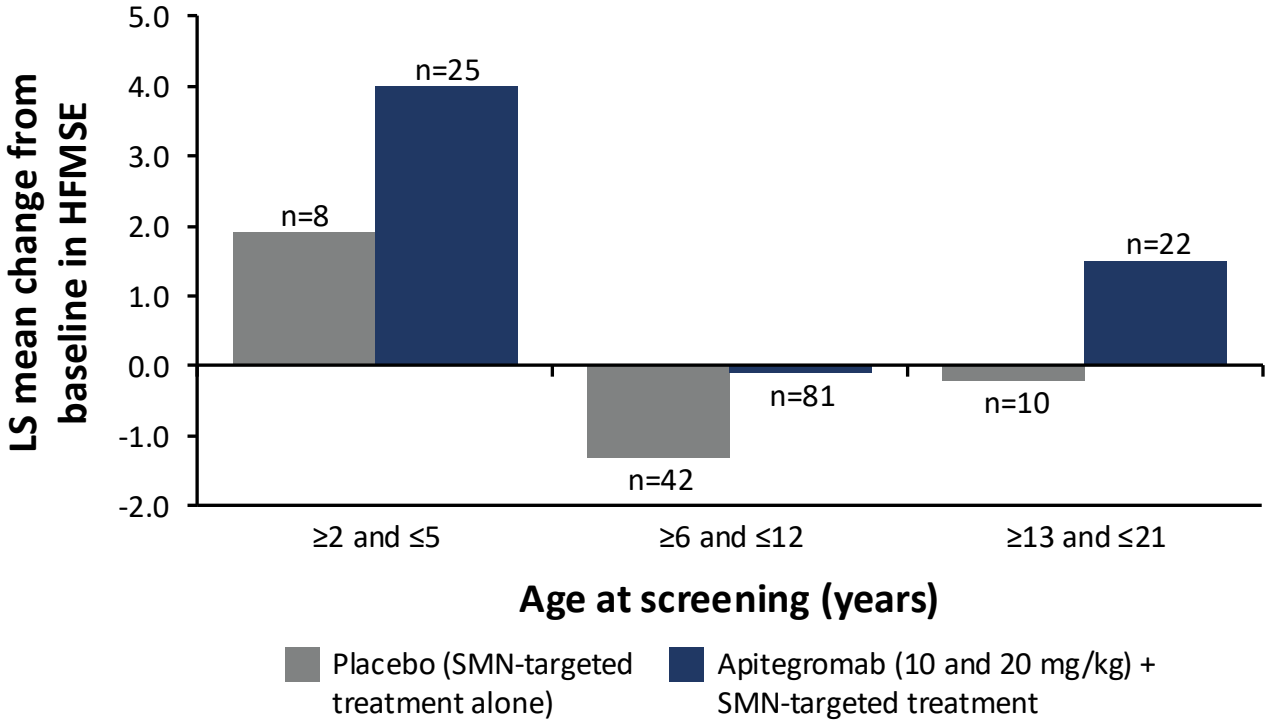
apit, apitegromab; CI, confidence interval; HFMSE, Hammersmith Functional Motor Scale–Expanded; LS, least squares; MMRM, mixed model for repeated measures; pbo, placebo; SMN, survival motor neuron.

Post hoc subgroup analysis: SAPPHIRE[a]

