Safety and efficacy of apitegromab in nonambulatory type 2 or type 3 spinal muscular atrophy (SAPPHIRE): a phase 3, double-blind, randomised, placebo-controlled trial

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Summary

Background Approved spinal muscular atrophy therapies greatly improve clinical outcomes; however, substantial motor function deficits persist. Apitegromab, a fully human monoclonal antibody, selectively inhibits myostatin activation, improving muscle function. We aimed to assess the safety and efficacy of apitegromab in patients with nonambulatory type 2 or type 3 spinal muscular atrophy receiving nusinersen or risdiplam.

Methods SAPPHIRE, a double-blind, placebo-controlled, phase 3 trial, was done in 48 hospitals in Belgium, France, Germany, Italy, Poland, Spain, the Netherlands, the UK, and the USA. Eligible participants were aged 2–21 years, had genetically documented SMN-deficient nonambulatory type 2 or type 3 spinal muscular atrophy, an estimated life expectancy greater than 2 years, Hammersmith Functional Motor Scale-Expanded (HFMSE) scores 10–45, and had received at least 10 months' nusinersen or at least 6 months' risdiplam therapy at screening. Participants aged 2–12 years were randomly assigned 1:1:1 to receive apitegromab 20 mg/kg, apitegromab 10 mg/kg, or placebo every 4 weeks; participants aged 13–21 years were randomly assigned 2:1 to receive apitegromab 20 mg/kg or placebo every 4 weeks. All participants, parents or caregivers, investigators, and site personnel were unaware of the treatment assignment. The primary endpoint, change from baseline in HFMSE at 12 months, was assessed in participants aged 2–12 years who received at least one dose of apitegromab or placebo and had at least one post-baseline evaluable HFMSE assessment (modified intention-to-treat set). Comparisons of the combined apitegromab dose (20 mg/kg and 10 mg/kg) versus placebo and the 20 mg/kg dose versus placebo were done with a mixed-effects model with repeated measurement. Safety was analysed in all participants who received at least one dose of apitegromab or placebo through evaluation of adverse events, physical examinations, vital signs and cardiac assessments, laboratory evaluations, and concomitant medications. SAPPHIRE is registered with ClinicalTrials.gov, NCT05156320, and is completed.

Findings From March 28, 2022, to Sept 4, 2024, we enrolled 188 patients (156 in the population aged 2–12 years and 32 in the population aged 13–21 years); of whom 128 participants received apitegromab and 60 participants received placebo. At 12 months, least squares mean difference in HFMSE change from baseline was 1·8 (95% CI 0·30 to 3·32, p=0·019) points for participants aged 2–12 years receiving apitegromab versus placebo (least squares mean 0·6 *vs* –1·2). Least squares mean difference in HFMSE change from baseline was 1·4 (95% CI –0·34 to 3·13; p=0·11) for apitegromab 20 mg/kg versus placebo (least squares mean 0·2 *vs* –1·2). The incidence and severity of adverse events were similar between apitegromab and placebo, and consistent with spinal muscular atrophy and background spinal muscular atrophy therapy. The most frequently reported adverse events were pyrexia (apitegromab, 33 [26%] of 128 *vs* placebo, 17 [28%] of 60), nasopharyngitis (32 [25%] *vs* 14 [23%]), cough (30 [23%] *vs* 12 [20%]), vomiting (29 [23%] *vs* ten [17%]), upper respiratory tract infection (28 [22%] *vs* 18 [30%]), and headache (27 [21%] *vs* 12 [20%]). No patients discontinued due to adverse events.

Interpretation Participants in the apitegromab treatment groups (combined 20 mg/kg and 10 mg/kg dose) achieved statistically significant improvements in motor function compared with placebo; however, the least squares mean difference was not significant between apitegromab 20 mg/kg and placebo. Overall, SAPPHIRE results build on findings from the phase 2 TOPAZ trial, showing improved motor function with a generally well tolerated safety profile, supporting the use of muscle-targeting therapy for spinal muscular atrophy.

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Research in context

Evidence before this study

We searched PubMed for articles from database inception to June 4, 2025, using the search term "myostatin inhibitor". The results were then filtered to only include articles that reported clinical trial data, which provided an output of 26 articles. Of the 26 articles, 18 were confirmed to have evaluated an anti-myostatin compound, 15 of which assessed the physiological role of myostatin in regulating muscle mass and seven reported clinical evidence in neuromuscular diseases. Despite decades of collective effort across academia and industry, targeting myostatin has not yielded the desired success due to either undesirable toxic effects as a result of a lack of selectivity in the approach, absence of efficacy, or suboptimal selection of disease or patient groups that undermined trial power. Currently, there are no approved muscle-targeted therapies for patients with any genetic or acquired neuromuscular diseases.

Currently approved therapies for spinal muscular atrophy target motor neuron degeneration by increasing the expression and function of the SMN protein, critical to the survival and function of motor neurons, thus slowing disease progression. These therapies do not, however, address the accompanying muscle atrophy that accumulates due to delayed treatment or insufficient correction of SMN deficiency. As a result, patients receiving SMN-targeted therapy experience persistent functional deficits, and preliminary long-term outcome data for patients with spinal muscular atrophy suggest further, additional loss of motor function might accumulate over time. Consequently, a substantial unmet need remains for a therapeutic strategy that improves motor function independent of motor neuron degeneration. A muscle-targeted therapy complementing SMN-targeted therapies could effectively address this unmet need. Proof of concept of this approach was established with apitegromab, a fully human monoclonal antibody that inhibits activation of latent myostatin and enables muscle growth. Initiating in 2019 and published in 2024, the phase 2 TOPAZ trial and its extension phase (NCT03921528) showed regular treatment with apitegromab was associated with improved motor function outcomes in patients with nonambulatory type 2 or 3 spinal muscular atrophy over 48 months.

Added value of this study

In this phase 3 SAPPHIRE trial, we present level 1 evidence that apitegromab treatment resulted in statistically and potentially clinically meaningful improvements in motor function compared with placebo in nonambulatory type 2 or type 3 spinal muscular atrophy. The SAPPHIRE trial is the first placebo-controlled clinical study to show functional benefit of selective myostatin inhibition in any disease. Furthermore, by targeting structurally distinct myostatin precursor forms, apitegromab avoids off target effects associated with blocking growth factors, such as growth differentiation factor 11, which is antigenically similar to mature myostatin. The benefit of this highly selective approach minimises undesirable off-target effects, which is supported by the favourable safety profile observed in the SAPPHIRE trial and by extensive literature on myostatin, including the knowledge that naturally occurring myostatin mutations in multiple species have no long-term negative outcomes.

Implications of all the available evidence

Given the significant unmet need—ie, muscle atrophy that current therapies do not address—and the early evidence indicating ongoing and worsening motor deficits in patients treated with SMN-targeted therapies, the results from the SAPPHIRE trial are encouraging. The findings support the potential of muscle-targeted therapies to benefit people with spinal muscular atrophy across a wide range of ages and functional abilities.

