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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INTRODUCTION

- Spinal muscular atrophy (SMA) is a rare, severe neuromuscular disease resulting in irreversible loss of motor neurons and progressive muscle atrophy[1]
- Even with ongoing survival motor neuron (SMN)-targeted treatments, children and adults continue to battle persistent motor function decline and may not reach full motor function potential[2-5]
- Apitegromab, an investigational, fully human monoclonal antibody, directly targets muscle by selectively and potently inhibiting myostatin, a naturally occurring negative regulator of muscle growth, to increase motor function[6] (**Figure 1**)
- In the Phase 3 SAPPHIRE trial (NCT05156320; **Figure 2**) of participants aged 2-21 years with SMA Type 2/3 who were receiving nusinersen or risdiplam, apitegromab treatment resulted in improved motor function with a generally well-tolerated safety profile, meeting its primary endpoint of change from baseline in Hammersmith Functional Motor Scale–Expanded (HFMSE) score at 12 months for participants aged 2-12 years[7]

Figure 1. Apitegromab mechanism of action

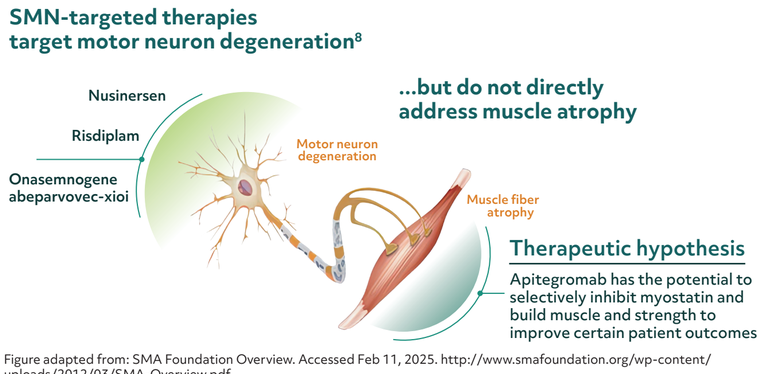


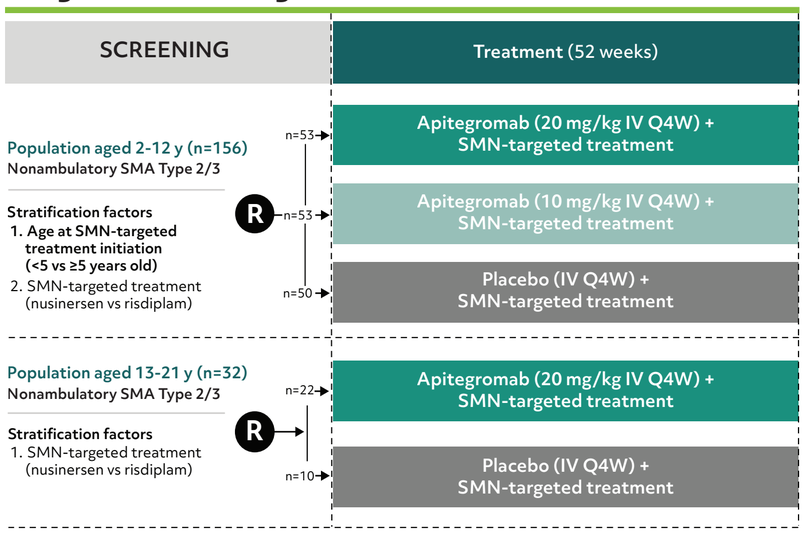
Figure adapted from: SMA Foundation Overview. Accessed Feb 11, 2025. http://www.smafoundation.org/wp-content/uploads/2012/03/SMA-Overview.pdf.
SMA, spinal muscular atrophy; SMN, survival motor neuron.

OBJECTIVE

- To evaluate the efficacy and safety of apitegromab across all age groups from the SAPPHIRE trial

METHODS

Figure 2. Trial design



Key eligibility criteria

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

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 trial
- Assessment of long-term safety and efficacy

Long-term safety follow-up
- Assessment of long-term safety for participants not enrolled in ONYX (20 weeks)

ADA, antidrug antibody; HFMSE, Hammersmith Functional Motor Scale–Expanded; IV, intravenous; PD, pharmacodynamics; PK, pharmacokinetics; Q4W, once every 4 weeks; R, randomized; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy; SMN, survival motor neuron; WHO, World Health Organization.

