Apitegromab in Spinal Muscular Atrophy (SMA): An Analysis of Multiple Efficacy Endpoints in the TOPAZ Trial

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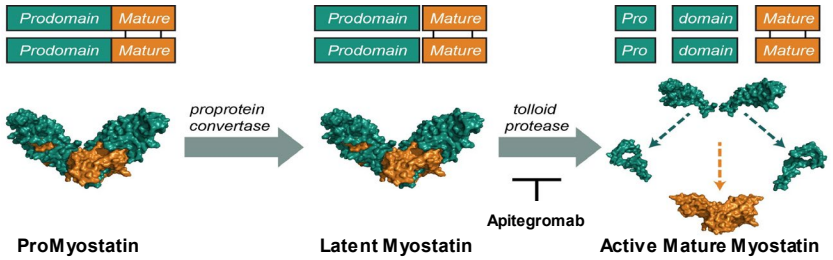
Background

Apitegromab is an investigational, fully human, monoclonal antibody that specifically binds to proforms of myostatin—promyostatin and latent myostatin—thereby inhibiting myostatin activation. We report the TOPAZ, 3 cohort, phase 2 pilot study (NCT03921528) results of 58 patients with later-onset SMA dosed with IV apitegromab Q4W for 52 weeks.[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]

Figure 1: TOPAZ Study Design[3]

NonAmbulatory ≥Age 2 Cohort

- Type 2; had started SMN upregulator **before** age 5
- Apitegromab (2 or 20 mg/kg IV q4w) + nusinersen

NonAmbulatory, Ages 5-21 Cohort

- Type 2/3; had started SMN upregulator **after** age 5
- Apitegromab (20 mg/kg IV q4w) + nusinersen

Ambulatory Age 5-21 Cohort

- Ambulatory Type 3
- Apitegromab or nusinersen + apitegromab (20 mg/kg IV q4w)

All 57 patients who completed the 12-month TOPAZ trial elected to opt into 52- week extension period*

12-month q4w apitegromab therapy until primary efficacy endpoint → **Mean Hammersmith Score Change from Baseline**

*Excludes one patient from Cohort 1 who discontinued from the trial.

Figure 2: TOPAZ Topline Results Demonstrate that Apitegromab Improves Motor Function in Patients with SMA[3]

	NonAmbulatory Patients HFMSE				Ambulatory Patients RHS
	Type 2; Age ≥2 Cohort†			Type 2/3; Ages 5-21 Cohort†	Type 3 Cohort‡
Primary Analysis ITT Population§	Apitegromab (2 mg/kg) +nusinersen	Apitegromab (20 mg/kg) +nusinersen	Pooled	Apitegromab (20 mg/kg) +nusinersen	Apitegromab (20 mg/kg) monotherapy
% (n) patients ≥3-pt increase in motor function	56% (5/9)	63% (5/8)	59% (10/17)	29% (4/14)	27% (3/11)

NonAmbulatory, Type 2 Apitegromab (20 mg/kg) - Motor Function Improvements:

- Majority of patients >60% experienced ≥6-point gains in HFMSE
- 38% experienced >10-point gains in HFMSE
- +7.1 point mean improvement in HFMSE (95% CI 1.8, 12.5)

NonAmbulatory, Type2/3; difficult-to-treat cohort: younger subset with greater Motor Function Increases

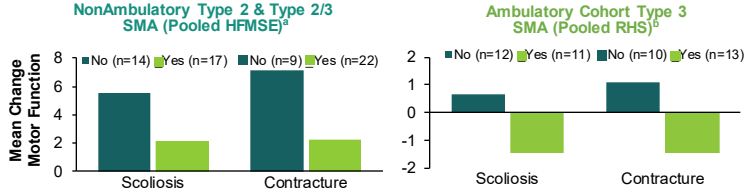
- A post-hoc exploration showed 50% of patients in the younger subset (5-12 years) experienced >3-point increases in HFMSE
- A +1.6 (-1.3, 4.6) mean improvement in HFMSE in younger (5-12 year) cohort vs mean +0.6 (-1.4, 2.7) improvement overall

Ambulatory, Type 3; Apitegromab (20 mg/kg) -Motor Function Improvements:

