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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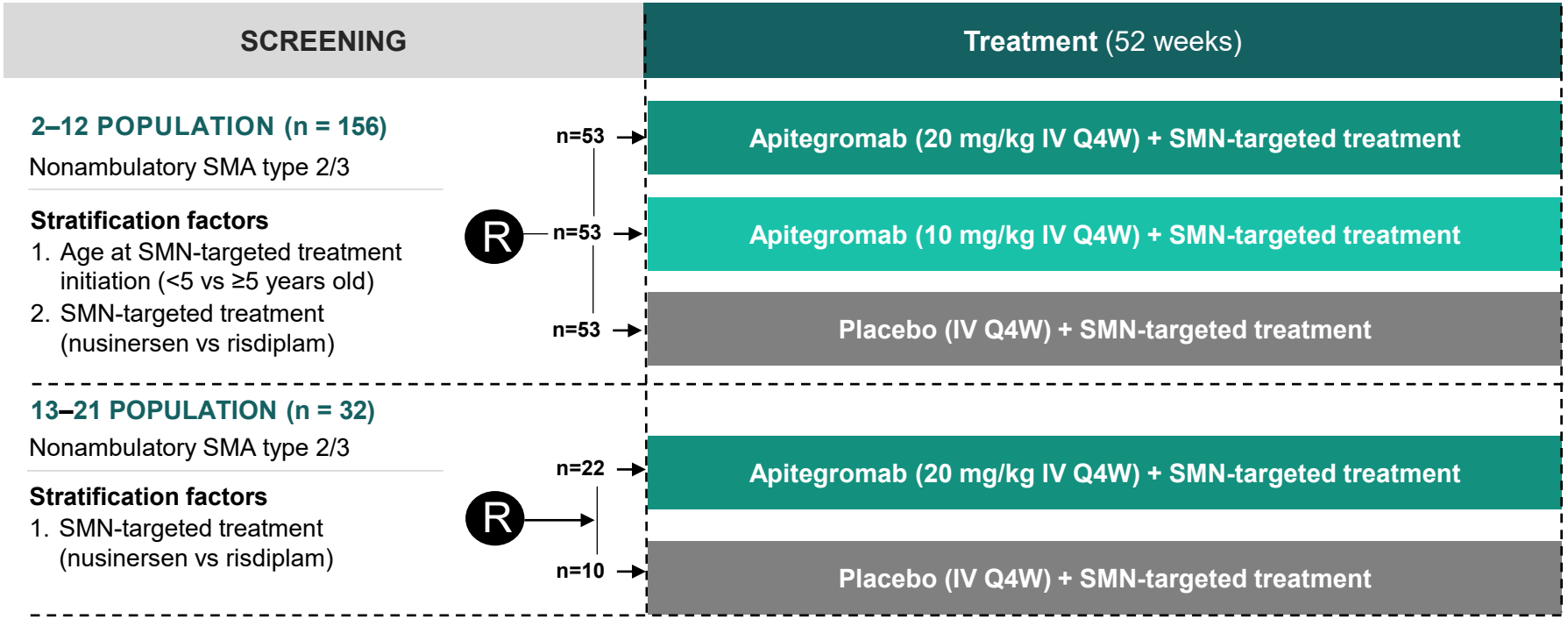
Disclosure

- I have the following conflict/s of interest to declare:
  - I am a principal investigator of the Scholar Rock, Inc., – sponsored Phase 3 SAPPHIRE trial, a paid consultant for Scholar Rock, Inc., and have received personal compensation from Audentes and Biogen

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

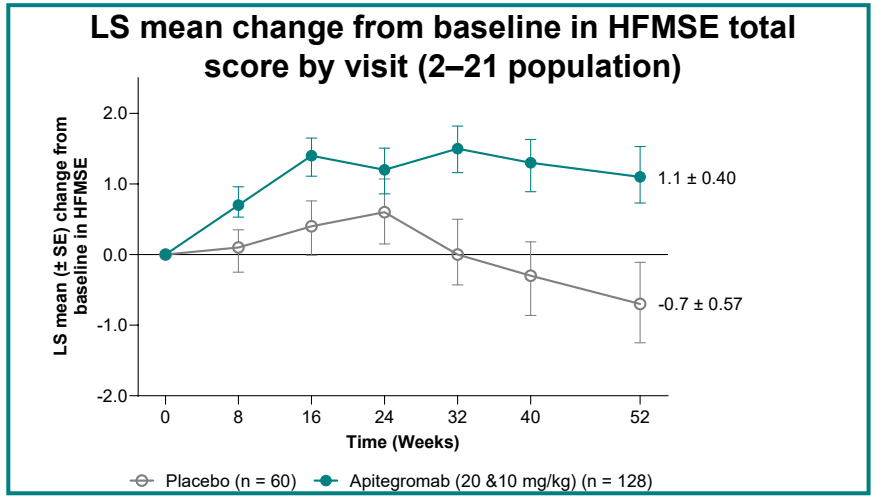
- Assessment of long-term safety for patients not enrolled in ONXY (20 weeks)

