Apitegromab in spinal muscular atrophy: Baseline characteristics of participants enrolled in the phase 3 SAPPHIRE study

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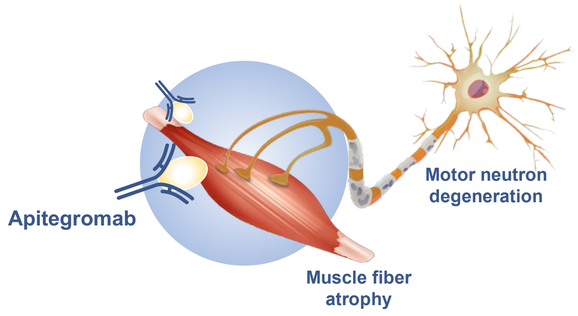
Thomas Crawford[1], Laurent Servais[2], Jena Krueger[3], Heike Kölbel[4], Marta Gomez Garcia[5], Claude Cances[6], Nancy Kuntz[7], Richard Finkel[8], Bert Yao[9], Guolin Zhao[9], Jing Marantz[9], Basil Darras[10], Eugenio Mercuri[11]

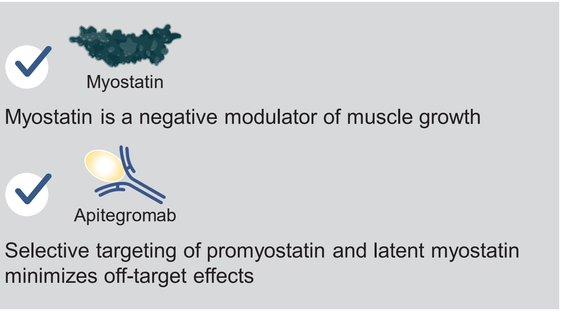
[1]Department of Neurology, Johns Hopkins Medical, Baltimore, MD, USA; [2]Department of Pediatrics, University of Oxford, Headington, Oxford, UK; [3]Helen Devos Children's Hospital Neurology-Grand Rapids, Grand Rapids, MI, USA; [4]Department of Pediatric Neurology, Centre for Neuromuscular Disorders, Center for Translational Neuro- and Behavioral Sciences, University Hospital Essen, Essen, Germany; [5]Institut de Myologie, I-Motion Clinical Trials Platform, Paris, France; APHP, Pediatric Neurology Department, Hôpital Armand Trousseau, Centre Référent pour les Maladies Neuromusculaires Nord/Est/Ile de France, Paris, France; APHP, Pediatric Neurology and ICU Department, Université Paris Saclay, DMU Santé de l'Enfant et de l'Adolescent, Hôpital Raymond Poincaré, Garches, France; [6]AOC (Atlantic-Oceania-Caribbean) Reference Centre for Neuromuscular Disorders, Paediatric Clinical Research Unit/Paediatric Multi-Thematic Module CIC 1436, Neuropaediatric Department, Toulouse University Hospital, Toulouse, France; [7]Division of Neurology, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA; Department of Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [8]Center for Experimental Neurotherapeutics St. Jude Children's Research Hospital, Memphis, TN, USA; [9]Scholar Rock, Inc., Cambridge, MA, USA; [10]Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA; [11]Centro Clinico Nemo, U.O.C. Neuropsichiatria Infantile Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy; Pediatric Neurology Unit, Catholic University, Rome, Italy

Introduction

- Spinal muscular atrophy (SMA) is a progressive genetic neuromuscular disorder characterized by the loss of motor neurons in the spinal cord and brain stem, which results in neurodegeneration, skeletal muscle atrophy, and weakness[1,2]
- Current SMA therapies target motor neurons; however, motor function deficits remain due to muscle atrophy[3]
- 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**)[4,5]

