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

Poster #189 M

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

INTRODUCTION

- Approved survival motor neuron (SMN)-targeted treatments slow spinal muscular atrophy (SMA) disease progression and significantly improve functional outcomes, with earlier treatment interventions leading to better motor function outcomes[1,2]
- SMN-targeted treatments do not directly address underlying muscle atrophy, and many patients continue to experience functional deficits[3-6]
- SAPPHIRE, a global, double-blind, placebo-controlled, Phase 3 trial (NCT05156320), assessed apitegromab, an investigational, muscle-targeted treatment, in patients with SMA aged 2-21 years (2-21) receiving SMN-targeted treatment[7]
  - Patients 2-12 years (2-12 population): randomized 1:1:1 for apitegromab 10 or 20 mg/kg or placebo once every 4 weeks (Q4W)
  - Patients 13-21 years (13-21 population): randomized 2:1 for apitegromab 20 mg/kg or placebo Q4W
- SAPPHIRE outcomes showed that 12 months of dual-modality apitegromab + SMN-targeted treatment significantly improved or stabilized motor function outcomes vs SMN-targeted treatment alone (placebo)[7,8]
  - The trial primary endpoint was met based on the Hammersmith Functional Motor Scale–Expanded (HFMSE) change from baseline of 1.8 points (P=0.0192) for the 2-12 population receiving apitegromab (10 and 20 mg/kg) vs placebo

Scan the QR code for additional information on the SAPPHIRE trial

Please scan the QR code to see the oral presentation "**Efficacy and safety of apitegromab in individuals with Type 2 and Type 3 spinal muscular atrophy evaluated in the Phase 3 SAPPHIRE trial"** presented at MDA 2025

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 (**Table 1**)

Table 1. Subgroup definitions and rationale

Subgroup characteristic	Subgroup categories and rationale
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
Baseline HFMSE score	• ≤20 (high risk of complications and functional declines) • 21-30 • ≥31 (likely to be a strong sitter/early stander)

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

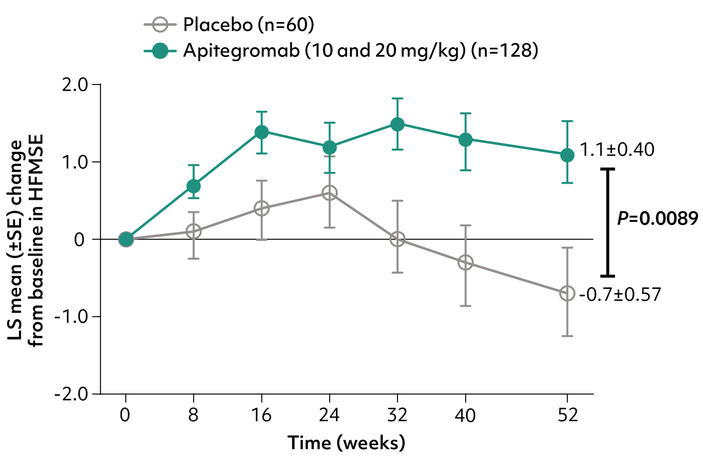
OBJECTIVE

- Post hoc analyses of SAPPHIRE data were conducted to assess the impact of several baseline characteristics on HFMSE outcomes following 12 months of apitegromab + SMN-targeted treatment vs SMN-targeted treatment alone

RESULTS

- 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; **Figure 1**)[7]
- In post hoc analyses, apitegromab efficacy was consistently observed across all subgroups defined by baseline characteristics (**Table 2**)

Figure 1. Least squares mean change from baseline in HFMSE total score by visit (overall study population)