Introduction

Spinal muscular atrophy is a genetic neuromuscular disorder characterised pathologically by degeneration of motor neurons in the spinal cord and brain stem and clinically by progressive weakness and atrophy of skeletal muscles.[1] Spinal muscular atrophy is caused by biallelic deletions or mutations of the survival motor neuron 1 (*SMN1*) gene, resulting in deficiency of SMN protein expression.[1] *SMN2*, an *SMN1* paralog, partly compensates for loss of protein expression from pathological variants of *SMN1*; genotypes with increased *SMN2* copy numbers are associated with decreased clinical severity.[2]

The natural history of spinal muscular atrophy has been substantially altered by the availability of SMN-targeted therapies that enhance SMN protein expression and slow disease progression.[3–5] Although clinical outcomes have improved, SMN-targeted therapies focus on the SMN protein, which is crucial to the survival and function of motor neurons; however, they do not address accompanying muscle atrophy, a key component of spinal muscular atrophy disease pathology. The benefit of SMN-targeted therapies is constrained by the level of pretreatment neurodegeneration due to degenerative changes in utero, delayed diagnosis, or delayed treatment.[6–8] Treated patients thus often manifest persistent motor function deficits of widely ranging severity, commensurate to the degree of pretreatment pathology.[8]

After motor neuron degeneration onset, spinal muscular atrophy skeletal muscle is comprised of a mixture of nonfunctioning denervated muscle fibres and normally functioning innervated muscle fibres,[9] which can lead to persistent functional deficits and continued loss of function over time. This point has been suggested by emerging long-term clinical outcomes data showing that following improvement of motor function in the initial 2–4 years, over time, patients with spinal muscular atrophy experience progressive loss of motor

function despite continuance of SMN-targeted therapy.[10,11] Patients participating in recent and ongoing clinical studies continue to have baseline Hammersmith Functional Motor Scale-Expanded (HFMSE) scores far below their healthy counterparts, further highlighting the substantial unmet need.[12] A muscle-targeted therapy complementing SMN-targeted therapies is therefore needed to address pathological changes that are independent of SMN protein deficit.[13]

Apitegromab is an investigational, fully human monoclonal antibody that promotes increased muscle mass and strength by binding to inactive myostatin precursors, promyostatin, and latent myostatin.[14] This high-affinity and high-specificity binding prevents cleavage and release of mature, active myostatin, a negative regulator of muscle mass.[14,15] Apitegromab binding to myostatin precursors causes extracellular release of inactive latent myostatin, providing an intermediate pharmacodynamic measure of target engagement.[14] In animals and humans, null mutations in the gene encoding myostatin lead to increased muscle microfibre size and strength throughout life without long-term negative outcomes.[15,16] Apitegromab differs from previous myostatin-targeting agents by selectively targeting structurally distinct myostatin precursors, thus minimising undesirable effects associated with off-target inhibition of similar myostatin family members such as growth differentiation factor 11.[14]

The phase 2 TOPAZ trial (NCT03921528) evaluated long-term safety and efficacy of apitegromab in patients aged 2–21 years with spinal muscular atrophy receiving nusinersen or no SMN-targeted therapy. Improvement in motor function, as measured by HFMSE and Revised Upper Limb Module (RULM), was observed in most patients after the primary 12-month treatment period, with dose-response shown in a cohort randomly assigned to apitegromab 2 mg/kg or 20 mg/kg.[12] Updated results showed sustained motor function improvement over the 36-month extension period with 20 mg/kg; treatment was associated with a favorable safety profile.[17]

In this phase 3, multicentre, double-blind, placebo-controlled trial, we evaluated the safety, efficacy, and improvement in motor function of apitegromab in nonambulatory individuals aged 2–21 years with type 2 or type 3 spinal muscular atrophy receiving nusinersen or risdiplam.

Methods

Study design

SAPPHIRE (NCT05156320) was a phase 3, 52-week, double-blind, placebo-controlled trial done at 48 hospitals in nine countries (Belgium, France, Germany, Italy, Poland, Spain, the Netherlands, the UK, and the USA). The SAPPHIRE protocol was approved by the institutional review board or independent ethics committee at participating sites (appendix p 3) and adhered to the Declaration of Helsinki and Good Clinical Practice guidelines. The authors and sponsor are actively working to share the protocol and statistical analysis plan through ClinicalTrials.gov.

Participants

Participants were recruited by the principal investigators (appendix p 3) and were screened for eligibility. Eligible participants with genetically documented SMN-deficient nonambulatory type 2 or type 3 spinal muscular atrophy were aged 2–21 years, had an estimated life expectancy greater than 2 years, HFMSE scores between 10 and 45, and had received at least 10 months of nusinersen or at least 6 months of risdiplam therapy at screening. Key exclusion criteria were previous treatment with onasemnogene abeparvovec-xioi or apitegromab, history of severe hypersensitivity reactions to nusinersen or risdiplam, or severe scoliosis or contractures, defined as common terminology criteria for adverse events grade 3 or anticipated to be unstable or likely to impact trial motor function assessment (full list in protocol). Written informed consent was obtained from participants or a parent or legal guardian before enrolment.

Randomisation and masking

Patients aged 2–12 years were randomly assigned (1:1:1) to receive apitegromab 10 mg/kg, apitegromab 20 mg/kg, or placebo every 4 weeks with randomisation stratified according to SMN-targeted therapy and age at therapy initiation (≥5 and <5 years). Patients aged 13 to 21 years were randomly assigned 2:1 to receive apitegromab 20 mg/kg every 4 weeks or placebo with randomisation stratified by SMN-targeted therapy. Randomisation was performed using an interactive web-based system. The trial team, participants, parents or caregivers, investigators, and site personnel, apart from the designated unblinded roles, were unaware of the treatment assignment. Site pharmacists preparing the treatment were aware of the treatment assignment. Pharmacokinetics, pharmacodynamics, and immunogenicity contain unblinding or potential unblinding information and therefore were restricted to the unblinded roles for samples handling, testing, and results. Data were collected and entered by the site investigators into an electronic data capture system that was verified by trial monitors. Safety data were reviewed approximately every 4 months on an ongoing basis by an independent data monitoring committee (appendix p 3) in an unblinded manner and by the medical monitor and sponsor in a blinded manner. If, for any reason, sponsor personnel needed to be made aware of the treatment assignment, the list of personnel and the reason for unblinding were documented.

Procedures

Participants received up to 13 doses of apitegromab or placebo by intravenous infusion every 4 weeks through 12 months at the clinical site. For the first two dosing

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See **Online** for appendix

sessions infusions lasted approximately 2 h, whereafter participants were monitored onsite for a maximum of 2 h for hypersensitivity reactions and contacted by telephone within 7 days for a safety check-in. If no acute infusion reactions occurred after the first two dosing sessions, and the investigator determined the participant's safety would not be at risk, the infusion duration could be reduced to less than 2 h (≥1 h) for subsequent doses. Motor assessments were conducted by the site clinical evaluator before dosing on study days 1, 57, 113, 169, 225, 281, and 365. Participants who completed the 12-month treatment period were offered the option to enroll in an open-label extension study (NCT05626855). Those who opted not to enroll were followed up for a 20-week safety follow-up period after study day 365.

Outcomes

The primary efficacy endpoint was change from baseline in HFMSE total score at 12 months in the population aged 2–12 years for apitegromab versus placebo. The HFMSE is a 33-item measure of motor function that is specifically developed and validated for assessing motor function in individuals with type 2 or type 3 spinal muscular atrophy. Each activity is scored on a scale ranging from 0 to 2 (0, unable; 1, performed with modification; 2, performed without modification). Total scores range from 0 to 66 points, with an increase in total score indicating motor function improvements.[18]

Secondary endpoints assessed at 12 months in the population aged 2–12 years were change from baseline in RULM total score (range 0–37; higher scores demonstrate better upper limb function),[19] proportion of participants who achieved at least a 3-point change from baseline in HFMSE total score,[20] and change from baseline in the number of WHO development motor milestones attained[21] for apitegromab 20mg/kg versus placebo; and change from baseline in HFMSE total score, change from baseline in RULM total score, proportion of participants who achieved at least a 3-point change from baseline in HFMSE total score and change from baseline in the number of WHO development motor milestones attained for apitegromab 10mg/kg versus placebo.[21] Additional prespecified exploratory endpoints included motor function outcomes for HFMSE, RULM, and WHO motor milestones, assessed in the pooled population aged 2–21 years. Prespecified pharmacokinetic and pharmacodynamic assessments were conducted throughout the trial for all participants who received at least one dose of apitegromab or placebo. Safety, including adverse events and their severity grade, were also evaluated in these participants.

Sample size determination

With a two-sided α=0·05, assuming 50 patients per group, the trial would yield at least 80% power to detect a mean difference of 3 points (SD 5) in the change from baseline in HFMSE between the apitegromab (20 mg/kg or 10 mg/kg) and placebo groups, and 90% power between the apitegromab combined dose and placebo groups.

For the population aged 2–12 years, approximately 156 patients were to be randomly assigned 1:1:1 to receive apitegromab 10 mg/kg, apitegromab 20 mg/kg, or placebo so that approximately 150 evaluable patients complete the visit 14 assessments. For the population aged 13–21 years, a maximum of 48 patients were to be randomly assigned 2:1 to receive apitegromab 20 mg/kg or placebo. This sample size is based on practical considerations.

