Efficacy of Apitegromab in Patients with Later-Onset Spinal Muscular Atrophy (SMA Types 2 and 3): Responder Analysis from the Phase 2 TOPAZ Study

J.W. Day[1]; T.O. Crawford[2]; B.T. Darras[3], G. Nomikos[4], G. Song[4], A. Place[4,5], D. Barrett[4], S. Cote[4], J. O'Neil[4], N. Kertesz[4], Y. Chyung[4]

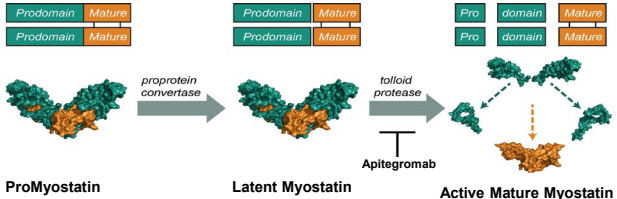
[1]Stanford Neuroscience Health Center, Palo Alto, CA; [2]Johns Hopkins University School of Medicine, Baltimore, MD; [3]Boston Children's Hospital, Boston, MA; [4]ScholarRock Inc. Cambridge, MA; [5]Corresponding author; MedicalInquiry@ScholarRock.com; https://scholarrock.com

POS310

Background

Apitegromab is an investigational, fully human, monoclonal antibody that specifically binds to proforms of myostatin, promyostatin and latent myostatin, thereby inhibiting myostatin activation. We will present responder analysis on efficacy data from the TOPAZ clinical trial (NCT03921528).[1]

Introduction[2]



- Activation of myostatin requires two distinct proteolysis events that generate the active mature growth factor; apitegromab inhibits the activity of the tolloid protease.[1,2]
- Apitegromab does not bind to mature myostatin or any form of GDF11, Activin A, or other TGF-β family members[1,2]

Methods

TOPAZ was a 52-week trial in subjects with later-onset SMA. 58 patients received IV Q4W apitegromab, assigned in 3 pilot cohorts: 20 randomized double-blind NonAmbulatory Type 2 ≥ age 2 subjects treated with concomitant nusinersen initiated prior to age 5 received 2 or 20 mg/kg apitegromab; 15 NonAmbulatory Type 2/3 subjects aged 5-21 with concomitant nusinersen initiated after age 5 received apitegromab 20mg/kg; 23 Ambulatory Type 3 subjects aged 5-21 years, received 20mg/kg apitegromab as monotherapy or with concomitant nusinersen.[3] Patients received ~2 years of nusinersen treatment at baseline.[4]

Figure 1: TOPAZ Study Design[3]

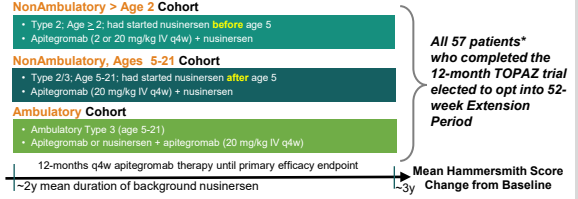
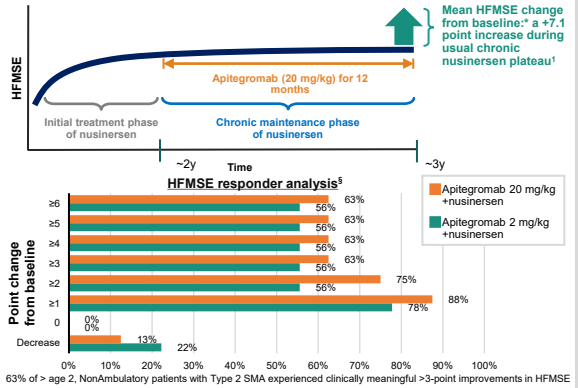
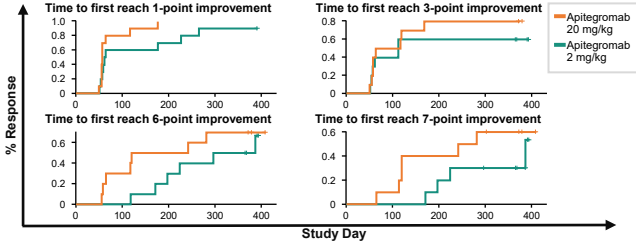


