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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Introduction

- Spinal muscular atrophy (SMA) is a genetic neuromuscular disorder characterized pathologically by degeneration of motor neurons in the spinal cord and brain stem and clinically by progressive weakness and atrophy of skeletal muscles[1,2]
- Patients with SMA may continue to experience progressive loss of motor function despite receiving survival motor neuron (SMN)-targeted therapy[3,4]
- Apitegromab is an investigational, fully human monoclonal antibody that selectively binds to both promyostatin and latent myostatin, blocking activation of mature myostatin, thereby enabling muscle growth (**Figure 1**)[5-7]

Figure 1. Mechanism of action of apitegromab

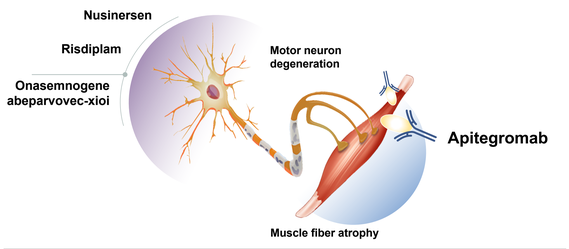


Figure adapted from: SMA Foundation Overview. Accessed February 11, 2025. http://www.smafoundation.org/wp-content/uploads/2012/03/SMA-Overview.pdf
SMA, spinal muscular atrophy.

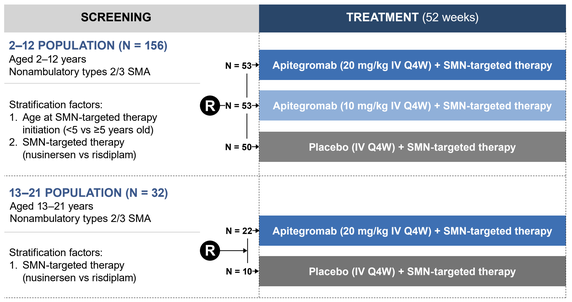
Objective

- To report the 12-month data from SAPPHIRE (NCT05156320), a double-blind, placebo-controlled, phase 3 study evaluating the efficacy and safety of apitegromab in patients with nonambulatory type 2/3 SMA receiving nusinersen or risdiplam

Methods

Study design

Figure 2. SAPPHIRE study design and eligibility criteria



KEY ELIGIBILITY CRITERIA

Inclusion criteria:
- Age ≥2 years
- Nonambulatory
- HFMSE score of ≥10 and ≤45
- Receiving SMN-targeted therapy (≥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 (2–12): Change from baseline in HFMSE total score at 12 months

Secondary efficacy measures: 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 ONYX (20 weeks)

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, once every 4 weeks; R, randomized; SMA, spinal muscular atrophy; SMN, survival motor neuron; WHO, World Health Organization.

Results

Participants

- The SAPPHIRE study population was broadly representative of the SMA patient population (**Table 1**)
- Baseline characteristics were well-balanced across treatment arms
- SAPPHIRE participants were in the advanced phase of their SMN-targeted therapy journey

Table 1. SAPPHIRE baseline demographics and clinical characteristics

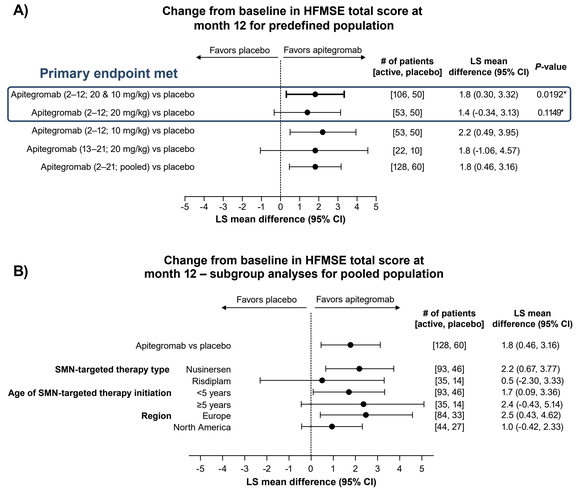
	2–12 population				13–21 population	
	Placebo (N = 50)	Apitegromab 20 mg/kg (N = 53)	Apitegromab 10 mg/kg (N = 53)	Apitegromab combined (N = 106)	Placebo (N = 10)	Apitegromab 20 mg/kg (N = 22)
Female sex, n (%)	25 (50.0)	26 (49.1)	23 (43.4)	49 (46.2)	5 (50.0)	15 (68.2)
Mean age at screening, y (min, 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 therapy 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, y	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 therapy initiation age, <5/≥5 y, %	88/12	84.9/15.1	86.8/13.2	85.8/14.2	N/A	N/A
Number of SMN-targeted therapies, 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

Baseline demographics and clinical characteristics are presented for all randomized participants. All randomized participants received apitegromab or placebo in addition to SOC 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; SMA, spinal muscular atrophy; SMN, survival motor neuron; SOC; standard of care.