Statistical analyses

The primary objective of SAPPHIRE was to assess the efficacy of apitegromab compared with placebo using HFMSE in the population aged 2–12 years. As modeling and simulations based on the phase 2 trial data suggested similar target engagement and efficacy between apitegromab 20 mg/kg and 10 mg/kg doses, two hypotheses were evaluated as the primary confirmatory test: (1) apitegromab combined dose (20 mg/kg and 10 mg/kg) versus placebo and (2) apitegromab 20 mg/kg versus placebo, with the Hochberg procedure used for multiplicity adjustment.

Primary analyses of the efficacy endpoints were performed in the modified intention-to-treat (mITT) set that included participants within the population aged 2–12 years who received at least one dose of apitegromab or placebo and had at least one postbaseline evaluable HFMSE assessment. The primary efficacy endpoint, change from baseline in HFMSE at 12 months, was analysed using a mixed-effects model with repeated measurement (MMRM). The model included the fixed effects of treatment, visit, treatment-by-visit interaction, baseline HFMSE total score, baseline HFMSE total score-by-visit interaction, type of SMN-targeting therapy at randomisation (ie, nusinersen or risdiplam), and age at initiation of SMN-targeted therapy (≥5 and <5 years). An unstructured covariance structure was used to model the within-patient variability. Given no deaths occurred in this study, all missing values were handled by MMRM under the missing at random assumption. Subgroup analyses were conducted to measure consistency of treatment across predefined groups.

The secondary efficacy endpoints change from baseline in RULM at 12 months and WHO milestones were also assessed using the MMRM models in the population aged 2–12 years. The proportion of participants achieving at least a 3-point change in HFMSE at 12 months was compared using a logistic regression model in the population aged 2–12 years.

A hierarchical testing strategy was used to control the overall significance level at α=0·05 for analysis of the primary and secondary efficacy endpoints in the population aged 2–12 years (appendix p 5). The two tests in the primary test are considered one step per the Hochberg procedure, and each subsequent test is

considered one step. Secondary endpoints were only tested if the two tests in the primary test were significant at the 0·05 level. For the following steps, if significance was not achieved for a preceding step within the testing hierarchy, the hierarchical testing approach stopped, and the subsequent tests were interpreted in an exploratory manner.

Prespecified analyses were performed for the same outcome measures for the pooled population aged 2–21 years to evaluate treatment consistency across age groups and are to be interpreted in an exploratory manner. Subgroup analyses were conducted to measure consistency of treatment across predefined groups.

Safety was analysed through evaluation of adverse events, physical examinations, vital signs assessments, cardiac assessments, laboratory evaluations, and concomitant medications in all treated participants and were descriptively summarised by treatment. Statistical analyses were conducted using SAS (version 9.4). SAPPHIRE is registered with ClinicalTrials.gov, NCT05156320, and is completed.

Role of the funding source

The funder of the trial was responsible for the trial design, statistical analysis plan, study drug procurement, trial management, and oversaw the trial conduct and including oversight of data collection and data analysis.

Results

A total of 188 patients were enrolled and randomly assigned (figure 1). Dosing began on April 14, 2022, and the last visit was Sept 4, 2024. At the data cutoff,

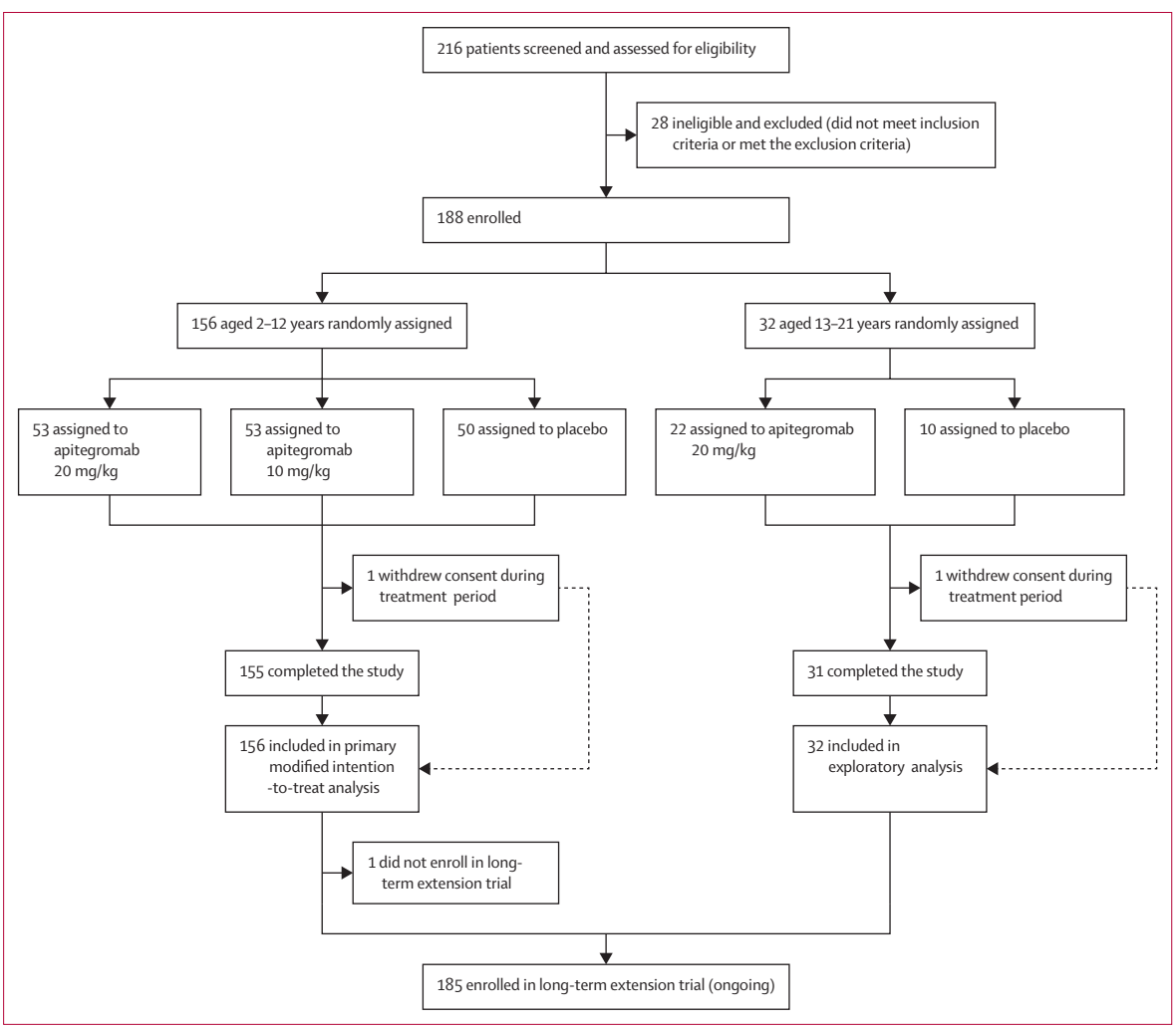

Figure 1: **Trial profile**
Before enrolment, 216 individuals were screened. Of these 216 individuals, 28 had screening failures. Randomisation was stratified by type of background SMN-targeted therapy (nusinersen or risdiplam) and age at initiation of nusinersen or risdiplam therapy (≥5 years and <5 years) for the population aged 2–12 years, and by type of background SMN-targeted therapy (nusinersen or risdiplam) for the population aged 13–21 years. Enrolled patients assigned to the population aged 2–12 years were randomly assigned 1:1:1 to apitegromab 20 mg/kg, 10 mg/kg, or placebo; those assigned to the population aged 13–21 years were randomly assigned 2:1 to receiving apitegromab 20 mg/kg or placebo treatment. SMN=survival motor neuron.