Figure 1. Mechanism of action of apitegromab





Objective

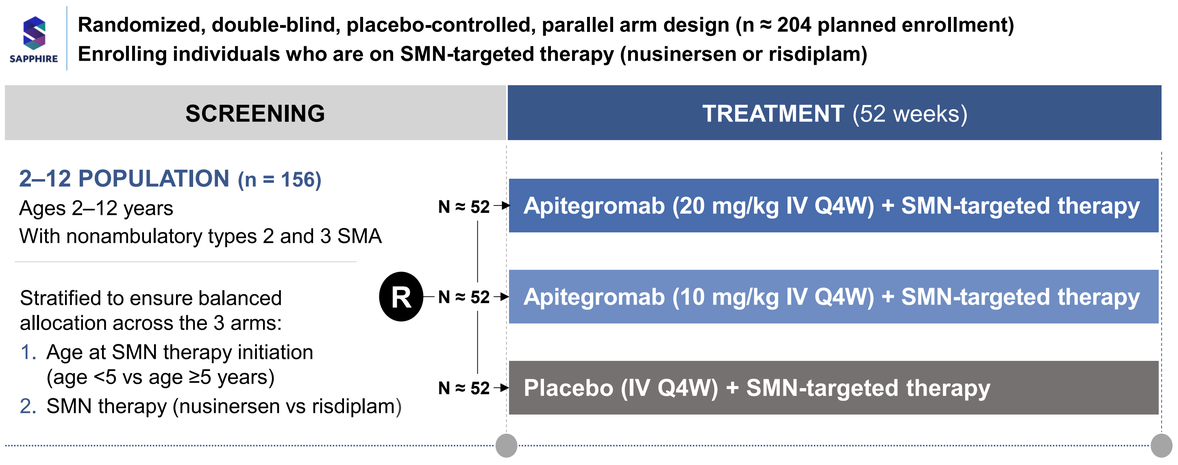
- To report the Baseline characteristics of participants enrolled in the phase 3 SAPPHIRE (NCT05156320) study evaluating the efficacy and safety of apitegromab

Methods

Study design

- SAPPHIRE (NCT05156320) is a randomized, double-blind, placebo-controlled phase 3 trial evaluating apitegromab in nonambulatory individuals with type 2 or 3 SMA who are receiving survival motor neuron (SMN)-targeted therapy
- The efficacy and safety of apitegromab will be evaluated in 2 separate populations: one including participants aged 2 to 12 years (2–12) and the other with participants aged 13 to 21 years (13–21)
  - Eligible participants were enrolled and randomized to receive apitegromab or placebo treatment every 4 weeks (Q4W) for 12 months (**Figure 2**)
  - The primary objective is to assess change from baseline in Hammersmith Functional Motor Scale Expanded (HFSME) total score at 12 months in the 2–12 population, and key secondary objectives are to assess endpoints including change from baseline in Revised Upper Limb Module (RULM) total score and change from baseline in the number of World Health Organization (WHO) motor milestones attained
  - The same motor function assessments were carried out in the 13–21 population

Figure 2. Study design



Efficacy and safety assessments will be conducted throughout the study.

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; PK/PD, pharmacokinetics/pharmacodynamics; Q4W, every 4 weeks;
R, randomization; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy; SMN, survival motor neuron; WHO, World Health Organization.

Motor assessments

- Motor function capabilities were assessed via the HFMSE, the RULM, and WHO motor milestones (**Figure 3**)
- Presented results are based on a data cut of date of 19 August 2024

Figure 3. Assessments used to evaluate motor function in participants

Motor function assessment		Clinical utility
HFMSE[6-8]	Assessment of 33 items of motor function; combines the original 20-item HFMS assessment with 13 items related to lying/rolling, crawling, kneeling, standing, and walking/running/jumping from the GMFM	Motor function
RULM[9]	Assessment of 20 items of upper limb function; scorable items (19) test movements related to everyday life (eg, placing hands from lap, pressing a button, picking up a token) in nonambulatory individuals with SMA	Upper limb motor function
WHO motor milestones[10]	Assessment of 6 gross motor milestones (walking alone, standing alone, walking with assistance, hands and knees crawling, standing with assistance, sitting without support)	Motor development

GMFM, Gross Motor Function Measure; HFMS, Hammersmith Functional Motor Scale; HFMSE, Hammersmith Functional Motor Scale Expanded; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy; WHO, World Health Organization.