Age at screening

Apitegromab outperformed SMN-targeted treatment alone across age groups





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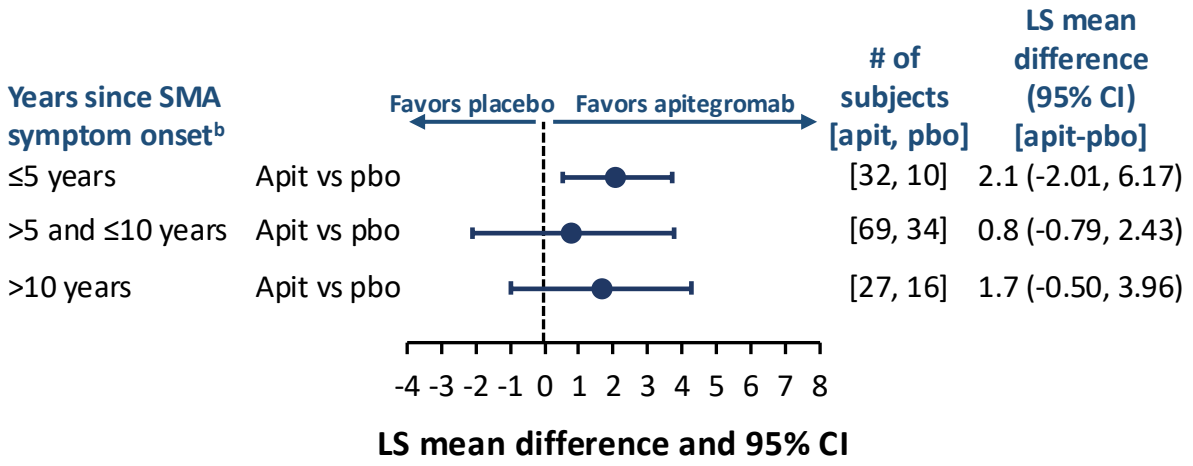
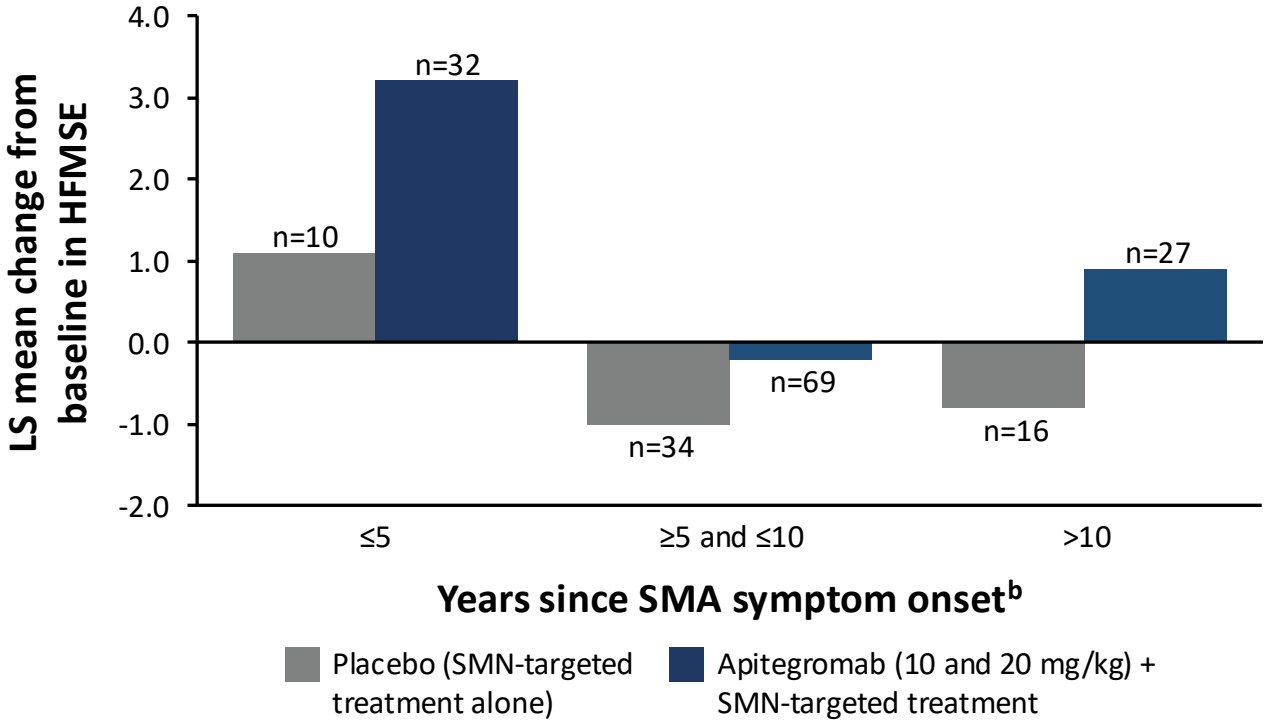
Post hoc subgroup analysis: SAPPHIRE[a]

Years since SMA symptom onset[b]

Apitegromab was associated with functional outcome benefits over SMN-targeted treatment alone regardless of time since SMA symptom onset