Figure 2: Type 2 NonAmbulatory > age 2 cohort: Substantial HFMSE increases follow apitegromab (20 mg/kg) [§ 3,4]



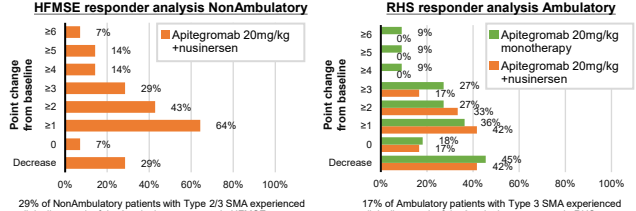
63% of > age 2, NonAmbulatory patients with Type 2 SMA experienced clinically meaningful >3-point improvements in HFMSE

Figure 3: Type 2 NonAmbulatory > Age 2 Cohort: Dose Responsive Improvement in Time to Reach HFMSE Motor Function Benefit[§4]



Both dosage groups manifest early benefit (as early as 2 months).
Greater latency of low dose cohort supports apitegromab attributable effect

Figure 4: Type 2/3 NonAmbulatory &Type 3 Ambulatory; Ages 5-21 Cohort: Majority of Patients Experienced Motor Function Improvements[§4]



29% of NonAmbulatory patients with Type 2/3 SMA experienced clinically meaningful > 3-point improvements in HFMSE

17% of Ambulatory patients with Type 3 SMA experienced clinically meaningful > 3-point improvements in RHS

Safety

Five most frequently reported TEAEs** from the TOPAZ trial: headache (24%), pyrexia (22%), URTI (22%), cough (22%), and nasopharyngitis (21%). Incidence and severity of AEs from the TOPAZ trial were consistent with underlying patient population and background therapy.

Summary

- Motor function improvements were observed in the primary efficacy endpoints in the Phase 2 TOPAZ clinical trial.
- Dose responsive improvement in time to reach motor function confirmed apitegromab benefit on top of underlying nusinersen benefit.
- 29-63% of patients in the NonAmbulatory cohort experienced > 3-point increases in Hammersmith Functional scores; and 22% of patients in the pooled Ambulatory cohort experienced > 3-point increases in Hammersmith Functional scores.
- This information may help to clarify patient response to apitegromab treatment.
- Apitegromab has the potential to be the first muscle-directed therapy to address motor function impairment in patients with SMA.

References 1. Dagbay KB et al. *J Biol Chem*. 2020;295(16):5404–5418. 2. Pirruccello-Straub M et al. *Sci Rep*. 2018;8(1):2292. 3. Place A et al. *Eu J Neurol*. 2021;28(Supp1)207–334:(EPR-184). 4. Data on File, Scholar Rock.

Acknowledgements
The authors thank the patients, caregivers, PIs and SCs in the TOPAZ trial; and the apitegromab preclinical and clinical teams.

Disclaimer: Apitegromab is an investigational drug candidate being developed and studied for SMA. The effectiveness and safety of apitegromab have not been established. Apitegromab has not been approved by the FDA or any other regulatory authority. *Excludes one patient from Cohort 1 who discontinued from the trial.; §Intent-to-treat analysis excluded 1 patient (per prespecified approach) who missed 3 doses due to COVID-19 related site access restrictions; 1 patient who had inadvertently been enrolled who was receiving (and continued to receive) an acetylcholinesterase inhibitor was removed, which is not permitted per the trial protocol **Treatment-emergent adverse events (TEAEs) are defined as AEs 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.TEAE rates are across all patients in TOPAZ trial; CI, confidence interval; GDF11, Growth differentiation factor 11 also known as BMP11; HFMSE, Hammersmith functional motor scale expanded; ITT, intent to treat; IV, intravenous; mg/kg, milligram/kilogram; min, minimum; max, maximum; PD, pharmacodynamic; PI, Principal Investigator; PK, pharmacokinetic; Q4W, dosed every 4 weeks; RHS, Revised Hammersmith scale; SC, study coordinator; SD, Standard deviation; SMA, spinal muscular atrophy; SMN, Survival motor neuron 1; SRK-015, apitegromab; TGF-β, Transforming growth factor β; URTI, upper respiratory tract infection