CONCLUSIONS

- Apitegromab, a muscle-targeted treatment, resulted in clinically meaningful improvements in motor function in the overall population aged 2-21 years, with consistent results across ages and background SMN-targeted treatments[7,9,10]
  - The LSM change from baseline in HFMSE scores was 1.8 points across populations aged 2-12, 13-21, and 2-21 years
  - Efficacy results were consistent across outcome measures (ie, HFMSE, RULM, and WHO)
- The safety profile of apitegromab in the populations aged 2-21 and 13-21 years was consistent with underlying SMA and a background SMN-targeted treatment
- SAPPHIRE results represent the first time a myostatin-targeting agent has demonstrated improved function in any disease in a placebo-controlled clinical setting

RESULTS

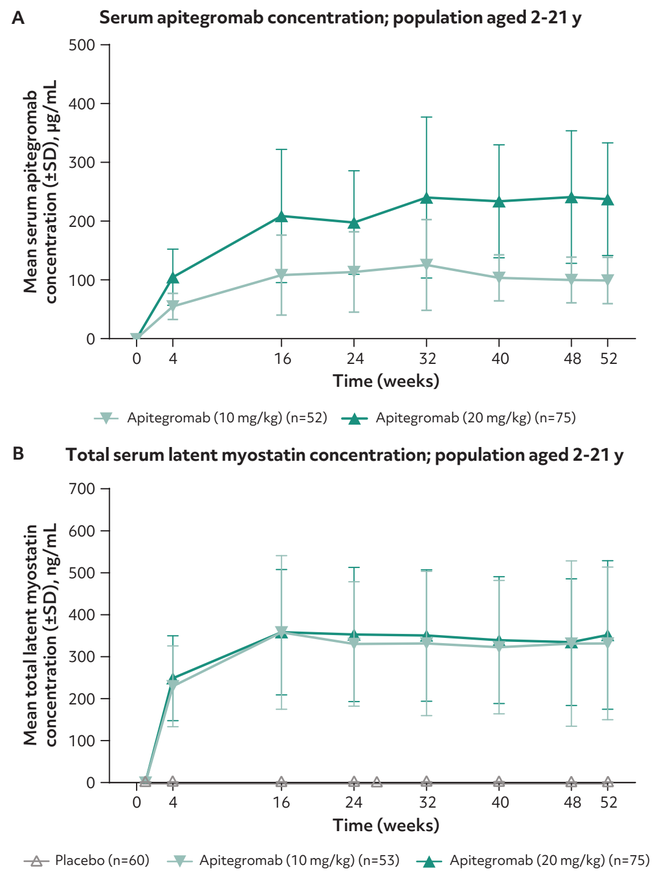
Participants

- The SAPPHIRE trial population was broadly representative of the overall population with SMA (**Table S1**, accessible by QR code)
- Baseline demographics and disease characteristics were well balanced across treatment arms

Pharmacokinetics and pharmacodynamics

- The mean serum apitegromab concentrations increased in a dose-proportional manner (**Figure 3A**) and remained relatively steady from Week 16 onward, including in participants aged 13-21 years (**Figure S1A**, accessible by QR code)
- Mean serum total latent myostatin concentration-time profiles for apitegromab 10 mg/kg and 20 mg/kg doses were nearly superimposable in the pooled population aged 2-21 years (**Figure 3B**), with sustained target engagement observed in participants aged 13-21 years (**Figure S1B**, accessible by QR code)

Figure 3. Apitegromab pharmacokinetics and pharmacodynamics in the pooled population aged 2–21 years

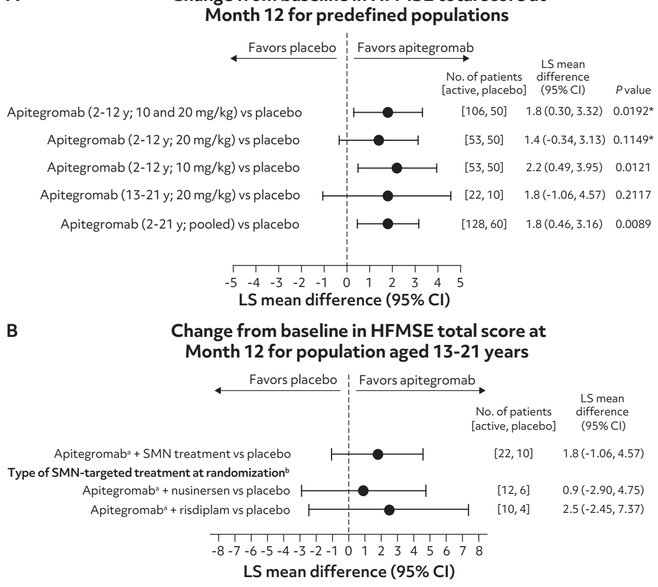


PK samples from patients receiving placebo were not tested and therefore not included in PK assessments.
PK, pharmacokinetics; SD, standard deviation.