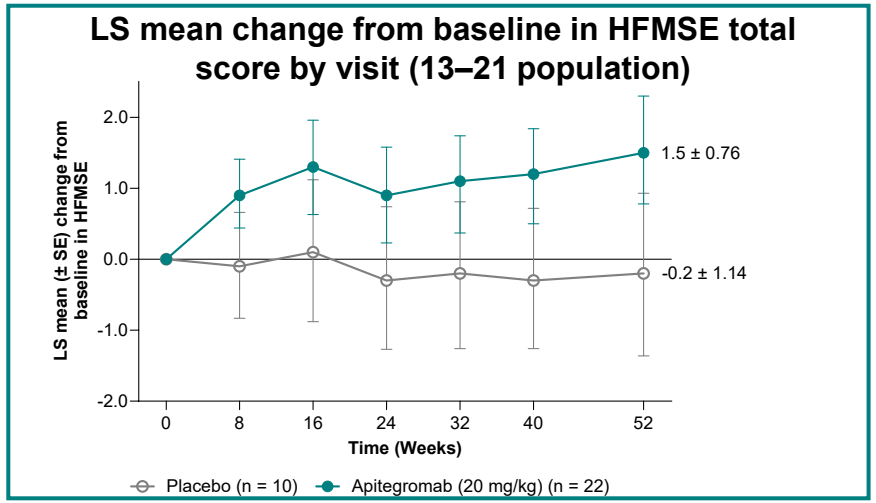
ClinicalTrials.gov Identifier: NCT05156320.

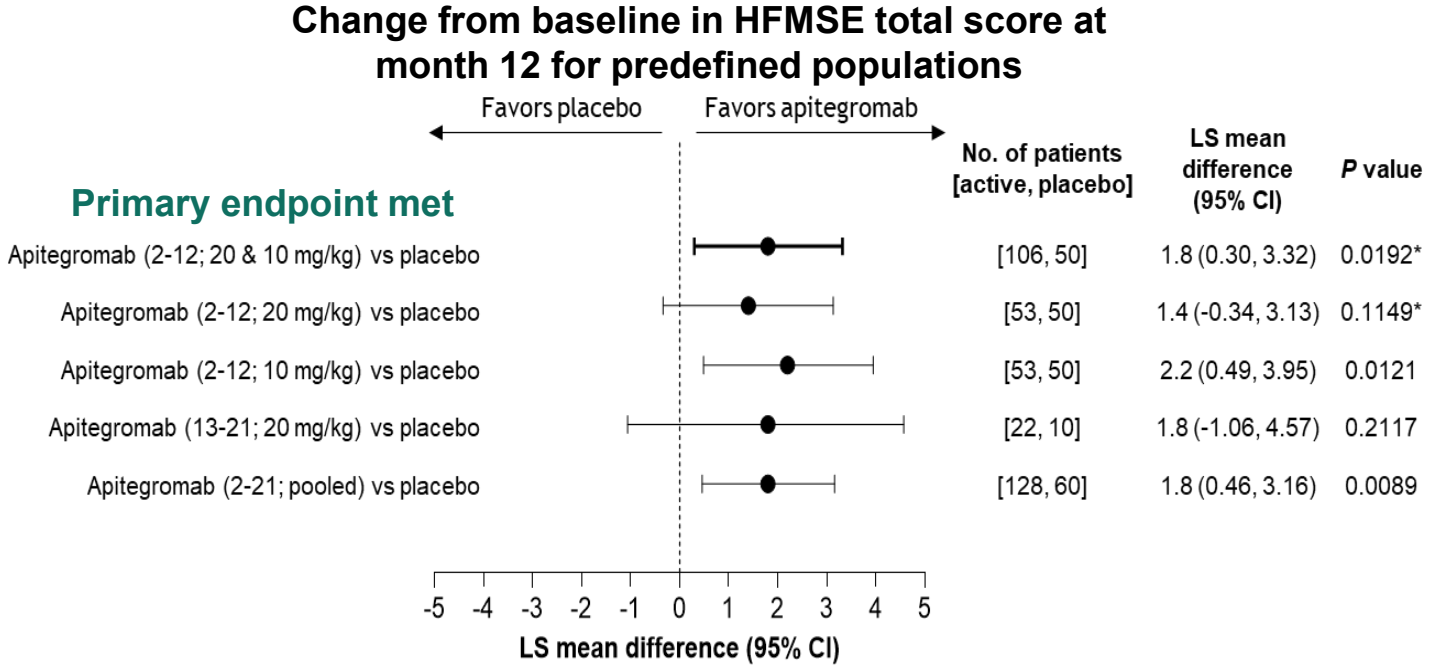
2–12, population aged 2 to 12 years; 13–21, population aged 13 to 21 years; ADA, antidrug antibody; HFMSE, Hammersmith Functional Motor Scale Expanded; IV, intravenous; PD, pharmacodynamics; PK pharmacokinetics; Q4W, every 4 weeks; R, randomization; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy; SMN, survival motor neuron; WHO, World Health Organization.

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

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.
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.

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

Well-tolerated safety consistent with established profile

	2–21 pooled population		13–21 population	
Summary of AEs, n (%)	**Placebo + SMN-targeted treatment** (n = 60)	**Apitegromab + SMN-targeted treatment** (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 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.
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; **shown in poster 426P**)
  - 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 (**shown in poster 426P**)
- 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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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.