155 (99%) of 156 participants aged 2–12 years completed the 12-month treatment period. Completion rates were similar for the population aged 13–21 years (31 [97%] of 32). Two patients receiving apitegromab 20 mg/kg, including one aged 2–12 years and one aged 13–21 years, withdrew consent and discontinued from the trial; neither discontinuation was due to adverse events. By the end of the 12-month treatment period, 185 (98%) of 188 SAPPHIRE participants opted to enroll in the long-term extension (NCT05626855).

The SAPPHIRE trial population was broadly representative of the spinal muscular atrophy population

	Population aged 2–12 years				Population aged 13–21 years		Population aged 2–21 years	
	Placebo (n=50)	Combined (n=106)	20 mg/kg (n=53)	10 mg/kg (n=53)	Placebo (n=10)	20 mg/kg (n=22)	Placebo (n=60)	Combined (n=128)
Age at screening, years								
Mean (SD)	8 (2)	8 (3)	8 (2)	7 (3)	15 (2)	16 (3)	9 (4)	9 (4)
Range	3–12	2–12	2–12	2–12	13–18	13–21	3–18	2–21
Sex								
Female	25 (50%)	49 (46%)	26 (49%)	23 (43%)	5 (50%)	15 (68%)	30 (50%)	64 (50%)
Male	25 (50%)	57 (54%)	27 (51%)	30 (57%)	5 (50%)	7 (32%)	30 (50%)	64 (50%)
Race								
Asian	2 (4%)	6 (6%)	4 (8%)	2 (4%)	0	0	2 (3%)	6 (5%)
Black or African American	1 (2%)	1 (1%)	0	1 (2%)	0	2 (9%)	1 (2%)	3 (2%)
White	41 (82%)	75 (71%)	40 (75%)	35 (66%)	6 (60%)	14 (64%)	47 (78%)	89 (70%)
Other	1 (2%)	3 (3%)	0	3 (6%)	0	0	1 (2%)	3 (2%)
Not reported or unknown	5 (10%)	21 (20%)	9 (17%)	12 (23%)	4 (40%)	6 (27%)	9 (15%)	27 (21%)
Ethnicity								
Hispanic or Latino	2 (4%)	9 (8%)	3 (6%)	6 (11%)	0	2 (9%)	2 (3%)	11 (9%)
Not Hispanic or not Latino	46 (92%)	85 (80%)	45 (85%)	40 (75%)	9 (90%)	18 (82%)	55 (92%)	103 (80%)
Not reported or unknown	2 (4%)	12 (11%)	5 (9%)	7 (13%)	1 (10%)	2 (9%)	3 (5%)	14 (11%)
Age at spinal muscular atrophy onset, years								
Mean (SD)	1 (0·5)	1 (0·5)	1 (0·5)	1 (0·5)	1 (0·3)	2 (1)	1 (0·5)	1 (0·6)
Range	0–3	0–2	0–2	0–2	1–2	1–5	0–3	0–5
Age at initiation of SMN-targeted therapy								
<5 years	45 (90%)	91 (86%)	46 (87%)	45 (85%)	1 (10%)	2 (9%)	46 (77%)	93 (73%)
≥5 years	5 (10%)	15 (14%)	7 (13%)	8 (15%)	9 (90%)	20 (91%)	14 (23%)	35 (27%)
SMN-targeted therapy at randomisation								
Nusinersen	40 (80%)	81 (76%)	41 (77%)	40 (75%)	6 (60%)	12 (55%)	46 (77%)	93 (73%)
Risdiplam	10 (20%)	25 (24%)	12 (23%)	13 (25%)	4 (40%)	10 (45%)	14 (23%)	35 (27%)
Duration on nusinersen prior to study drug exposure, years								
Mean (SD)	6 (2)	5 (2)	5 (2)	4 (2)	7 (3)	6 (2)	6 (2)	5 (2)
Range	2–11	1–10	1–10	1–8	4–11	3–10	2–11	1–10
Duration on risdiplam prior to study drug exposure, years								
Mean (SD)	3 (2)	3 (2)	3 (2)	3 (2)	3 (2)	4 (2)	3 (2)	3 (2)
Range	1–6	1–6	1–6	1–6	1–5	1–6	1–6	1–6
Number of copies of *SMN2* gene								
2	2 (4%)	10 (9%)	4 (8%)	6 (11%)	0	1 (5%)	2 (3%)	11 (9%)
3	45 (90%)	87 (82%)	46 (87%)	41 (77%)	8 (80%)	13 (59%)	53 (88%)	100 (78%)
≥4	1 (2%)	7 (7%)	3 (6%)	4 (8%)	1 (10%)	4 (18%)	2 (3%)	11 (9%)
Unknown or not determined	2 (4%)	2 (2%)	0	2 (4%)	1 (10%)	4 (18%)	3 (5%)	6 (5%)
Disease history of scoliosis	35 (70%)	76 (72%)	38 (72%)	38 (72%)	9 (90%)	19 (86%)	44 (73%)	95 (74%)
Baseline contractures status								
Yes	42 (84%)	93 (88%)	45 (85%)	48 (91%)	10 (100%)	22 (100%)	52 (87%)	115 (90%)
Severe contractures*	3 (6%)	7 (7%)	5 (9%)	2 (4%)	1 (10%)	6 (27%)	4 (7%)	13 (10%)
SMN-targeted therapies ever received								
1	43 (86%)	91 (86%)	45 (85%)	46 (87%)	8 (80%)	20 (91%)	51 (85%)	111 (87%)
2	7 (14%)	15 (14%)	8 (15%)	7 (13%)	2 (20%)	2 (9%)	9 (15%)	17 (13%)

(Table 1 continues on next page)

	Population aged 2–12 years				Population aged 13–21 years		Population aged 2–21 years	
	Placebo (n=50)	Combined (n=106)	20 mg/kg (n=53)	10 mg/kg (n=53)	Placebo (n=10)	20 mg/kg (n=22)	Placebo (n=60)	Combined (n=128)
(Continued from previous page)								
HFMSE total score								
Mean (SD)	27·8 (10·6)	25·5 (9·8)	25·5 (10·2)	25·5 (9·5)	22·8 (12·9)	20·6 (9·2)	27·0 (11·0)	24·7 (9·8)
Range	9–46	9–48	10–43	9–48	10–45	8–43	9–46	8–48
RULM total score								
Mean (SD)	27·3 (5·8)	25·6† (6·1)	25·7 (5·6)	25·6† (6·8)	26·3 (6·6)	26·3 (5·4)	27·1 (5·9)	25·8 (6·0)
Range	18–37	9–37	13–37	9–37	17–37	20–37	17–37	9–37
WHO motor milestones attained (median [IQR])	1·5 (1–2)	1·0 (1–2)	1·0 (1–2)	1·0 (1–2)	1·0 (1–2)	1·0 (1–2)	1·0 (1–2)	1·0 (1–2)

Baseline demographics and clinical characteristics are presented for all randomly assigned participants. Race was not collected in France and Germany and therefore not reported. Ethnicity was not collected in France and therefore not reported. Baseline HFMSE and RULM scores, and WHO motor milestones were defined as the last non-missing measurement before or on the day of the first dosing. Combined groups represent all apitegromab doses. HFMSE=Hammersmith Functional Motor Scale-Expanded. RULM=Revised Upper Limb Module. SMN=survival motor neuron. *Severe contractures were present in at least one location. †One participant from the apitegromab 10 mg/kg dose group was too young at baseline to undergo the RULM.

Table 1: **Participant baseline demographics and clinical characteristics (randomised set)**

(table 1; appendix p 15). The ratio of males to females enrolled in SAPPHIRE was 1:1 with 30 males and 30 females in the placebo group and 64 males and 64 females in the combined apitegromab group. Most participants were White (136 [72%] of 188) and not Hispanic or not Latino (158 [84%] of 188). The mean age was 9 years (range 2–21) for all enrolled participants (8 years [2–12] for the population aged 2–12 years and 16 years [13–21] for the population aged 13–21 years). A majority of participants (139 [74%] of 188) were receiving nusinersen at enrolment. Of 188 participants, 13 (7%) had two copies of the *SMN2* gene, 153 (81%) had three copies of the *SMN2* gene, and 13 (7%) had four or more copies of the *SMN2* gene. Importantly, the baseline demographics and disease characteristics were all well balanced across treatment arms.