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

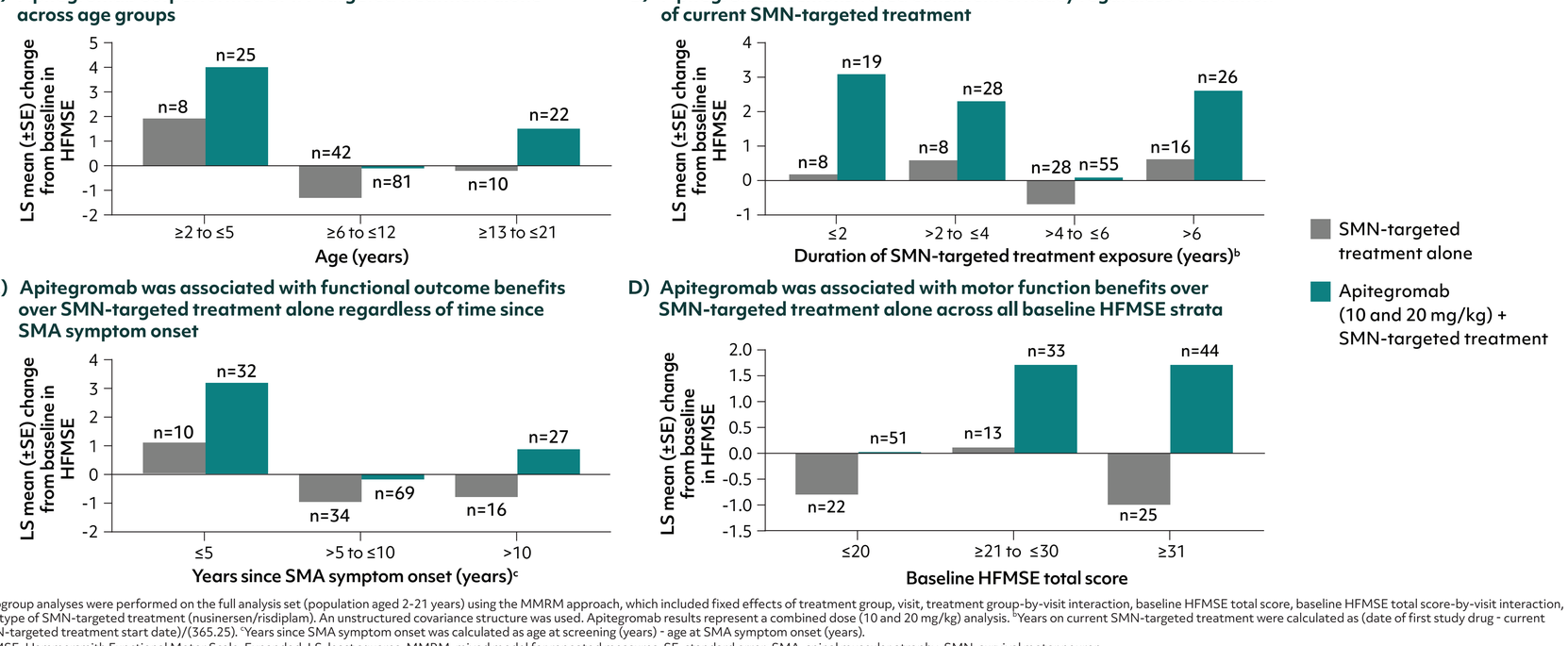
Table 2. Efficacy of apitegromab[a] at 12 months

Subgroup	Subgroup category	LS mean difference in change from baseline in HFMSE (95% CI)
Full analysis set[b]		1.8 (0.46 to 3.16)
Age at enrollment (years)	≥2 to ≤5	2.1 (-2.71 to 6.95)
	≥6 to ≤12	1.1 (-0.32 to 2.54)
	≥13 to ≤21	1.8 (-1.06 to 4.57)
Duration of current SMN-targeted treatment (years)	≤2	2.9 (-1.41 to 7.19)
	>2 to ≤4	1.7 (-2.22 to 5.62)
	>4 to ≤6	0.8 (-0.95 to 2.50)
	>6	1.9 (-0.96 to 4.85)
Time since SMA symptom onset (years)	≤5	2.1 (-2.01 to 6.17)
	>5 to ≤10	0.8 (-0.79 to 2.43)
	>10	1.7 (-0.50 to 3.96)
Baseline HFMSE score (total score)	≤20	0.8 (-0.68 to 2.22)
	≥21 to ≤30	1.6 (-2.32 to 5.47)
	≥31	2.6 (0.49 to 4.80)

[a]Apitegromab results represent a combined dose analysis (10 and 20 mg/kg). [b]Population aged 2-21 years.
CI, confidence interval; HFMSE, Hammersmith Functional Motor Scale–Expanded; LS, least squares; SMA, spinal muscular atrophy; SMN, survival motor neuron.

