Effect of apitegromab on motor function and patient-reported outcomes at 36 months in patients aged 2–21 years with spinal muscular atrophy

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Introduction

- Spinal muscular atrophy (SMA), a genetic neuromuscular disease, is characterized by the loss of motor neurons in the spinal cord and brain stem that results in progressive muscle weakness and atrophy of the voluntary muscles of the limbs and trunk[1,2]
- Apitegromab is an investigational, fully human monoclonal antibody that binds pro- and latent forms of myostatin, blocking the conversion of the latent form to mature myostatin, thereby directly increasing innervated skeletal muscle mass[3]
- In the phase 2 TOPAZ study, treatment with apitegromab was associated with improved motor function in patients with Types 2 or 3 SMA and a favorable safety profile at 12 months

Objective

- To report the long-term efficacy and safety results from 36 months of treatment with apitegromab in patients with SMA who were enrolled in the TOPAZ open-label extension study

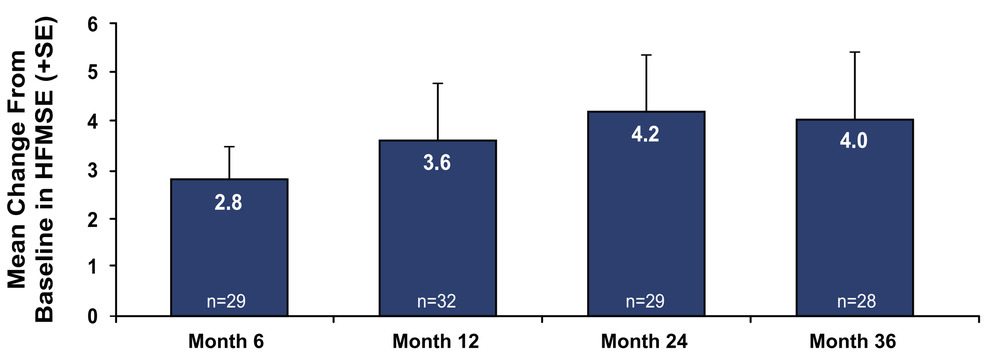
Methods

- TOPAZ (NCT03921528) is a multicenter, phase 2, active treatment study evaluating the safety and efficacy of apitegromab in patients aged 2–21 years with Types 2 or 3 SMA at 16 sites across the USA and Europe
- In the 52-week treatment period, patients (N=58) were divided into 3 cohorts: 2 open-label cohorts of patients with ambulatory Type 3 SMA (Cohort 1) and Type 2 SMA or nonambulatory Type 3 SMA (Cohort 2), and 1 Type 2 SMA double-blind cohort, randomized to either low-(2 mg/kg) or high-dose (20 mg/kg) apitegromab (Cohort 3)
- All patients received apitegromab by intravenous infusion every 4 weeks
- Study completers could enroll in 3 sequential extension periods (52 weeks each), where all patients received 20 mg/kg apitegromab
- Efficacy analyses presented here evaluate the effects of apitegromab in the nonambulatory patient population (Cohorts 2 and 3) from the TOPAZ study (n=35) over 36 months
- The safety analysis comprises data from all 58 patients enrolled in the TOPAZ study

Results

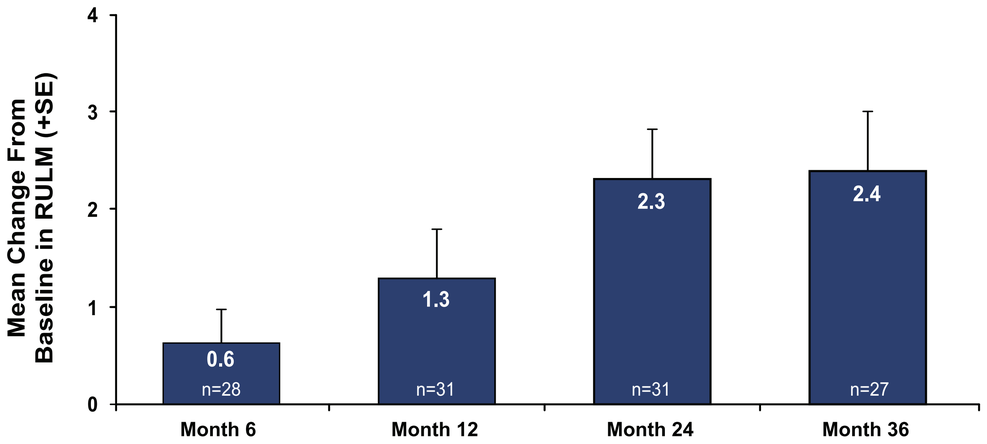
- The nonambulatory patient population had a mean age of 7.3 years (range 2–19) with an average age of symptom onset of 1.12 years
- Motor function outcomes as assessed by Hammersmith Functional Motor Scale–Expanded (HFMSE) (**Figure 1**) and Revised Upper Limb Module (RULM) (**Figure 2**) showed sustained improvements from baseline throughout the 36-month study period

Figure 1. Improvements in Motor Function Outcomes by HFMSE Increase



Error bars represent standard error of means. This analysis excludes data post scoliosis surgery from 6 patients.
HFMSE, Hammersmith Functional Motor Scale–Expanded; SE, standard error.