Pharmacokinetic results showed exposure increases were dose proportional following apitegromab administration (figure 2A), and both doses had similar pharmacodynamic effect as indicated by superimposable concentrations of total latent myostatin (figure 2B). After 12 months, apitegromab treatment was associated with statistically significant and potentially clinically meaningful improvement in HFMSE total score for the population aged 2–12 years. The least squares mean difference in HFMSE change from baseline at 12 months was 1·8 points (95% CI 0·30 to 3·32; p=0·019) for apitegromab (20 mg/kg and 10 mg/kg) versus placebo (least squares mean 0·6 *vs* –1·2), favouring apitegromab (table 2, figure 2C). The least squares mean difference in HFMSE change from baseline was 1·4 (–0·34 to 3·13; p=0·11) for apitegromab 20 mg/kg versus placebo (least squares mean 0·2 *vs* –1·2). HFMSE scores increased from baseline in patients receiving apitegromab as early as the 8-week (first) post baseline observation. By contrast, HFMSE decreased in patients receiving placebo, with a change from baseline of –1·2 (SE 0·66) by week 52. The separation in HFMSE appears to widen toward the end of the treatment period (figure 2C).

	Hierarchy order	Treatment effect
Primary endpoints		
Change from baseline in HFMSE total score at 12 months—apitegromab (20 mg/kg and 10 mg/kg) *vs* placebo	1	1·8 (0·30 to 3·32); p=0·019
Change from baseline in HFMSE total score at 12 months—apitegromab 20 mg/kg *vs* placebo	1	1·4 (–0·34 to 3·13); p=0·11
Secondary endpoints		
Change from baseline in RULM total score at 12 months—apitegromab 20 mg/kg *vs* placebo	2	0·7 (–0·31 to 1·71)
Proportion of patients with ≥3-point change from baseline in HFMSE at 12 months—apitegromab 20 mg/kg *vs* placebo	3	OR 2·4 (0·82 to 7·07)
Change from baseline in number of WHO motor development milestones attained at 12 months—apitegromab 20mg/kg *vs* placebo	4	0·2 (–0·10 to 0·40)
Change from baseline in HFMSE total score at 12 months—apitegromab 10 mg/kg *vs* placebo	5	2·2 (0·49 to 3·95)
Change from baseline in RULM total score at 12 months—apitegromab 10 mg/kg *vs* placebo	6	0·6 (–0·42 to 1·61)
Proportion of patients with ≥3-point change from baseline in HFMSE at 12 months—apitegromab 10 mg/kg *vs* placebo	7	OR 3·8 (1·33 to 10·90)
Change from baseline in number of WHO motor development milestones attained at 12 months—apitegromab 10 mg/kg *vs* placebo	8	0·1 (–0·15 to 0·35)

Data are least squares mean difference (95% CI), unless otherwise indicated. HFMSE=Hammersmith Functional Motor Scale Expanded. OR=odds ratio. RULM=Revised Upper Limb Module.

Table 2: **Hierarchical testing procedure for the primary and secondary endpoints for the main efficacy population (modified intention-to-treat set)**

With α=0·05 for the two comparisons evaluated by Hochberg procedure, significance was achieved for the primary endpoint based on the comparison of apitegromab (20 mg/kg and 10 mg/kg) versus placebo with p<0·025. Given the comparison of 20 mg/kg versus placebo had p>0·05, all subsequent endpoint analyses from the hierarchical testing strategy were considered exploratory; the results are presented in table 2.

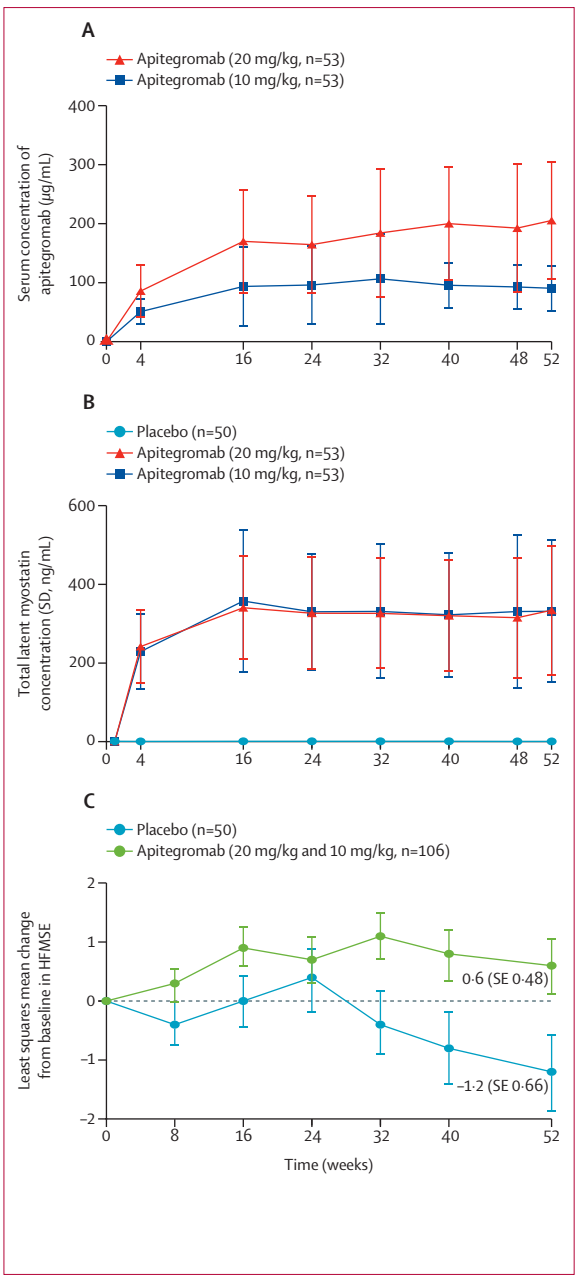

***Figure 2*: Pharmacokinetic, pharmacodynamic, and HFMSE motor function outcomes following apitegromab treatment in the population aged 2–12 years**

Geometric mean (SD) serum concentrations of apitegromab (A) and mean (SD) latent myostatin concentration over time (B). Least squares mean (SE) change from baseline in HFMSE total score for each assessment through the end of the 12-month treatment period (C). Trough concentrations of apitegromab and total latent myostatin are depicted. Pharmacokinetic samples from patients receiving placebo were not tested, therefore were not included in pharmacokinetic assessments. HFMSE=Hammersmith Functional Motor Scale-Expanded.

Prespecified exploratory analyses showed the least squares mean difference in HFMSE change from baseline was 1·8 points for both the population aged 13–21 years (95% CI −1·06 to 4·57) and the pooled population aged 2–21 years (0·46 to 3·16; appendix p 9) Additional exploratory analysis outcomes are presented in the appendix (pp 9–14).

The incidence and severity of adverse events were similar in the pooled apitegromab and placebo groups (91% and 87% overall) and generally consistent with known manifestations of underlying spinal muscular atrophy and background SMN-targeted therapy (table 3).[12] Adverse events with an incidence of at least 5% higher in patients receiving apitegromab compared with placebo included vomiting, gastroenteritis, diarrhoea, rhinorrhoea, and pneumonia. Treatment-related adverse events were similarly balanced between treatment groups in the pooled population (apitegromab, 24 [19%] of 128; placebo, 11 [18%] of 60) with headache, in nine (5%) participants, and nausea, myalgia, and rash, in four (2%) participants each, being the most frequently reported treatment-related adverse events between both groups (n=188). There were no treatment-related serious adverse events, adverse events leading to discontinuation, or deaths. The overall incidence of serious adverse events was higher in those receiving apitegromab (21 [16%] of 128) relative to placebo (six [10%] of 60), with the incidence of infection and respiratory events driving the difference. None, however, was assessed as related to apitegromab. There were no adverse events of special interest prespecified or identified.