- Across all subgroups and subgroup categories, dual-modality apitegromab + SMN-targeted treatment consistently outperformed SMN-targeted treatment alone in motor function changes from baseline to Month 12 (**Figure 2A-D**)
- Across age groups, apitegromab consistently outperformed SMN-targeted treatment alone, demonstrating maintenance or improvement from baseline in motor function; patients aged ≥6 to ≤12 years saw motor function stabilization compared with decline among participants who received SMN-targeted treatment alone (**Figure 2A**)
- Among patients with ≤2, >2 to ≤4, or >6 years of prior SMN-targeted treatment, apitegromab treatment was associated with greater HFMSE score increases from baseline than with SMN-targeted treatment alone; among patients with >4 to ≤6 years of prior SMN-targeted treatment, motor function was maintained for those receiving apitegromab compared with a numerical decline among those receiving SMN-targeted treatment alone (**Figure 2B**)
- HFMSE score improvements with apitegromab were greatest among patients who initiated apitegromab treatment ≤5 years after symptom onset; patients who initiated apitegromab treatment >5 years after symptom onset saw motor function stabilization or improvement compared with declines among participants who received SMN-targeted treatment alone (**Figure 2C**)
- Apitegromab was associated with stabilization of motor function among patients with lower motor function at baseline (HFMSE score ≤20) and motor function improvements among patients with greater baseline function (HFMSE score ≥21) compared with maintenance or decline of HFMSE scores among participants receiving SMN-targeted treatment alone (**Figure 2D**)

Figure 2. Subgroup analyses of apitegromab efficacy at 12 months according to baseline characteristics of age at enrollment, duration of current SMN-targeted treatment, years since SMA symptom onset, and baseline HFMSE score[a]



[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. Apitegromab results represent a combined dose (10 and 20 mg/kg) analysis. [b]Years on current SMN-targeted treatment were calculated as (date of first study drug - current SMN-targeted treatment start date)/(365.25). [c]Years since SMA symptom onset was calculated as age at screening (years) - age at SMA symptom onset (years).
HFMSE, Hammersmith Functional Motor Scale–Expanded; LS, least squares; MMRM, mixed model for repeated measures; SE, standard error; SMA, spinal muscular atrophy; SMN, survival motor neuron.

CONCLUSIONS

- Post hoc analyses of data from the Phase 3 SAPPHIRE trial illustrate that 12 months of apitegromab treatment conferred functional benefits regardless of patient age, duration of current SMN-targeted treatment, time since symptom onset, or functional status, and mitigates functional declines seen in the absence of a muscle-targeted treatment
- Although sample sizes in each subgroup category were relatively small, benefits of muscle-targeted treatment with apitegromab were consistently greater, especially when apitegromab treatment was initiated early in a patient's disease journey
- These insights may help set treatment expectations for patients with SMA and their caregivers

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Acknowledgments

- We are grateful to the patients who participated in the study and to their families, caregivers, healthcare professionals, and patient advocacy groups for their dedication and support.
- Medical writing and editorial support were provided by Kevin Corcoran, PhD, and Dena McWain of Helios Global Group, and funded by Scholar Rock.
- Project management support was provided by Taryn Bosquez-Berger, PhD, CMPP, of Scholar Rock.

Disclosures

LS has received grants and personal fees from AveXis/Novartis Gene Therapies, Biogen, Biohaven, Roche, and Scholar Rock and personal fees from argenx and NMD Pharma. **AS** is a principal investigator of the Scholar Rock,-sponsored Phase 3 SAPPHIRE trial, a paid consultant for Scholar Rock, and has received personal compensation from Audentes and Biogen. **JMK** 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. **VAS** has served as a consultant, participated in teaching activities, and received honoraria from Biogen, Novartis, and Roche. **EM** has received personal compensation for clinical trial consulting and serving on scientific advisory boards and received research funding from Novartis Gene Therapies. **TB**, **CW**, **LL**, and **MG** are employees of and stockholders in Scholar Rock. **TOC** is the lead principal investigator of the Scholar Rock-sponsored Phase 2 TOPAZ trial and a consultant and/or advisory board member for AveXis/Novartis Gene Therapies, Biogen, Pfizer, and Roche/Genentech.

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Presented at the Muscular Dystrophy Association Clinical & Scientific Conference | March 8-11, 2026 | Orlando, FL

Email: medicalinformation@scholarrock.com