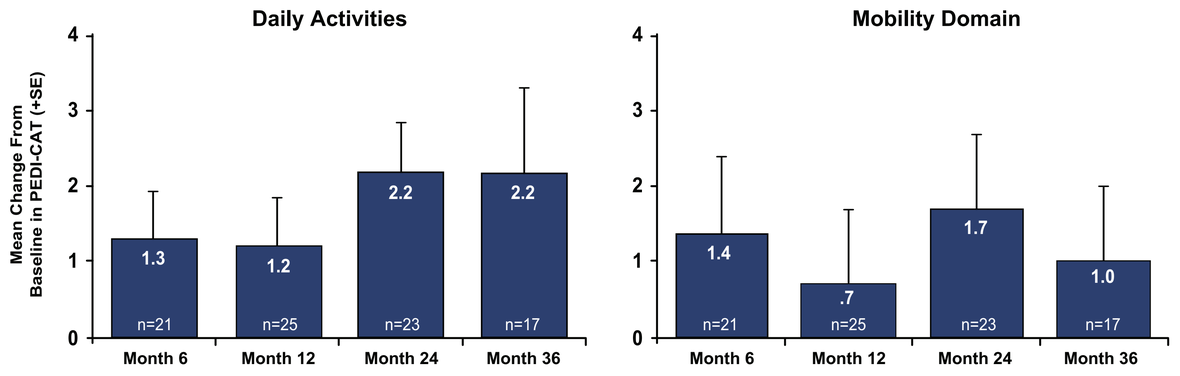
Figure 2. Improvements in Motor Function Outcomes by RULM Increase



Error bars represent standard error of means. This analysis excludes data post scoliosis surgery from 6 patients.
RULM, Revised Upper Limb Module; SE, standard error.

- The Pediatric Evaluation of Disability Inventory Computer Adaptive Test (PEDI-CAT; assessed via caregiver proxy), which can assess a patient's motor improvement in their natural environment, showed sustained improvements from baseline over 36 months (**Figure 3**)

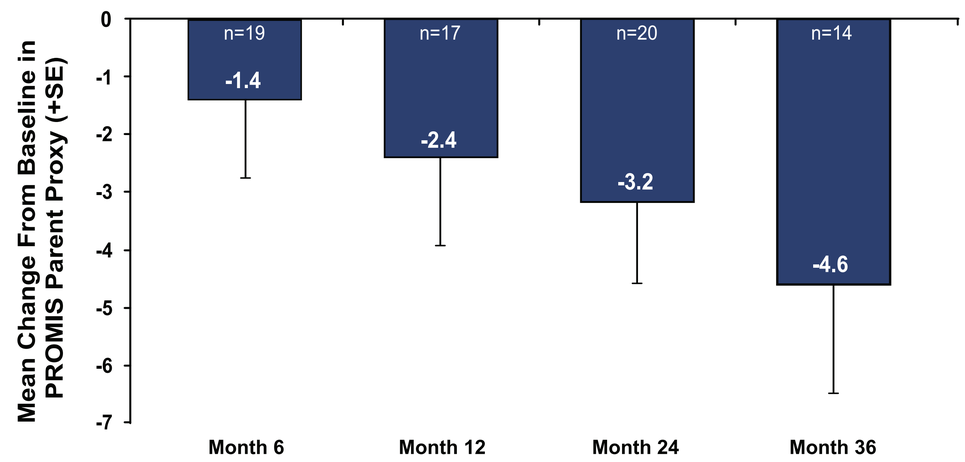
Figure 3. Sustained Improvements in PEDI-CAT



Error bars represent standard error of means. This analysis population included nonambulatory patients 2–21 years old receiving either low-dose (2 mg/kg) or high-dose (20 mg/kg) apitegromab (inclusive of patients in Cohort 3 who transitioned from 2 mg/kg to 20 mg/kg in Year 2). PEDI-CAT, Pediatric Evaluation of Disability Inventory Computer Adaptive Test; SE, standard error.