A relative increase in serum creatine kinase concentration was observed with apitegromab compared with placebo, with 32 (25%) of 128 apitegromab participants versus seven (12%) of 60 placebo participants experiencing an increase in creatine kinase severity grade from baseline. One patient receiving apitegromab 10 mg/kg tested positive for anti-drug antibodies at a single timepoint (week 48) post treatment initiation, with a titre below the limit of sensitivity in the titration assay; there was no meaningful effect on the pharmacokinetics, pharmacodynamics, safety, and efficacy of apitegromab. No clinically relevant patterns or trends related to apitegromab treatment were observed in other laboratory assessments. No clinically relevant trends in vital signs and ECG parameters were observed in the trial. Furthermore, no clinically significant infusion or hypersensitivity reactions associated with the trial drug were reported. The safety profile was generally consistent across treatment arms, with no clinically relevant differences by dose or age group.

Discussion

In this phase 3 SAPPHIRE trial, statistically significant and potentially clinically meaningful improvements in motor function were observed with apitegromab treatment compared with placebo in patients with type 2 or type 3 spinal muscular atrophy receiving nusinersen or risdiplam. Motor function, as measured by HFMSE, improved in patients receiving apitegromab and decreased in those receiving placebo despite all

	Population aged 2–12 years				Population aged 13–21 years		Population aged 2–21 years	
	Placebo (n=50)	Combined (n=106)	20 mg/kg (n=53)	10 mg/kg (n=53)	Placebo (n=10)	20 mg/kg (n=22)	Placebo (n=60)	Combined (n=128)
Participants with at least one								
Adverse event	43 (86% [74–93])	97 (92% [85–95])	46 (87% [75–93])	51 (96% [87–99])	9 (90% [60–98])	19 (86% [67–95])	52 (87% [76–93])	116 (91% [84–95])
Serious adverse event	5 (10% [4–21])	21 (20% [13–28])	12 (23% [13–36])	9 (17% [9–29])	1 (10% [2–40])	0 (0–15)	6 (10% [5–20])	21 (16% [11–24])
Treatment-related adverse event	7 (14% [7–26])	18 (17% [11–25])	8 (15% [8–27])	10 (19% [11–31])	4 (40% [17–69])	6 (27% [13–48])	11 (18% [11–30])	24 (19% [13–26])
Adverse event grade ≥3	5 (10% [4–21])	20 (19% [13–27])	11 (21% [12–33])	9 (17% [9–29])	1 (10% [2–40])	1 (5% [1–22])	6 (10% [5–20])	21 (16% [11–24])
Adverse events leading to treatment discontinuation								
Adverse event leading to study withdrawal	0 (0–7)	0 (0–3)	0 (0–7)	0 (0–7)	0 (0–28)	0 (0–15)	0 (0–6)	0 (0–3)
Adverse event leading to death	0 (0–7)	0 (0–3)	0 (0–7)	0 (0–7)	0 (0–28)	0 (0–15)	0 (0–6)	0 (0–3)
Adverse events with highest incidence								
Pyrexia	16 (32% [21–46])	31 (29% [21–39])	13 (25% [15–38])	18 (34% [23–47])	1 (10% [2–40])	2 (9% [3–28])	17 (28% [19–41])	33 (26% [19–34])
Nasopharyngitis	10 (20% [11–33])	26 (25% [17–34])	11 (21% [12–33])	15 (28% [18–42])	4 (40% [17–69])	6 (27% [13–48])	14 (23% [14–35])	32 (25% [18–33])
Cough	11 (22% [13–35])	26 (25% [17–34])	11 (21% [12–33])	15 (28% [18–42])	1 (10% [2–40])	4 (18% [7–39])	12 (20% [12–32])	30 (23% [17–31])
Vomiting	8 (16% [8–29])	27 (25% [18–35])	11 (21% [12–33])	16 (30% [20–44])	2 (20% [6–51])	2 (9% [3–28])	10 (17% [9–28])	29 (23% [16–31])
Upper respiratory tract infection	17 (34% [22–48])	26 (25% [17–34])	14 (26% [16–40])	12 (23% [13–36])	1 (10% [2–40])	2 (9% [3–28])	18 (30% [20–43])	28 (22% [16–30])
Headache	8 (16% [8–29])	21 (20% [13–28])	9 (17% [9–29])	12 (23% [13–36])	4 (40% [17–69])	6 (27% [13–48])	12 (20% [12–32])	27 (21% [15–29])
Serious adverse events with highest incidence								
Pneumonia	0 (0–7)	7 (7% [3–13])	4 (8% [3–18])	3 (6% [2–15])	0 (0–28)	0 (0–15)	0 (0–6)	7 (5% [3–11])
Dehydration	0 (0–7)	3 (3% [1–8])	1 (2% [0–10])	2 (4% [1–13])	0 (0–28)	0 (0–15)	0 (0–6)	3 (2% [1–7])
Scoliosis	1 (2% [0–10])	2 (2% [1–7])	1 (2% [0–10])	1 (2% [0–10])	1 (10% [2–40])	0 (0–15)	2 (3% [1–11])	2 (2% [0–6])
Adenovirus infection	0 (0–7)	2 (2% [1–7])	2 (4% [1–13])	0 (0–7)	0 (0–28)	0 (0–15)	0 (0–6)	2 (2% [0–6])
Gastroenteritis	0 (0–7)	2 (2% [1–7])	1 (2% [0–10])	1 (2% [0–10])	0 (0–28)	0 (0–15)	0 (0–6)	2 (2% [0–6])
Acute respiratory failure	0 (0–7)	2 (2% [1–7])	0 (0–7)	2 (4% [1–13])	0 (0–28])	0 (0–15)	0 (0–6)	2 (2% [0–6])
Constipation	0 (0–7)	2 (2% [1–7])	1 (2% [0–10])	1 (2% [0–10])	0 (0–28)	0 (0–15)	0 (0–6)	2 (2% [0–6])
Adverse event with an incidence ≥5% in apitegromab group *vs* placebo group								
Vomiting	8 (16% [8–29])	27 (25% [18–35])	11 (21% [12–33])	16 (30% [20–44])	2 (20% [6–51])	2 (9% [3–28])	10 (17% [9–28])	29 (23% [16–31])
Gastroenteritis	3 (6% [2–16])	11 (10% [6–18])	4 (8% [3–18])	7 (13% [7–25])	0 (0–28)	2 (9% [3–28])	3 (5% [2–14])	13 (10% [6–17])
Diarrhoea	0 (0–7)	11 (10% [6–18])	2 (4% [1–13])	9 (17% [9–29])	1 (10% [2–40])	2 (9% [3–28])	1 (2% [0–9])	13 (10% [6–17])
Rhinorrhoea	2 (4% [1–13])	10 (9% [5–17])	4 (8% [3–18])	6 (11% [5–23])	0 (0–28)	2 (9% [3–28])	2 (3% [1–11])	12 (9% [5–16])
Pneumonia	1 (2% [0–10])	8 (8% [4–14])	5 (9% [4–20])	3 (6% [2–15])	0 (0–28)	1 (5% [1–22])	1 (2% [0–9])	9 (7% [4–13])

Data are n (% [95% CI]). Percentage is calculated based on the number of participants in the safety set within each age group and treatment group. Wilsons CIs are presented for percentages. All participants within the safety set received at least one dose of apitegromab or placebo.

Table 3: **Adverse events following treatment (safety set)**

continuing on SMN-targeted therapy. Efficacy results were generally consistent across dose, age, SMN-targeted therapy type, age at therapy initiation, and region. The safety profile of apitegromab was consistent with observations from the phase 2 TOPAZ trial, and the underlying spinal muscular atrophy patient population receiving SMN-targeted therapy.[12]

Although spinal muscular atrophy is a rare disease, it was the most common monogenic cause of infant death until the approvals of SMN-targeted therapies; with therapy, the overall prognosis has substantially improved. Even with this remarkable change,[3–5,22] the benefits might be limited due to loss of motor neurons before treatment initiation.[6–8] Even with newborn screening now widely being implemented in the USA, with Europe gradually following suit, there are still many newborns that have clinical or biochemical evidence of neurodegeneration before newborn screening diagnosis and treatment initiation.[6–8] Delayed diagnoses or treatment can occur due to reasons such as non-deletion mutations undetectable with newborn screening,[1] unavailability of the screening, and reduced access to health care.[23] Any of these limitations will constrain the benefit from SMN-targeted therapies, commensurate with the level of pre-treatment motor neuron degeneration.