Motor function

- The primary endpoint was met based on the comparison of apitegromab (20 and 10 mg/kg) vs placebo (**Figure 3A**)
  - At month 12, motor function outcomes were consistent across the 2–12 and 13–21 populations, favoring apitegromab
- Positive trends for functional improvements were observed across prespecified 2–21 populations (type of SMN-targeted therapy, age of SMN-targeted therapy initiation, and region; **Figure 3B**) for apitegromab, relative to placebo

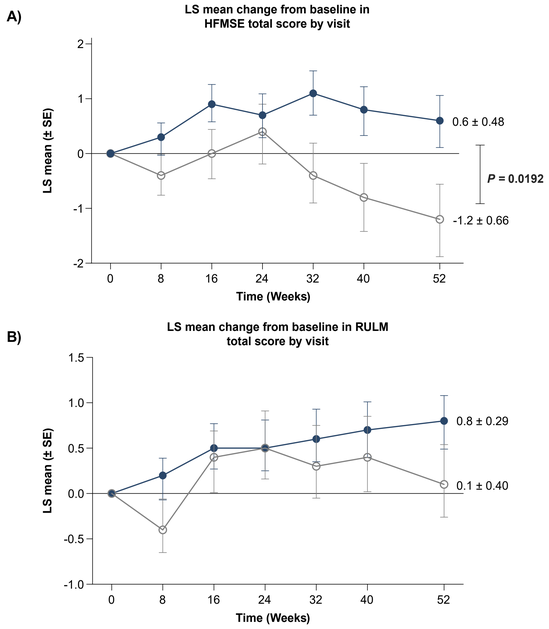
Figure 3. Change from baseline in HFMSE total score at month 12



*P-values controlled for multiplicity.
"Apitegromab" without any dose indication represents combined dose data (20 and 10 mg/kg) for the 2–21 population. SMN-targeted therapy type was a randomization stratification factor for both the 2–12 population and 13–21 population. Age at initiation of SMN-targeted therapy (<5 years or ≥5 years) is derived from the age the participant received the first dose of SMN-targeted therapy in months.
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.

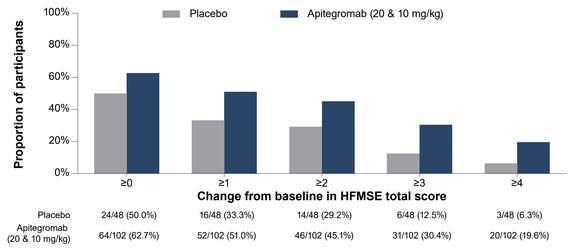
- Over the 12-month treatment period, apitegromab was associated with stabilization or improvements in motor function, consistently across outcome measures (**Figure 4**)
- Higher proportions of participants receiving apitegromab achieved HFMSE improvements across all point thresholds relative to placebo (**Figure 5**)

Figure 4. Motor outcomes between the apitegromab combined-dose and placebo groups over 12 months (2–12 population)



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.

Figure 5. Any point change from baseline in HFMSE total score at month 12 (2–12 population)



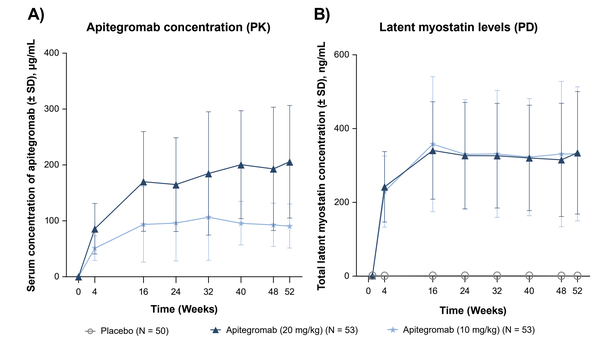
	≥0	≥1	≥2	≥3	≥4
Placebo	24/48 (50.0%)	16/48 (33.3%)	14/48 (29.2%)	6/48 (12.5%)	3/48 (6.3%)
Apitegromab (20 & 10 mg/kg)	64/102 (62.7%)	52/102 (51.0%)	46/102 (45.1%)	31/102 (30.4%)	20/102 (19.6%)

A greater proportion of patients treated with apitegromab achieved ≥3-point improvements with the odds ratio 3.0, nominal $P = 0.03$.
2–12, population aged 2 to 12 years; HFMSE, Hammersmith Functional Motor Scale Expanded.

Pharmacology

- Observed increase in exposure to apitegromab was dose-proportionate (**Figure 6A**)
- Robust and sustained target engagement was observed following apitegromab dosing and was similar between each apitegromab dose (**Figure 6B**)

Figure 6. Pharmacokinetics and pharmacodynamics over 12 months of treatment



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.

