Effect of apitegromab on motor function at 36 months in patients with nonambulatory spinal muscular atrophy aged 2–12 years old

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Introduction

- Spinal muscular atrophy (SMA) is a neuromuscular disease resulting in muscle atrophy and associated muscle weakness[1]
- Apitegromab, an investigational, fully human monoclonal antibody being investigated in SMA, inhibits the pro- and latent forms of myostatin, thereby directly targeting muscle atrophy[2]
- Improvements in motor function measures were observed with apitegromab in patients with Type 2 and nonambulatory Type 3 SMA receiving nusinersen in the initial 52-week treatment period of the TOPAZ study

Objective

- To determine the effects of apitegromab on muscle function as measured by Hammersmith Functional Motor Scale – Expanded (HFMSE), Revised Upper Limb Module (RULM), and World Health Organization (WHO) motor development milestones at 36 months in patients with nonambulatory SMA

Methods

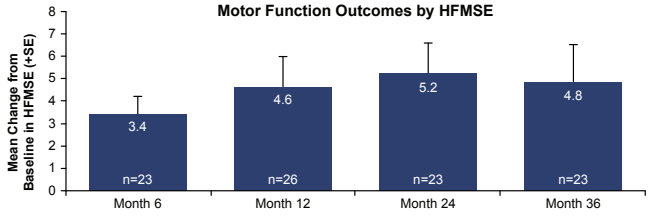
Study design and treatment interventions

- TOPAZ (NCT03921528) is an ongoing multicenter, phase 2, active treatment study to evaluate the safety and efficacy of apitegromab in patients (2–21 years old) with Types 2 and 3 SMA at 16 sites across the US and Europe
- The study consisted of a 28-day screening period and a 52-week treatment period. Patients who completed the 52-week treatment period had the option to enroll in up to 3 extension periods of 52-week duration for a total of 36 months (enrollment was dependent upon completion of the prior extension period)
- In the 52-week treatment period, patients 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)
- In the extension periods, patients originally receiving 2 mg/kg in the primary treatment period switched to 20 mg/kg, while all patients on 20 mg/kg continued their dose
- This report focuses on efficacy findings for nonambulatory patients aged 2–12 years old (focus of the pivotal SAPPHIRE trial) and safety findings for patients 2–21 years old

Results

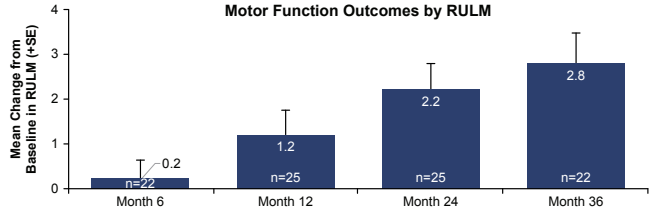
- Of 58 patients enrolled in the TOPAZ study, 57 completed the primary treatment period and enrolled in the extension study (1 patient withdrew from the study)
- Fifty-seven patients enrolled in the extension period, 6 discontinued: 2 withdrew consent due to concerns with COVID-19, and 4 patients receiving apitegromab monotherapy discontinued due to lack of benefit or scheduling difficulty
- Of 35 patients with nonambulatory SMA, 1 discontinued, 29 were aged 2–12
- In patients receiving either low dose (2 mg/kg) or high dose (20 mg/kg) apitegromab, motor function as assessed by HFMSE (**Figure 1**) and RULM (**Figure 2**) showed sustained improvements throughout 36 months

Figure 1. Improvements in Motor Function Outcomes by HFMSE Increase Over 36 Months



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

Figure 2. Improvements in Motor Function Outcomes by RULM Increase Over 36 Months



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

- Analysis of WHO motor milestones showed achievement of new milestones (**Figure 3**). Thirty-one percent (9/29) of nonambulatory participants aged 2–12 gained at least one new milestone achievement at specific time points of 12, 24, and 36 months

Figure 3. Nonambulatory Patients Achieved New WHO Development Milestones Over Time

New WHO development milestones achieved	Individual Patient Ages (years)									Study Month
	2	4	5	2	2	4	5	8	9	
Hands and knees crawling		✗	✗	✗	✗	✗			✗	BL
		✗	✓	✓	N/R	✗			✓	12M
		✓	✗	✓	✓	N/R			✗	24M
		✗	✓	✓	✓	✓			✗	36M
Standing with assistance				✗				✗	✗	BL
				✓				✓	✓	12M
				✓				N/R	✗	24M
				✓				✗	✗	36M
Walking with assistance				✗						BL
				✓						12M
				✓						24M
				✓						36M
Standing alone	✗			✗						BL
	✓			✗						12M
	✓			✗						24M
	✓			✓						36M
Walking alone	✗						✗			BL
	✗						✓			12M
	✓						✓			24M
	✓						✓			36M

✗ Unable ✓ Able

BL, baseline; M, month; NR, not recorded; WHO, World Health Organization.

Safety

- Treatment-emergent adverse events (TEAEs) were consistent with previous reports, with no new findings after 198 patient-years of exposure (**Table 1**)
- TEAEs were mostly mild to moderate in severity and generally consistent with the underlying patient population and nusinersen therapy
- The most frequently reported TEAEs were headache (38%), pyrexia (38%), COVID-19 (36%), nasopharyngitis (36%), and upper respiratory tract infection (33%)
- Three patients tested positive for the presence of anti-apitegromab antibodies (ADAs), but confirmatory tests showed titers were below the level of sensitivity, and the results were therefore interpreted as negative
- No deaths or suspected unexpected serious adverse reactions or hypersensitivity reactions to apitegromab were reported

Table 1. TOPAZ Safety Summary Over 36 Months (total population)

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

- When added to nusinersen, treatment with apitegromab in patients with Type 2 and nonambulatory Type 3 SMA aged 2–12 years was associated with sustained clinical benefit for 36 months as measured by HFMSE, RULM, and WHO motor development milestones
- Patients achieved new WHO development milestones within the longer follow-up period
- These results support further development of apitegromab in SMA

References

1. Kolb SJ, Kissel JT. *Neurol Clin*. 2015;33(4):831-846.
2. Pirruccello-Straub M, et al. *Sci Rep*. 2018;8(1):2292.

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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, 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. **DCDV** 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. **EM, AN,** and **ESM** have nothing to disclose. **AW, GS, RE,** and **JLM** are employees of Scholar Rock.