This unmet need was evident in the low motor function baseline scores for the SAPPHIRE population, all of whom received chronic SMN-targeted therapy. Despite years of treatment with an effective

SMN-targeted therapy, baseline HFMSE scores remained well below normal function for healthy individuals. Emerging preliminary long-term data (conference abstracts) on two well followed cohorts suggest that after initial improvement of motor function, HFMSE scores generally plateau; patients might experience functional declines over time despite continuing on an effective SMN-targeted therapy.[10,11] Continued loss of function could be due to inadequate SMN restoration or other accumulating disease confounders such as scoliosis or contractures.

SAPPHIRE results recapitulated this decline, with HFMSE showing a similar decrease over time for patients receiving placebo with SMN-targeted therapy. In contrast, motor function improved for SAPPHIRE patients receiving apitegromab in combination with SMN-targeted therapy. The separation between apitegromab and placebo was observed as early as 8 weeks and increased over time: HFMSE scores increased from baseline at month 12 by 0·6 points (SE 0·48) in patients receiving apitegromab and decreased by 1·2 points (SE 0·66) in patients receiving placebo, suggesting a cumulative effect of apitegromab on the disease course. Notably, compared with TOPAZ, participants in SAPPHIRE had been on SMN-targeted therapy for a longer duration at enrolment, with average exposure greater than 5 years and 3 years to nusinersen and risdiplam compared to approximately 2 years to nusinersen at enrolment for TOPAZ.[12,17] The benefit of apitegromab on motor function observed in both studies underscores that the effect is broadly applicable across the SMN-targeted therapy journey of advance and decline.

Recent reports have recognised the substantial benefit in quality of life derived from small changes in function and the importance of maintaining function or preventing decline.[18] As what constitutes a meaningful change is patient-dependent, clinicians increasingly recognise that setting a single meaningful threshold is challenging. The definition of clinically meaningful outcomes has generally broadened to include stabilisation as a realistic endpoint.[13,24] Surveys of patients and caregivers indicated that 1-point to 2-point gains on individual items of HFMSE (eg, the ability to roll over in bed, to feed oneself, to sit up, or to stand) reflect a measure of independence, and are therefore relevant to patients and caregivers. A 1·5-point improvement in HFMSE total score was identified as clinically meaningful for type 2 or type 3 spinal muscular atrophy.[25] In this context, the difference of 1·8-point versus placebo for both the population aged 2–12 years (95% CI 0·30 to 3·32) and population aged 13–21 years (95% CI –1·06 to 4·57) is considered substantial and potentially clinically meaningful.

Although a positive trend was observed on RULM, the difference was not significant (appendix p 12). RULM, designed to measure upper limb function, includes fine motor elements. As such, the treatment effect on RULM generally takes longer to manifest, consistent with previous reports from other spinal muscular atrophy trials, and with what was observed in our phase 2 TOPAZ study.[12,17] The odds ratio of achieving an improvement of at least 3 points in HFMSE score, a secondary endpoint, was 3·0 (95% CI 1·15 to 8·0) for patients treated with apitegromab versus those receiving SMN-targeted therapy alone, which further illustrates the benefit of apitegromab treatment. Similar to the outcomes for RULM, WHO motor milestones showed positive trends towards improvement; however, the difference from placebo was not significant.

The pivotal clinical trials for SMN-targeted therapies nusinersen and risdiplam showed better outcomes in participants who initiated treatment in infancy, early after symptom onset or presymptomatically.[26,27] This contrasts with the results of SAPPHIRE, where improvements associated with apitegromab in the individuals receiving SMN-targeted therapy spanned subgroups of age, SMN-targeted therapy type, age at therapy initiation, and region. The difference could be related to the differences in target: increased SMN expression reduces the rate of motor neuron degeneration, whereas the intent of apitegromab myostatin-signalling inhibition is a salutary effect on muscle. By selectively inhibiting myostatin, apitegromab treatment could increase the contractile force within residual innervated muscle fibres,[9] leading to improved motor function. SAPPHIRE builds on the observations of TOPAZ and its extension, where apitegromab was associated with improved motor function in patients with nonambulatory type 2 or type 3 spinal muscular atrophy over 36 months.[12,17]

No new safety concerns were identified.[12] Pneumonia rates were higher in those receiving apitegromab (7%) compared with placebo (2%); however, this was probably due to the small number of affected individuals and lower incidence in the placebo group compared with other placebo-controlled spinal muscular atrophy trials (2–14%).[4,24] Moderate elevations of serum creatine kinase, which are common in individuals with spinal muscular atrophy,[28] were observed. Based on the limited relative change and absence of adverse events, these creatine kinase elevations might represent a downstream effect of increased physical activity associated with increased muscle mass or motor function among apitegromab treated individuals rather than a safety concern. Overall, safety data suggest apitegromab was well tolerated, with a favourable safety profile across the SAPPHIRE trial population.

SAPPHIRE evaluated two apitegromab doses based on modelling and simulation analyses of data from TOPAZ. While the combined 20 mg/kg and 10 mg/kg apitegromab dose showed a statistically significant difference compared with placebo, the difference between apitegromab 20 mg/kg and placebo was not significant. The difference in effect size probably reflects the inherent heterogeneity

of spinal muscular atrophy disease characteristics and its potential effect on motor function assessment. Consistent with this notion, the increases in total latent myostatin, a pharmacodynamic marker, were superimposable for both doses, suggesting target saturation is achieved at 10 mg/kg and that the 10 mg/kg and 20 mg/kg doses are pharmacologically indistinguishable. Exposure–efficacy modelling that evaluated the relationship between total latent myostatin concentration and change from baseline in HFMSE at 12 months, showed a model-predicted placebo-corrected HFMSE effect of 1·67 for the 20 mg/kg dose and of 1·66 for the 10 mg/kg dose. Furthermore, there were no notable differences in safety events. Taken together, based on indistinguishable pharmacodynamic profiles, comparable safety profiles between the two apitegromab dose levels, and consistent efficacy results, the benefit–risk of apitegromab is optimised with 10 mg/kg.

To enrol in SAPPHIRE, individuals were required to have documented diagnosis of 5q spinal muscular atrophy with nonambulatory type 2 or type 3 spinal muscular atrophy and were receiving an approved SMN-targeted therapy (nusinersen or risdiplam). The study eligibility criteria included a wide age range (2–21 years), with a mean age of 9 years for the enrolled population at screening. Although the global spinal muscular atrophy patient population includes many young children, individuals with type 2 or type 3 spinal muscular atrophy can reach their teens and adulthood,[4,22] which is reflected in the diverse age range of the overall patient population, and representative of the patients enrolled in SAPPHIRE. Moreover, given the underlying disease pathology of spinal muscular atrophy is the same across the global patient population—regardless of age, disease severity, and ambulation status—our observations from the phase 2 TOPAZ trial,[12] which included a small cohort of ambulatory patients, and the SAPPHIRE trial could be broadly applicable to all people living with spinal muscular atrophy.

Sex, race, and ethnicity were self-reported by participants. The ratio of males to females enrolled in SAPPHIRE was 1:1 and no sex effect was observed on the efficacy in HFMSE based on a post-hoc analysis. Most participants in SAPPHIRE were White and not Hispanic or not Latino which reflects the study sites where the study was conducted geographically (ie, Europe and North America). However, spinal muscular atrophy occurs in all races and ethnic groups.[29] Given this limitation, it will be important to continue to investigate the effect of apitegromab treatment in non-White and Hispanic or Latino patient populations.