Motor function outcomes

- At 12 months, the primary endpoint was met in the population aged 2-12 years receiving apitegromab 20 mg/kg and 10 mg/kg compared with placebo, with a least squares mean (LSM) difference (standard error [SE]) change from baseline (CFB) in HFMSE score of 1.8 (0.76; *P*=0.0192) points
- Similarly, at 12 months the LSM difference (SE) CFB in HFMSE score was 1.8 (1.37; nominal *P*=0.2117) points in the population aged 13-21 years receiving apitegromab 20 mg/kg vs placebo and 1.8 points (0.68; nominal *P*=0.0089) in the population aged 2-21 years receiving apitegromab 10 mg/kg and 20 mg/kg vs placebo (**Figure 4**)

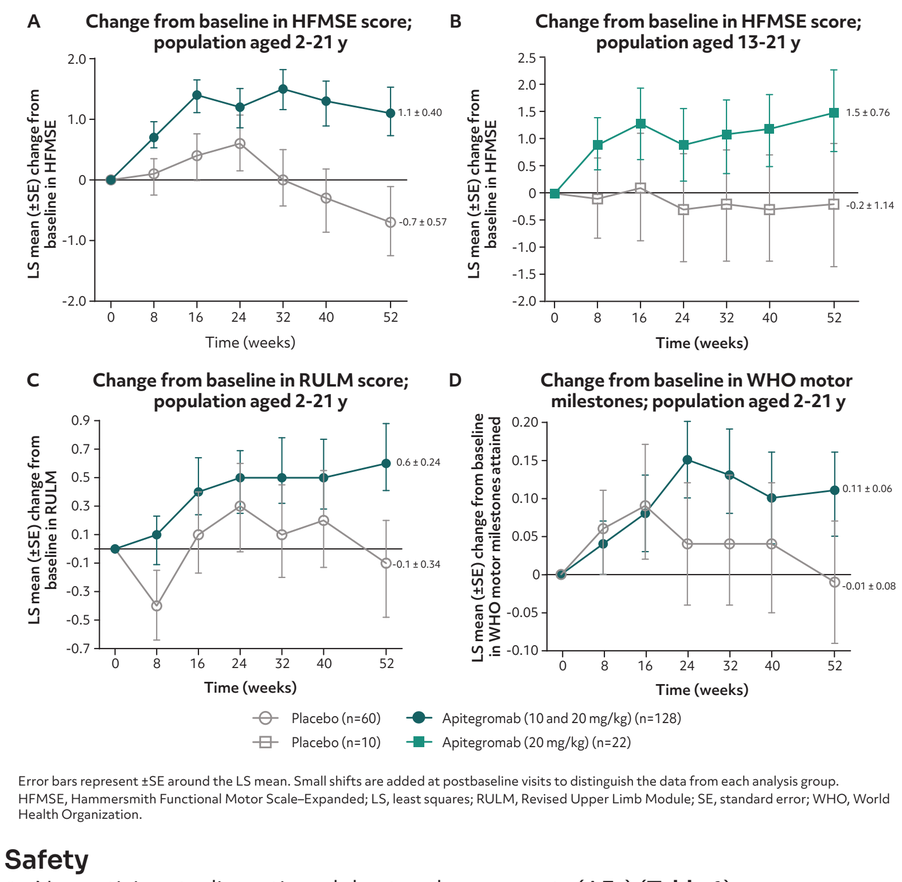
Figure 4. Change from baseline in HFMSE score at 12 months



*P values controlled for multiplicity.
[a]Apitegromab dose: 20 mg/kg. [b]SMN-targeted treatment type was a randomization stratification factor for the population aged 13-21 y.
CI, confidence interval; HFMSE, Hammersmith Functional Motor Scale–Expanded; LS, least squares; SMN, survival motor neuron.

- Over the 12-month period, apitegromab was associated with stabilization or improvements in HFMSE score in the populations aged 2-21 years (**Figure 5A**) and aged 13-21 years (**Figure 5B**)
  - Motor function stabilization or improvement was consistent across multiple outcome measures in the populations aged 2-21 years (**Figures 5C**, **5D**) and aged 13-21 years (**Figures S2A**, **S2B**, accessible by QR code).