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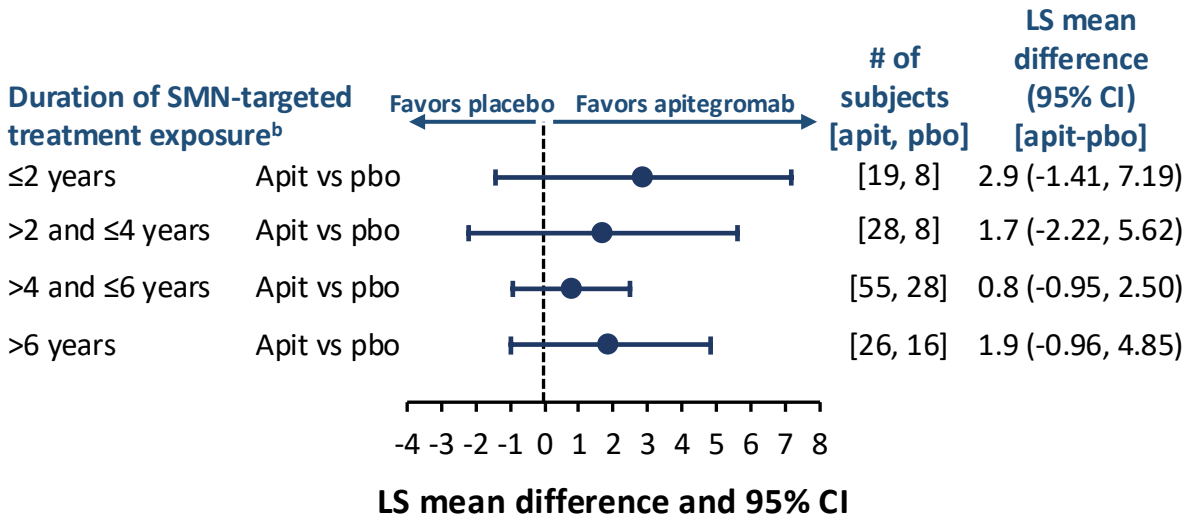
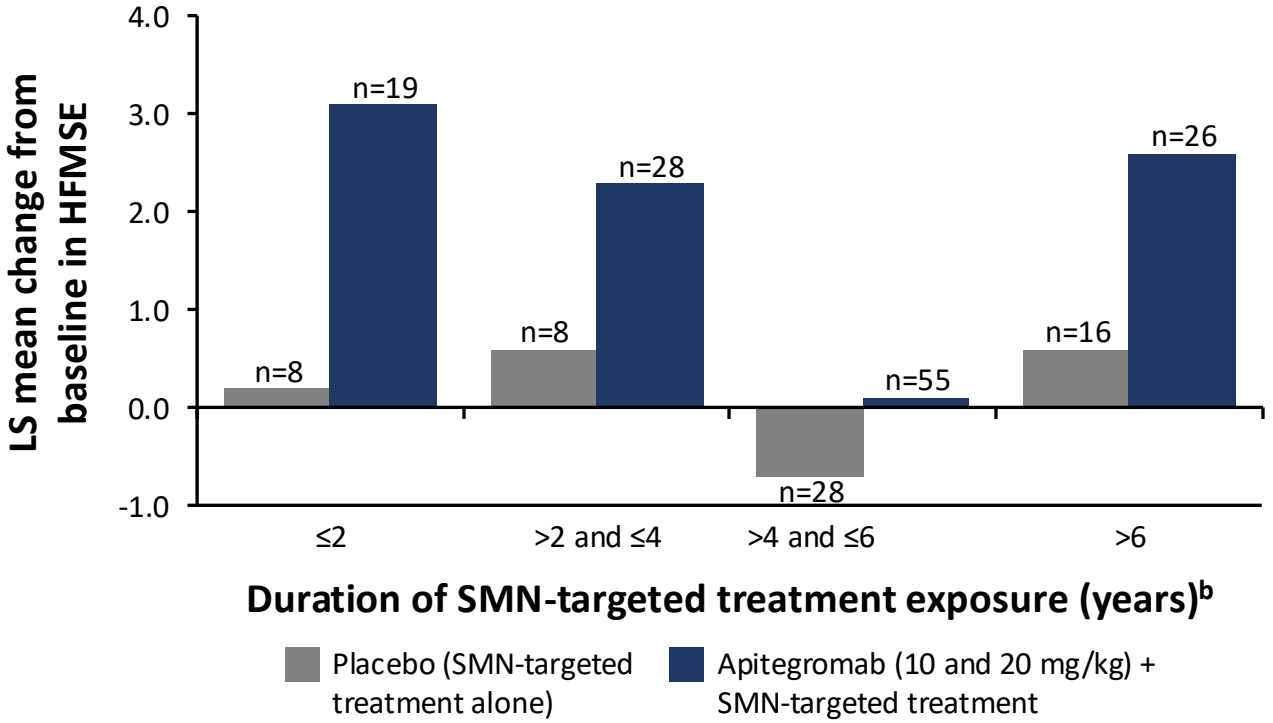
Post hoc subgroup analysis: SAPPHIRE[a]

Duration of SMN-targeted treatment exposure[b]

Apitegromab consistently demonstrated efficacy over SMN-targeted treatment alone, regardless of duration of current SMN-targeted treatment





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Conclusions

- Post hoc analyses of data from the Phase 3 SAPPHIRE trial illustrate that 12 months of apitegromab treatment conferred functional benefits regardless of functional status, patient age, duration of current SMN-targeted treatment, and time since symptom onset, and can mitigate functional declines seen in the absence of a muscle-targeted treatment
- Although sample sizes in each subgroup category were relatively small, these insights may help set treatment expectations for patients with SMA and their caregivers, as benefits of muscle-targeted treatment with apitegromab and SMN-targeted treatment were consistently greater than with SMN-targeted treatment alone
- These findings suggest that assessment of 12-month response with apitegromab treatment should account for the anticipated disease progression without apitegromab. In some patients, functional stability may indicate a clinical meaningful improvement compared with expected natural decline with SMN-targeted treatment

Acknowledgments

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SMA, spinal muscular atrophy; SMN, survival motor neuron.