Longer-term efficacy, safety, and patient-reported outcomes of apitegromab in patients with nonambulatory SMA: Results from the 48-month TOPAZ study

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Introduction

- Spinal muscular atrophy (SMA) is characterized by neuronal degeneration and muscle atrophy, leading to progressive motor function loss[1]
- Apitegromab, an investigational, fully human monoclonal antibody, inhibits both promyostatin and latent myostatin, a negative regulator of muscle growth, directly targeting muscle atrophy[2,3]
- Primary results at 12 months from the phase 2 study TOPAZ (NCT03921528) showed improvements in muscle function and patient/caregiver-reported outcomes for participants with type 2/3 nonambulatory SMA, which were sustained through 36 months of apitegromab treatment as recently reported in the ongoing extension[4]

Objective

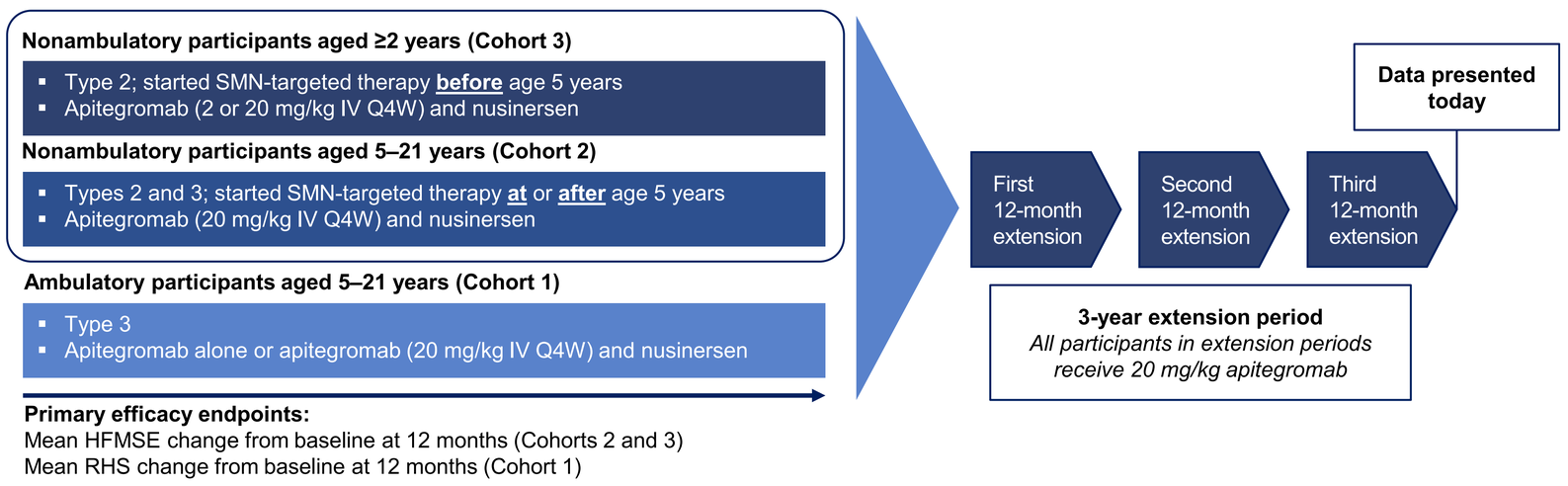
- To report updated results in nonambulatory participants from the TOPAZ open-label extension study who received apitegromab and survival motor neuron (SMN)-targeted therapy for 48 months

Methods

Study design

- TOPAZ (NCT03921528) is a multicenter, phase 2, active treatment study evaluating the safety and efficacy of apitegromab in individuals aged 2 to 21 years with types 2/3 SMA at 16 sites across the US and Europe
- In the 52-week treatment period, participants (N = 58) were divided into 3 cohorts (**Figure 1**)
  - Two open-label cohorts consisted of individuals with ambulatory type 3 SMA (Cohort 1) or type 2/nonambulatory type 3 SMA (Cohort 2) who received 20 mg/kg apitegromab
  - One double-blind cohort comprised individuals with type 2 SMA, randomized to either 2 mg/kg or 20 mg/kg apitegromab (Cohort 3)
- Study completers could enroll in 3 sequential extension periods (12 months each), where those who originally received 2 mg/kg apitegromab every 4 weeks (Q4W) would switch to 20 mg/kg Q4W
  - Primary efficacy endpoints assessed mean Hammersmith Functional Motor Scale Expanded (HFMSE) change from baseline at 12 months (Cohorts 2 and 3) and mean Revised Hammersmith Scale change from baseline at 12 months (Cohort 1)

Figure 1. TOPAZ study design



Each cohort was defined by age and ambulatory status at time of enrollment.
HFMSE, Hammersmith Functional Motor Scale Expanded; IV, intravenous; Q4W, every 4 weeks; RHS, Revised Hammersmith Scale; SMN, survival motor neuron.