Results

Participants

- At baseline (n = 188), mean age was 7.8 years for the 2–12 population and 15.8 years for the 13–21 population; mean age of SMA onset was 1.0 and 1.5 years for the 2–12 and 13–21 populations, respectively (**Table 1**)

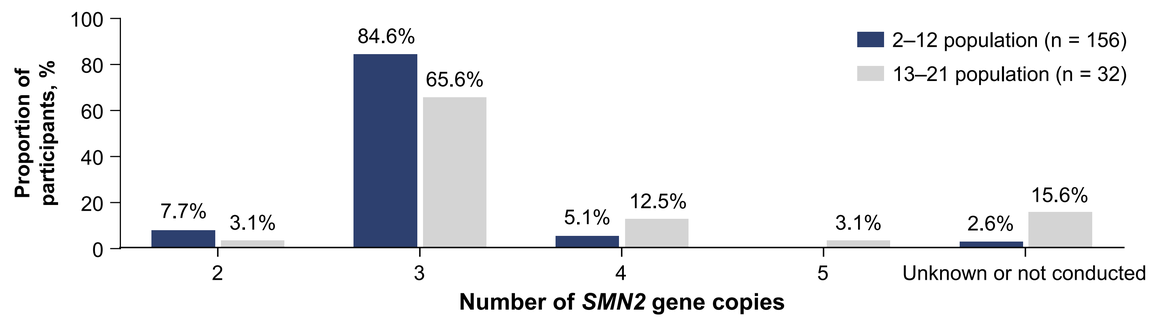
Table 1. SAPPHIRE participant demographics and baseline characteristics

Baseline characteristics	2–12 population (n = 156)	13–21 population (n = 32)
Age (years) at screening		
Mean ± SD	7.8 ± 2.50	15.8 ± 2.37
Median (min, max)	8.0 (2.0, 12.0)	15.5 (13.0, 21.0)
Ethnicity, n (%)[a]		
Hispanic or Latino	11 (7.1)	2 (6.3)
Not Hispanic or Latino	131 (84.0)	27 (84.4)
Not reported/unknown	14 (9.0)	3 (9.4)
Sex, n (%)		
Male	82 (52.6)	12 (37.5)
Female	74 (47.4)	20 (62.5)
SMA type, n (%)		
Type 2	139 (89.1)	15 (46.9)
Type 3	17 (10.9)	17 (53.1)
Age of SMA onset (years)		
Mean ± SD	0.99 ± 0.462	1.48 ± 0.810
Median (min, max)	0.96 (0.2, 3.0)	1.25 (0.6, 5.0)
Age at initiation of SMN therapy (years)		
Mean ± SD	3.17 ± 1.602	10.95 ± 3.841
Median (min, max)	3.00 (0.6, 8.4)	10.88 (3.5, 19.7)
SMN-targeted therapy at randomization, n (%)		
Nusinersen	121 (77.6)	18 (56.3)
Risdiplam	35 (22.4)	14 (43.8)
Duration of nusinersen prior to study drug exposure, (years)		
n	121	18
Mean ± SD	5.06 ± 1.887	6.13 ± 2.365
Median (min, max)	5.09 (0.9, 10.8)	5.79 (3.1, 11.3)
Duration of risdiplam prior to study drug exposure, (years)		
n	35	14
Mean ± SD	3.08 ± 1.910	3.64 ± 1.989
Median (min, max)	2.45 (0.6, 6.1)	3.59 (0.6, 6.3)
Baseline contractures status, n (%)		
Yes	135 (86.5)	32 (100)
Severe contractures in at least 1 location	10 (6.4)	7 (21.9)
No	21 (13.5)	0 (0)
Disease history of scoliosis, n (%)		
Yes	111 (71.2)	28 (87.5)
No	45 (28.8)	4 (12.5)

Percentages were calculated based on the number of participants in the randomized set within each population.
[a]Ethnicity is not collected in France and therefore not reported.
2–12, population aged 2 to 12 years; 13–21, population aged 13 to 21 years; max, maximum; min, minimum; SD, standard deviation; SMA, spinal muscular atrophy; SMN, survival motor neuron.