Figure 5. Motor outcomes between apitegromab and placebo groups over 12 months



Error bars represent ±SE around the LS mean. Small shifts are added at postbaseline visits to distinguish the data from each analysis group.
HFMSE, Hammersmith Functional Motor Scale–Expanded; LS, least squares; RULM, Revised Upper Limb Module; SE, standard error; WHO, World Health Organization.

Safety

- No participants discontinued due to adverse events (AEs) (**Table 1**)
- AEs were consistent with underlying SMA and SMN-targeted treatment[9,10]

Table 1. TEAEs over the 12-month period

	Pooled population aged 2-21 y		Population aged 13–21 y	
Summary of AEs, n (%)	Placebo + SMN-targeted treatment (n=60)	Apitegromab + SMN-targeted treatment, combined (n=128)	Placebo + SMN-targeted treatment (n=10)	Apitegromab 20 mg/kg + SMN-targeted treatment (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 trial 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)
SAE with highest incidence				
Pneumonia	0	7 (5)	0	0

All participants within the safety set received at least 1 dose of apitegromab or placebo. All AEs were coded using MedDRA version 26.1.
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event; SMN, survival motor neuron; TEAE, treatment-emergent adverse event.

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Disclosures

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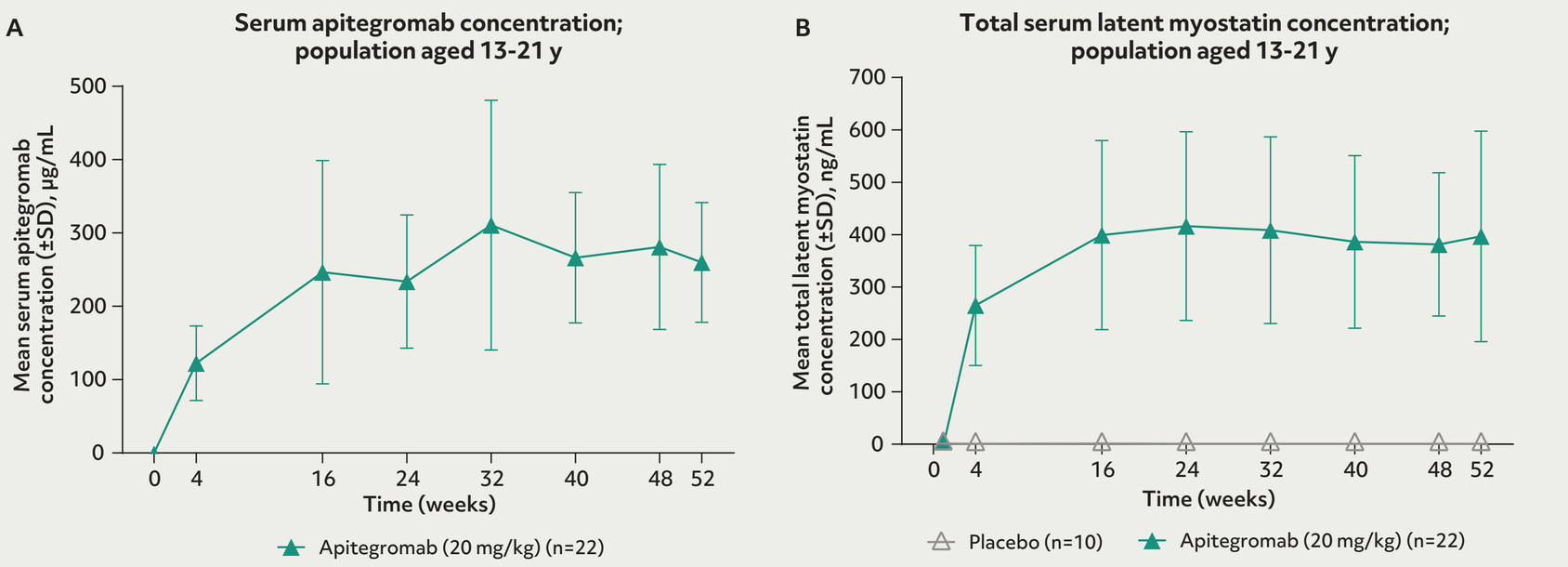
SUPPLEMENTARY MATERIAL