SAPPHIRE enrolled patients at 48 sites across nine countries, with a trial population generally representative of the global spinal muscular atrophy population in terms of age, sex, SMN-targeted therapy exposure, and hampered motor function. Several limitations should be considered when interpreting the trial results. For example, severe contractures or scoliosis were excluded, as they confound HFMSE outcome assessments; so too were other characteristics such as age younger than 2 years. Patients with severe or mild weakness were excluded because their outcome assessments could be affected by floor or ceiling effects. Although further research is needed, the underlying biology of myostatin and apitegromab mechanism of action provide strong biological plausibility that the efficacy of apitegromab extends to individuals with severe scoliosis or contractures and those with severe or mild deficits.[14–16] Despite the overall consistency of efficacy results across all predefined subgroups, the effect size observed in patients on risdiplam appeared to be smaller relative to those on nusinersen in the population aged 2–12 years. This effect was likely due to the small number of patients in the population aged 2–12 years receiving risdiplam. However, a post-hoc analysis also showed that the difference in effect size was at least partly attributed to a higher proportion of the patients on risdiplam that had two prior SMN-targeted therapies (risdiplam, 19 [54%] of 35 *vs* nusinersen, three [2%] of 121; population aged 2–12 years). Although results for the two doses were consistent, the mean difference was not significant at the 0·05 level for the apitegromab 20 mg/kg dose, reflecting the limitation of the sample size and the inherent heterogeneity of the study population. Lastly, long-term safety of apitegromab is primarily derived from the TOPAZ open-label extension, with additional data from both TOPAZ and SAPPHIRE participants enrolled in the long-term ONYX extension trial (NCT05626855). While long-term treatment adherence is needed, data from the TOPAZ extension trial suggest it is achievable and maintained.[17]

Notwithstanding the limitations, the findings presented in our manuscript represent the first time that a myostatin-targeting agent has demonstrated improved function in any disease in a placebo-controlled clinical setting. The SAPPHIRE results build on insights gained from many failed efforts over decades, and as such offer important insights for future research. Myostatin has been identified as a therapeutic target since 1997, with a total of 32 trials conducted to date across 18 different diseases, including neuromuscular diseases such as spinal muscular atrophy and Duchenne muscular dystrophy.[30] Clinical trials failed for a number of reasons, including off-target toxic effects associated with a less selective myostatin-targeting approach, choice of diseases with primary muscle defect impacting structural integrity or lacking effective corrective therapy (eg, Duchenne muscular dystrophy), use of a less effective antimyostatin agent, or a heterogeneous trial population. The SAPPHIRE study design benefited from these learnings, including the importance of having sufficient muscle integrity and appropriate patient selection and stratification within a patient population with a stable disease course. Though this report addresses an unmet

need in the spinal muscular atrophy community, these results are not specific to spinal muscular atrophy. Genetic and acquired neuromuscular disorders where muscle atrophy is a feature of disease pathogenesis (eg, Duchenne muscular dystrophy, amyotrophic lateral sclerosis, facioscapulohumeral muscular dystrophy) might also potentially benefit from a muscle-targeting therapy that complements current corrective therapies.

In conclusion, the SAPPHIRE results showed that apitegromab treatment (combined 20 mg/kg and 10 mg/kg dose) was associated with statistically significant improvements in motor function compared with placebo. Despite statistical significance being achieved for the combined apitegromab dose analysis, significance was not achieved for the individual apitegromab 20 mg/kg dose group. Overall, SAPPHIRE showed that apitegromab improved motor function and was generally well tolerated, supporting the use of muscle-targeting therapy for individuals with spinal muscular atrophy.

Contributors

TOC, LS, EM, HK, NK, RSF, JK, KB, SDY, ESM, RJB, MGGB, AMS, VAS, LDW, WLvdP, CC, AP, and BTD collected the data. GS and GZ conducted the statistical analyses. TOC, LS, EM, HK, NK, RSF, JK, KB, SDY, JLM, GS, BY, GZ, JR, GST, ESM, RJB, MGGB, AMS, VAS, LDW, WLvdP, CC, AP, and BTD interpreted the data and wrote or contributed to the writing of the manuscript. TOC, GS, and GZ have accessed and verified all the data in the trial. All authors had full access to all the data in the trial on request and had final responsibility for the decision to submit for publication.

Declaration of interests

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. LS has received grants and personal fees from AveXis/Novartis Gene Therapies, Biogen, and Roche and personal fees from Biohaven, Cytokinetics, and Scholar Rock, outside the submitted work. EM has received personal compensation for clinical trial consulting and serving on scientific advisory boards and research funding from Novartis Gene Therapies. HK is serving on a scientific advisory board for AveXis and received travel expenses and speaker honoraria from Biogen, Pfizer, Roche, and Sanofi-Aventis. NK serves on medical advisory boards for Argenx, Biogen, Novartis, Roche, and Sarepta. Her institution receives research funds from Biogen, Novartis, Roche, and Sarepta. RSF has received personal compensation for consulting and for advisory board participation from Biogen, Novartis, Novartis Gene Therapies, Roche, and Scholar Rock; 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. JK is a site principal investigator for AveXis/Novartis Gene Therapies, Biohaven, FibroGen, Roche/Genentech, and Scholar Rock, and serves as a Data and Safety Monitoring Board member for Astellas. KB receives research support from Biogen, Elpida, FibroGen, Novartis, NS Pharma, PTC Therapeutics, Regenxbio, ReveraGen, Sarepta Therapeutics, Scholar Rock, and Cure SMA. She has served on medical advisory boards for Biogen, Catalyst, Pfizer, PTC Therapeutics, Reata Pharmaceuticals, Sarepta Therapeutics, and UCB. SDY has been a member of advisory boards for Biogen, Roche/Genentech, and Scholar Rock; received personal compensation for activities with Biogen, Cure SMA, and Scholar Rock as a consultant; and received research support from Cure SMA and the SMA Foundation. JLM, GS, BY, GZ, JR, and GST are Scholar Rock employees and stockholders. ESM has received consulting fees from Biogen, Novartis, Roche, and Scholar Rock. RJB receives funding via contracts for clinical trials from AveXis, Biogen, Pfizer, PTC Therapeutics, and Sarepta Therapeutics. He serves on scientific advisory boards for AveXis, Biogen, Pfizer, and Sarepta Therapeutics. MGGB serves as a scientific advisory board member for Biogen, Novartis Gene Therapies, and Roche. AMS has no conflicts to disclose. VAS serves as a scientific advisory board member for Biogen, Novartis, Roche, and Sarepta. LDW has received grant funding from the Belgian Government of Health and grant funding and honoraria for advisory board meetings, lectures, and travel expenses from Baxter, BBraun, Cardinal Health, Danone-Nutricia, and Fresenius Kabi. WLvdP receives research support from the Prinses Beatrix Spierfonds, and Stichting Spieren voor Spieren. His employer receives fees for consultancy services to AveXis, Biogen, Biohaven, NMD Pharma, Novartis, Roche, and Scholar Rock. He was involved as an investigator at a participating centre in trials on the safety and efficacy of olesoxime for children with SMA types 2 and 3a (NCT02628743) and is involved as an investigator of the single-centre placebo-controlled trial on pyridostigmine in children and adults with SMA types 2–4 (SPACE 2014). 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. AP has received compensation for advisory boards, training activities and research grants from Biogen and Novartis. BTD has served as an ad hoc scientific advisory board member for AveXis/Novartis Gene Therapies, Biogen, Merck, Roche/Genentech, Sarepta Therapeutics, and Scholar Rock; steering committee member for Roche FIREFISH and MANATEE studies; and Data and Safety Monitoring Board member for Amicus, ArgenXBV, and Lexeo Therapeutics; he has no financial interests in these companies. He has received research support from the National Institutes of Health/National Institute of Neuruological Disorders and Stroke, the Spinal Muscular Atrophy Foundation, Cure SMA, and has received grants from Ionis Pharmaceuticals, for ENDEAR, CHERISH, CS1/CS2/CS12 studies, from Biogen for CS11 and ASCEND studies, and from Fibrogen, Novartis (AveXis), PTC Therapeutics, Roche, Sarepta Therapeutics, and Scholar Rock. He has also received royalties for books and online publications from Elsevier and Wolters Kluwer.

Data sharing

Scholar Rock is committed to sharing deidentified clinical trial data with external investigators upon reasonable request. Individual researchers requesting clinical trial data for academic or noncommercial use must include a research proposal clarifying how the data will be used, including proposed analysis methodology. Scholar Rock will consider and evaluate unsolicited requests for clinical trial data on a case-by-case basis.

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