Assessments

- Efficacy analyses presented here evaluate the effects of apitegromab in the nonambulatory participant population (Cohorts 2 and 3) from the TOPAZ study (n = 35) over 48 months
  - Motor function assessments included HFMSE, Revised Upper Limb Module, and World Health Organization (WHO) motor milestones based on observed case analysis, censoring assessments after scoliosis surgery
  - Caregiver-reported outcome assessments included the Pediatric Evaluation of Disability Inventory–Computer Adaptive Test (PEDI-CAT) Daily Activities and the Patient-Reported Outcome Measurement Information System (PROMIS)-Fatigue questionnaire via caregiver by proxy
- The safety analysis comprises data from all 58 participants enrolled in the TOPAZ study

Results

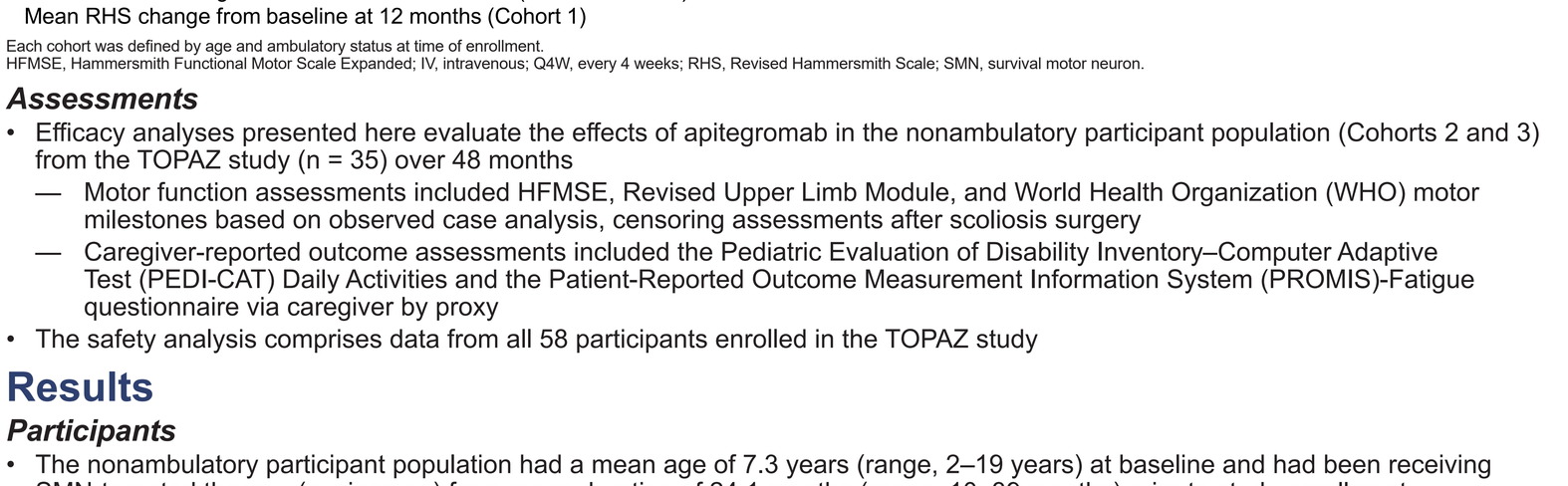
Participants

- The nonambulatory participant population had a mean age of 7.3 years (range, 2–19 years) at baseline and had been receiving SMN-targeted therapy (nusinersen) for a mean duration of 24.1 months (range, 10–39 months) prior to study enrollment
- Of the 35 participants with nonambulatory SMA, 33 (94%) completed the 48-month study period and 11 (31.4%) had scoliosis surgery

Motor assessments

- Motor function outcomes (excluding assessments after scoliosis surgery) showed sustained improvements from baseline throughout the 48-month study period (**Figure 2**)
- Excluding those who had scoliosis surgery, 83% (19/23) of participants maintained or gained WHO motor milestones at 48 months

Figure 2. Mean change from baseline in A) HFMSE total score and B) RULM total score