- Majority of patients maintained or improved RHS from baseline
- Increases from baseline of up to 8-points observed (monotherapy subset)
- Majority of patients showed stabilization (the goal of treatment where natural history suggests decline is common) with a mean pooled RHS score from baseline of -0.3 (-2.1, 1.4)[4]

A 3-point HFMSE increase represents clinically meaningful improvements in 2 or 3 motor skills[5]
A 6-point increase in HFMSE represents improvements in 3 to 6 motor skills[5]

Figure 3: Greater improvements in Hammersmith Scores Inversely Correlate With Characteristics of Advanced Disease[6]



Patients who skipped 3 consecutive doses due to site restrictions which were due to COVID-19, were excluded; [a]SD Scoliosis (7.7) min-7, max 20, SD (5.4) min-7, max 13; [a]SD Contracture (7.1) min-3, max 20, SD (2.3) min-7, max 13; [b]SD Scoliosis (0.7) min-4, max 4, SD (-1.5) min -12, max 8; [b]SD Contracture (1.1) min-2, max 4, SD (-1.5) min -12, max 8

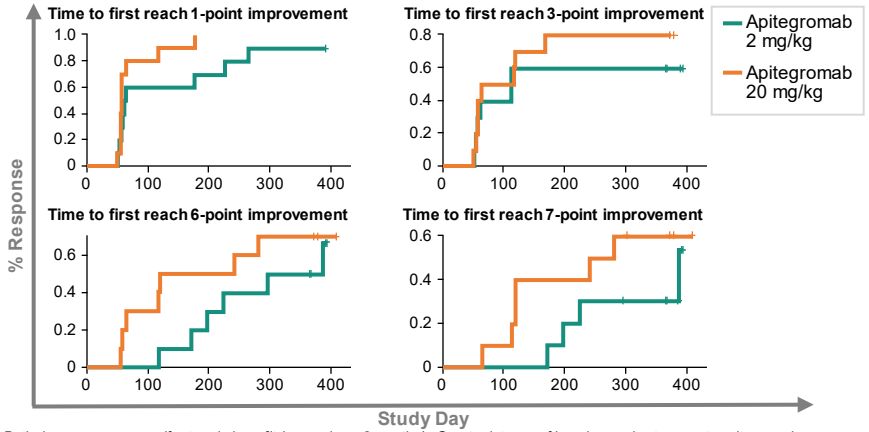
Figure 4: NonAmbulatory Cohorts: Substantial RULM Improvements With Apitegromab[6]

	NonAmbulatory Patients HFMSE			
	Type 2; Age ≥2 Cohort†			Type 2/3; Ages 5-21 Cohort†
Primary Analysis (ITT population)§	Apitegromab (2 mg/kg) +nusinersen	Apitegromab (20 mg/kg) +nusinersen	Pooled	Apitegromab (20 mg/kg) +nusinersen
% (n) patients achieving ≥2-pt improvements from Baseline in Revised Upper Limb Motor (RULM) Function	33% (3/9)	29% (2/7)	31% (5/16)	36% (5/14)

Mean improvements in RULM from baseline: Type 2, ≥2y: +1.0 (-1.7, 3.7) and Type 2/3, 5-21y: +1.2 (95% CI-0.5, 2.9)

A 2-point increase in RULM is considered clinically meaningful[7]

Figure 5: Type 2 NonAmbulatory, ≥Age 2 Cohort: Dose Responsive Improvement in Time to Reach HFMSE Motor Function Benefit



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

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 and secondary 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.
- Positive correlation of improvement in motor milestone score with SMA severity, length of nusinersen treatment and inverse relationship with age and characteristics of advanced disease such as scoliosis and contractures.
- The information presented here may be helpful in understanding 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(Suppl1) 207–334:(EPR-184). **4.** Vuillerot C, et al. *Arch Phys Med Rehabil*. 2013;94:1555-61. **5.** Rouault F, et al. *Neuromuscul Disord*. 2017;27:428-38. 6. Data on File, Scholar Rock, Inc. 7. Coratti G, et al. *Muscle Nerve*. 2019; 59: 426-430.

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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. †4 patients (1 in Cohort 2 and 3 in Cohort 3) each missed 3 doses of apitegromab during the 12-month treatment period due to COVID-19-related site access restrictions and were not included in the primary analysis; ‡includes 2 patients in monotherapy and 2 patients in apitegromab + nusinersen subgroup who maintained RHS score (0-point change from baseline); §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