- Fatigue, both physical and cognitive, can be a major side effect of SMA. Utilizing the Patient-Reported Outcomes Measurement Information System (PROMIS) perceived fatigue questionnaire (assessed via caregiver proxy), improvements in fatigue from baseline were observed over 36 months (**Figure 4**)

Figure 4. PROMIS Fatigue Questionnaire Improvement



Error bars represent the standard error of means. This analysis population included nonambulatory patients 2–21 years old receiving either low-dose (2 mg/kg) or high-dose (20 mg/kg) apitegromab (inclusive of patients in Cohort 3 who transitioned from 2 mg/kg to 20 mg/kg in Year 2).
PROMIS, Patient-Reported Outcomes Measurement Information System; SE, standard error.

- Over 36 months, 86% (30/35) of patients improved or maintained World Health Organization (WHO) motor milestones that they had achieved at baseline
- Excluding those who had scoliosis surgery, 93% (27/29) of participants improved or maintained baseline WHO motor milestones
  - Of 20 patients receiving nusinersen earlier than 5 years of age, 6 gained new WHO motor milestones, including 2 who were able to walk independently

Safety

- The safety profile was consistent with previous reports, with no new safety signals identified during the 36-month extension period (**Table 1**)
- Treatment-emergent adverse events were mostly mild to moderate in severity and were generally consistent with the underlying patient population and nusinersen therapy

Treatment-Emergent Adverse Events (TEAEs)*	Apitegromab 2 mg/kg n=10	Apitegromab 20 mg/kg n=48	Total N=58
Any TEAE, n (%)	10 (100.0)	46 (95.8)	56 (96.6)
Any serious TEAE, n (%)	5 (50.0)	16 (33.3)	21 (36.2)
Any TEAE leading to study drug discontinuation, n (%)	0 (0.0)	1 (2.1)	1 (1.7)
Any grade 3 (severe) or higher TEAE, n (%)	4 (40.0)	16 (33.3)	20 (34.5)

*Defined as adverse events that start after the first dose of study drug or start prior to the administration of study drug and worsen in severity/grade or relationship to investigational medication after the administration of study drug.

Conclusions

- Treatment with apitegromab was associated with sustained clinical benefit and improvements in patient- and caregiver-reported outcomes of function and perceived fatigue in patients with Types 2 or 3 SMA for 36 months
- These findings support further development of apitegromab in nonambulatory SMA

References

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Disclosures

TOC is the lead principal investigator of the TOPAZ trial; and a consultant and/or advisory board member for AveXis/Novartis, Biogen, Pfizer, and Roche/Genentech. **BTD** has served as an ad hoc scientific advisory board member for AveXis/Novartis Gene Therapies, Biogen, Pfizer, Sarepta Therapeutics, Vertex, and Roche/Genentech; steering committee chair for Roche FIREFISH and MANATEE studies; and DSMB member for Amicus Inc. 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 Neurological Disorders and Stroke, the Slaney Family Fund for SMA, the Spinal Muscular Atrophy Foundation, CureSMA, and Working on Walking Fund; received grants from Ionis Pharmaceuticals, Inc. for the ENDEAR, CHERISH, and CS2/CS12 studies; from Biogen for CS11; and from AveXis, Sarepta Pharmaceuticals, Novartis (AveXis), PTC Therapeutics, Roche, Scholar Rock, and Fibrogen; and has received royalties for books and online publications from Elsevier and UpToDate, Inc. **JWD** has received consulting fees from Biogen, Cytokinetics, Ionis Pharmaceuticals, NGT, Pfizer, Roche, and Sarepta Therapeutics; license fees or royalty payments from Athena Diagnostics; and research funding from Biogen, Cytokinetics, NGT, Roche, Sanofi-Genzyme, and Sarepta Therapeutics. **DCD** reports grants from Biogen during the conduct of the study; Department of Defense, Hope for Children Research Foundation, National Institutes of Health, and Spinal Muscular Atrophy Foundation; personal fees from AveXis, Biogen, Cytokinetics, Ionis Pharmaceuticals, Inc., Roche, and Sarepta. **JMK** was site principal investigator for clinical trials sponsored by Novartis Gene Therapies, Inc., Biogen, and Scholar Rock. **EM**, **AN**, **ESM**, and **AP** have nothing to disclose. **TD** is an advisory board member for Biogen, CureSMA, Novartis, Roche, and Scholar Rock; and a consultant for Astellas, Avidity, Biohaven, Dyne, Genentech, Novartis, Roche, and Sarepta Therapeutics. **SB**, **GS**, **RE**, **LL**, **MS**, and **JLM** are employees of Scholar Rock.

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