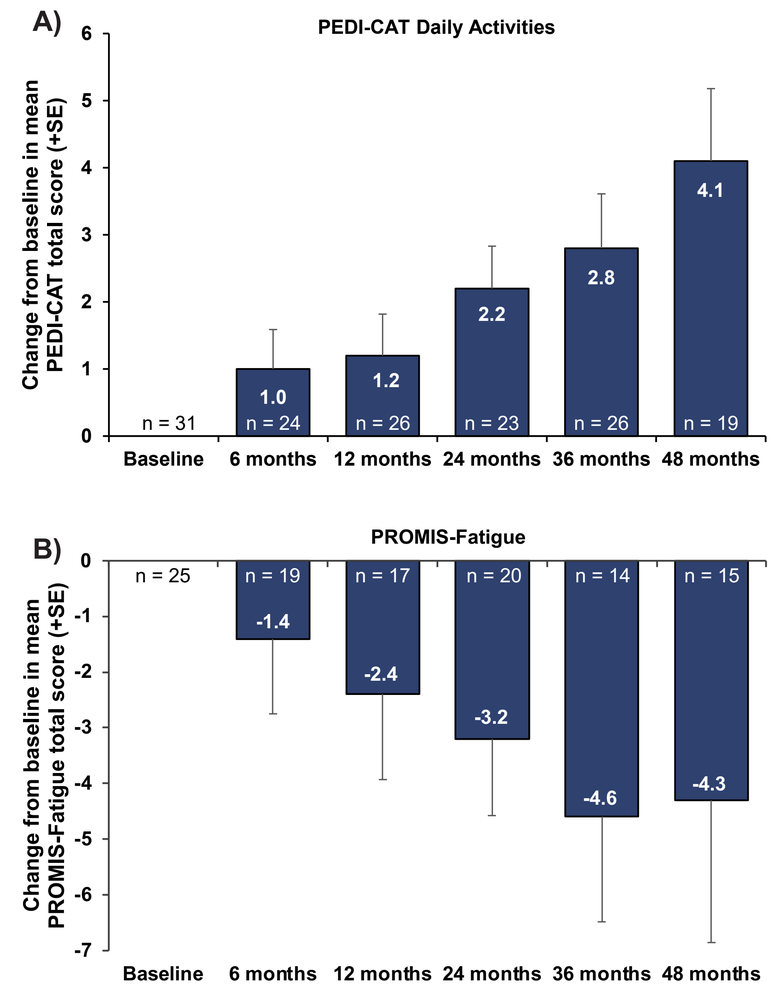


The analysis pooled the nonambulatory participant population from Cohorts 2 and 3 and included individuals who were receiving either 2 or 20 mg/kg apitegromab prior to the extension period (inclusive of participants from Cohort 3 who switched from 2 mg/kg to 20 mg/kg after 12 months). At baseline, one participant was too young for the RULM and was excluded from the analysis. During the extension periods, all participants switched or continued to receive 20 mg/kg of apitegromab monthly. Error bars represent SE of means. An observed case analysis was conducted using available data by analysis time point, censoring motor function assessments (HFMSE and RULM) after the participant had scoliosis surgery.
HFMSE, Hammersmith Functional Motor Scale Expanded; RULM, Revised Upper Limb Module; SE, standard error.

Patient/caregiver-reported outcomes

- The PEDI-CAT, which assesses an individual's daily living skills in their natural environment, showed that improvements from baseline were sustained through 48 months (**Figure 3A**)
- Improvements in perceived fatigue, as assessed by the PROMIS-Fatigue caregiver assessment, were also sustained (**Figure 3B**)

Figure 3. Mean change from baseline in A) PEDI-CAT Daily Activities score and B) PROMIS-Fatigue caregiver questionnaire score



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PEDI-CAT, Pediatric Evaluation of Disability Inventory–Computer Adaptive Test; PROMIS, Patient-Reported Outcome Measurement Information System; SE, standard error.

Safety

- The safety profile was consistent with previous reports, with no new safety signals identified during the final extension period (**Table 1**)
- The most common treatment-emergent adverse events (TEAEs) were COVID-19, pyrexia, upper respiratory tract infection, headache, cough, and nasopharyngitis
- TEAEs were generally consistent with the underlying participant population and SMN-targeted therapy

Table 1. TEAEs over the 48-month study period

TEAEs[a] during the study	Total (N = 58)
Any TEAE, n (%)	57 (98.3)
Any serious TEAE, n (%)	28 (48.3)
Any TEAE leading to study drug discontinuation, n (%)	1 (1.7)
Any grade 3 (severe) or higher TEAE, n (%)	27 (46.6)

[a]An adverse event was considered treatment-emergent if onset occurred after administration of the first dose of apitegromab or the onset preceded the first dose of apitegromab, but the AE increased in severity during the study.
TEAE, treatment-emergent adverse event.

Conclusions

- Continued apitegromab treatment provided sustained benefit across motor function and caregiver-reported outcome measures
- These updated results support further clinical development of apitegromab in nonambulatory SMA

References

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Conflicts of interest

TOC is the lead principal investigator of the Scholar Rock, Inc.–sponsored phase 2 TOPAZ trial and a consultant and/or advisory board member for AveXis/Novartis Gene Therapies, Biogen, Pfizer, and Roche/Genentech. **DCDV** received grants from Biogen during the study and from the Department of Defense, Hope for Children Research Foundation, National Institutes of Health, and Spinal Muscular Atrophy Foundation and personal fees from AveXis, Biogen, Cytokinetics, Ionis Pharmaceuticals, Roche, and Sarepta Therapeutics. **JMK** is a site principal investigator for AveXis/Novartis Gene Therapies, Biohaven Pharmaceuticals, FibroGen, Roche/Genentech, and Scholar Rock, Inc. **ESM** has received consulting fees from Biogen, Novartis, Roche, and Scholar Rock, Inc. **GS**, **JLM**, **MG**, **DY**, **BY**, and **KU** are Scholar Rock, Inc., employees and stockholders. **BTD** has served as an ad hoc scientific advisory board member for AveXis/Novartis Gene Therapies, Biogen, Roche/Genentech, Sarepta Therapeutics, and Scholar Rock, Inc.; steering committee chair for Roche FIREFISH and MANATEE studies; and a data and safety monitoring board member for Amicus Therapeutics, ArgX, 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.

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