Safety

- Treatment with apitegromab was well tolerated across all age groups, consistent with the established safety profile (**Table 2**)[5,6]
- There were no clinically relevant differences in the adverse event (AE) profile by dose
- Serious AEs (SAEs) were consistent with underlying disease and SMN treatment[8,9]; no SAEs were assessed as related to apitegromab
- There were no deaths or study-drug discontinuations due to AEs
- A single participant tested positive for antidrug antibodies; samples were further assessed and determined to be below the sensitivity cutoff point

Table 2. Adverse events over the 12-month period

	2–12 population				13–21 population	
Summary of AEs n (%)	Placebo (N = 50)	Apitegromab 20 mg/kg (N = 53)	Apitegromab 10 mg/kg (N = 53)	Apitegromab combined (N = 106)	Placebo (N = 10)	Apitegromab 20 mg/kg (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

All participants within the safety set received at least one dose of apitegromab or placebo in addition to SOC treatment with either nusinersen or risdiplam. All AEs were coded using the MedDRA version 26.1.
2–12, population aged 2 to 12 years; 13–21, population aged 13 to 21 years; AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities Terminology; SAE, serious AE; SOC; standard of care.

Conclusions

- Apitegromab treatment resulted in statistically significant and clinically meaningful improvements[10-12] in motor function
  - Efficacy results were consistent across outcomes measures (HFMSE, RULM, and WHO)
  - Efficacy results were consistent across age, background SMN therapy, age of SMN therapy initiation, and region
  - Based on similar pharmacodynamics, efficacy, and safety, benefit-risk profile was optimized at 10 mg/kg
- Safety profile was consistent with the underlying SMA patient population and background SMN-targeted therapy[5,6,8,9]
- SAPPHIRE results represent the first time a myostatin-targeting agent has demonstrated improved function in any disease in a placebo-controlled clinical setting

References

1. Mercuri E, et al. *Primer*. 2022;8:52. **2.** Keinath MC, et al. *App Clin Genet*. 2021;14:11-25. **3.** Finkel RS, et al. Poster at Annual SMA Research and Clinical Care Meeting; June 5-7, 2024. P95. **4.** Oskoui M, et al. Poster at the MDA Clinical and Scientific Conference; March 19-22, 2023. Poster 158. **5.** Crawford TO, et al. *Neurology*. 2024;102:e209151. **6.** Crawford TO, et al. *Front Neurol*. 2024;15:1419791. **7.** Barrett D, et al. *Adv Ther*. 2021;38:3203-22. **8.** Spinraza. Package insert. Biogen; 2024. **9.** Evrysdi. Package insert. Genentech; 2024. **10.** Pera MC, et al. *BMN Neurol*. 2017;17:39. **11.** Stolte B, et al. *Eur J Neurol*. 2020;27:2586-94. **12.** Wu JW, et al. *Am J Phys Med Rehabil*. 2022;101:590-608.

Conflicts of Interests

TOC is the lead principal investigator of the Scholar Rock, Inc.-sponsored phase 2 TOPAZ trial and a consultant and/or advisory board member for AveXis/Novartis Gene Therapies, Biogen, Pfizer, and Roche/Genentech. **BTD** has served as an ad hoc scientific advisory board member for AveXis/Novartis Gene Therapies, Biogen, Roche/Genentech, Sarepta Therapeutics, and Scholar Rock, Inc.; steering committee member for Roche FIREFISH and MANATEE studies; and Data and Safety Monitoring Board member for Amicus and Lexeo Therapeutics; he has no financial interests in these companies. He has also received royalties for books and online publications from Elsevier and Wolters Kluwer. **LS** has received grants and personal fees from AveXis/Novartis Gene Therapies, Biogen, and Roche and personal fees from Biohaven, Cytokinetics, and Scholar Rock, Inc., outside the submitted work. **JK** is a site principal investigator for AveXis/Novartis Gene Therapies, Biohaven, FibroGen, Roche/Genentech, and Scholar Rock, Inc., and serves as a Data and Safety Monitoring Board member for Astellas. **HK** is serving on a scientific advisory board for AveXis and received travel expenses and speaker honoraria from Biogen, Pfizer, Roche, and Sanofi-Aventis. **AMS** has no conflicts to disclose. **CC** is a site principal investigator for Biogen, Novartis Gene Therapies, and Roche clinical trials, serves as a scientific advisory board member for Novartis Gene Therapies, Roche, and Pfizer, and has received advisory fees from Pfizer and Roche. **NK** serves on medical advisory boards for Argenx, Biogen, Novartis, Roche, and Sarepta. Her institution receives research funds from Biogen, Novartis, Roche, and Sarepta. **RF** has received personal compensation for consulting and for advisory board participation from Biogen, Novartis, Novartis Gene Therapies, Roche, and Scholar Rock, Inc.; editorial fees from Elsevier for coediting a neurology textbook; license fees from the Children's Hospital of Philadelphia; and research funding from Biogen, Novartis Gene Therapies, Roche/Genentech, and Scholar Rock, Inc. **BY**, **JR**, **GZ**, **GS**, and **JLM** are Scholar Rock, Inc., employees and stockholders. **EM** has received personal compensation for clinical trial consulting and serving on scientific advisory boards and research funding from Novartis Gene Therapies.

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