- Within each study population, over 60% had 3 *SMN2* gene copies (**Figure 4**)

Figure 4. *SMN2* gene copy number

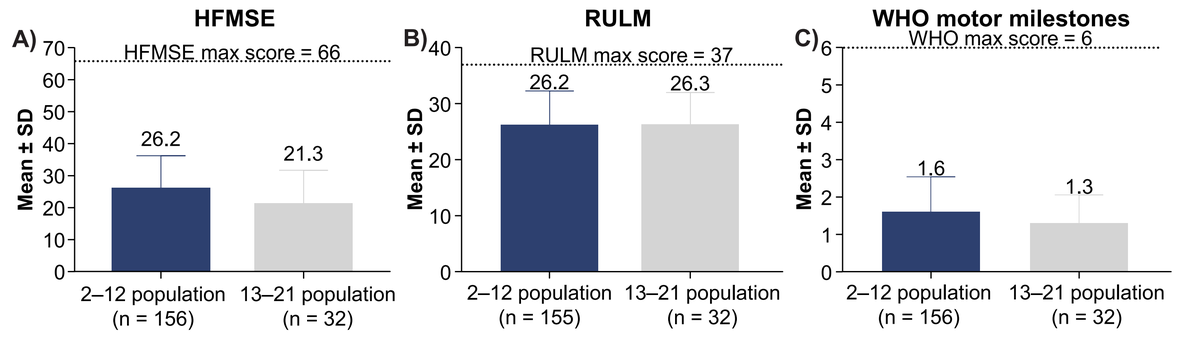


Percentages were calculated based on the number of participants with each *SMN2* gene copy number and the total number of participants in each respective population. The *SMN2* gene copy number for 7 participants from the 2–12 population and 6 participants from the 13–21 population were either unknown or the copy number analysis was not conducted.
2–12, population aged 2 to 12 years; 13–21, population aged 13 to 21 years; *SMN2*, survival motor neuron 2 gene.

Baseline motor function

- Respective, mean HFMSE (**Figure 5A**) and RULM total scores (**Figure 5B**) at baseline were 26.2 and 26.2 for the 2–12 population, and 21.3 and 26.3 for the 13–21 population
- Fewer than 2 WHO motor milestones were attained during baseline assessments for each population (**Figure 5C**)

Figure 5. Baseline mean A) HFMSE total score, B) RULM total score, and C) WHO motor milestones attained



2–12, population aged 2 to 12 years; 13–21, population aged 13 to 21 years; HFMSE, Hammersmith Functional Motor Scale Expanded; RULM, Revised Upper Limb Module; SD, standard deviation; WHO, World Health Organization.

Conclusions

- Despite SMN-targeted therapy, baseline HFMSE and RULM scores and WHO milestones attained indicate motor function deficits are prevalent in our study population, illustrating the continued unmet need for individuals with SMA
- SAPPHIRE will assess whether apitegromab addresses this unmet need by directly targeting muscle atrophy to enhance motor function

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Conflicts of Interests

TC 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. **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. **HK** is serving on a scientific advisory board for AveXis and received travel expenses and speaker honoraria from Biogen, Pfizer, Roche, and Sanofi-Aventis. **MGG** serves as a scientific advisory board member for Biogen, Novartis Gene Therapies, and Roche. **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 Roche and Pfizer. **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** is a Scholar Rock, Inc., employee and stockholder. **GZ** is a Scholar Rock, Inc., employee and stockholder. **JM** is a Scholar Rock, Inc., employee and stockholder. **BD** has served as an ad hoc scientific advisory board member for AveXis/Novartis Gene Therapies, Biogen, Pfizer, Roche/Genentech, Sarepta Therapeutics, and Vertex; steering committee chair 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 received research support from the NIH/National Institute of Neurological Disorders and Stroke, the Slaney Family Fund for SMA, the Spinal Muscular Atrophy Foundation, CureSMA, and Working on Walking Fund; received grants from AveXis/Novartis Gene Therapies, Biogen for CS11, FibroGen, Ionis Pharmaceuticals for the ENDEAR, CHERISH, CS2/CS12 studies, PTC Therapeutics, Roche, Sarepta, and Scholar Rock, Inc.; and has received royalties for books and online publications from Elsevier and UpToDate. **EM** has received personal compensation for clinical trial consulting, serving on scientific advisory boards, and research funding from Novartis Gene Therapies.

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