Table S1. SAPPHIRE baseline demographics and clinical characteristics

	Pooled population 2-21 y		Population aged 2-12 y			Population aged 13-21 y	
	Placebo + SMN-targeted treatment (n=60)	Apitegromab + SMN-targeted treatment, combined (n=128)	Placebo + SMN-targeted treatment (n=50)	Apitegromab 20 mg/kg + SMN-targeted treatment (n=53)	Apitegromab 10 mg/kg + SMN-targeted treatment (n=53)	Placebo + SMN-targeted treatment (n=10)	Apitegromab 20 mg/kg + SMN-targeted treatment (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)
Mean baseline RULM score (min, max)	27.1 (17, 37)	25.8 (9, 37)	27.3 (18, 37)	25.7 (13, 37)	25.6 (9, 37)	26.3 (17, 37)	26.3 (20, 37)
Mean baseline WHO motor development milestones attained (min, max)	1.7 (1, 5)	1.5 (1, 5)	1.7 (1, 5)	1.5 (1, 5)	1.7 (1, 5)	1.5 (1, 5)	1.1 (1, 2)
History of scoliosis, %	73.3	74.2	70.0	71.7	71.7	90.0	86.4

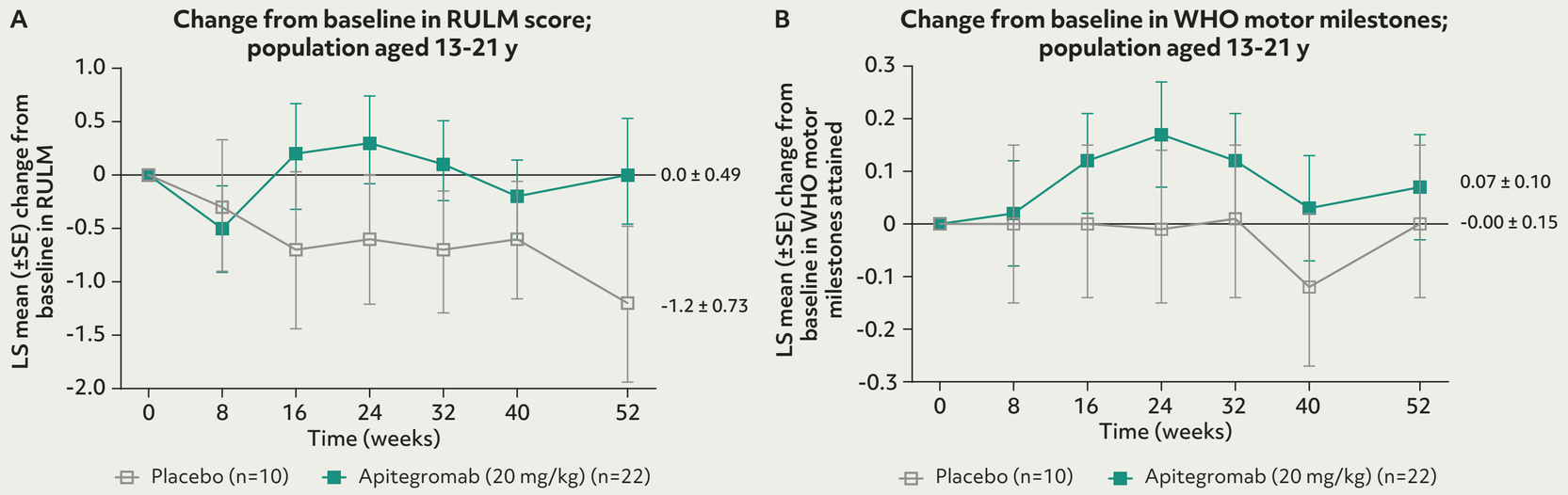
[a]In the population aged 2-12 y, 3 participants were mis-stratified for age at initiation of SMN-targeted treatment at randomization. [b]The population aged 13-21 y was stratified by type of SMN-targeted treatment only; age at initiation of SMN-targeted treatment at randomization is not applicable as the randomization stratification.
HFMSE, Hammersmith Functional Motor Scale–Expanded; min, minimum; max, maximum; N/A, not applicable; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy; SMN, survival motor neuron; WHO, World Health Organization.

Figure S1. Apitegromab pharmacokinetics and pharmacodynamics in the population aged 13–21 years



SD, standard deviation.

Figure S2. Motor outcomes between apitegromab and placebo groups over 12 months in the population aged 13–21 years



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