Relationship of Pharmacodynamics (PD) to Apitegromab Efficacy in Patients With SMA (Types 2 and 3): Results from TOPAZ

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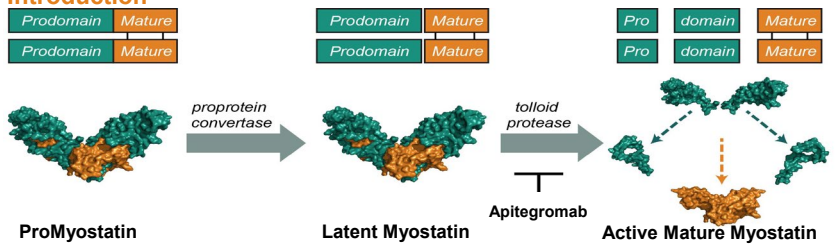
Background

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 following results from the TOPAZ, 3 cohort, phase 2 study (NCT03921528): the relationship of pharmacokinetics (PK) and pharmacodynamics (PD, measure of total latent myostatin in the serum) to efficacy of 58 patients with later-onset SMA dosed with IV apitegromab q4w for 52 weeks.[1]

Introduction[2]



- Activation of myostatin (negative regulator of muscle mass) 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]
- It is proposed that apitegromab bound latent myostatin is pulled from muscle into systemic circulation, and this is measured as part of total myostatin in circulation.[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 & Type 3; had started SMN upregulator **after** age 5
- Apitegromab (20 mg/kg IV q4w) + nusinersen

Ambulatory, Ages 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 Demonstrates Apitegromab May Improve 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 Ages 5-21 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)

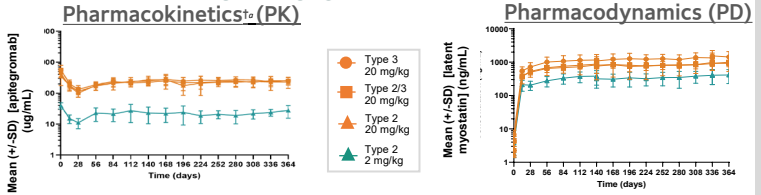
NonAmbulatory, Type 2 Apitegromab (20 mg/kg) - Motor Function Improvements:
- Majority of patients >60% experienced ≥ 6-point gains in HFMSE
- 38% experienced > 10-point gains in HFMSE
- +7.1 point mean improvement in HFMSE (95% CI 1.8, 12.5)

NonAmbulatory, Type 2&3: younger subset with greater Motor Function Increases:
- A post-hoc exploration showed 50% of patients in the younger (5-12 years) subset experienced >3-point increases in HFMSE
- A +1.6 (-1.3, 4.6) mean improvement in HFMSE in younger (n=8) cohort vs mean +0.6 (-1.4, 2.7) overall

Ambulatory, Type 3; Apitegromab (20 mg/kg) - Motor Function Improvements:
- Majority of patients maintained or improved RHS from baseline
- Majority of patients showed stabilization (goal of treatment where 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: PK and PD Data Reveal Robust and Sustained Drug Exposure and Target Engagement[6]

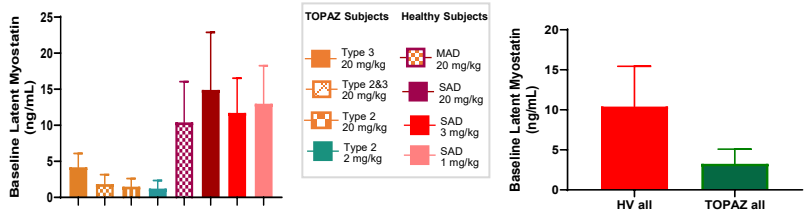


Dose-proportional and sustained drug exposure following chronic administration of apitegromab

Both doses yielded high levels of target engagement (>100-fold increase from baseline) as assessed by serum latent myostatin levels
Higher levels of target engagement with higher dose group
Ambulatory cohort had the highest average baseline latent myostatin concentration

[a]Starting at day 28, measures are predose trough levels

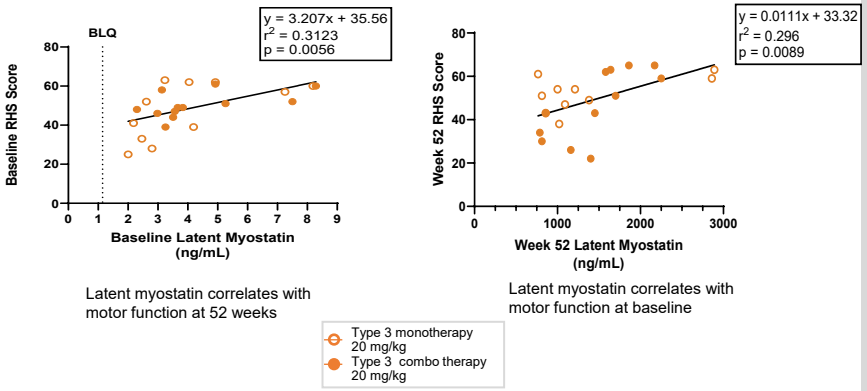
Figure 4: Baseline Latent Myostatin Concentrations Were Significantly Higher in Healthy Volunteer Subjects than in Subjects with SMA[6]



Baseline latent myostatin concentrations are higher in subjects with healthier muscle
Ambulatory subjects with SMA have higher levels of latent myostatin than nonambulatory subjects

SAD: n=6 at each dose; MAD n=6; TOPAZ: n= 23 for Type 3; n= 15 for Type 2&3; n= 10 for Type 2 at each dose.

Figure 5: Positive Correlations Between Magnitude of Latent Myostatin and Magnitude of Motor Function Measures in TOPAZ Ambulatory Subjects[#6]



Latent myostatin correlates with motor function at 52 weeks

Latent myostatin correlates with motor function at baseline

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.
- PK: Dose-proportional and sustained drug exposure; PD: Dose-dependent and sustained increase in serum latent myostatin, used as proxy to target engagement.
- Substantial correlations between magnitude of target engagement (PD, serum latent myostatin) and magnitude of motor function measures in ambulatory subjects
- This information may 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(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.

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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; #Similar correlations were not found in the nonambulatory subjects. Additional post hoc analyses to understand the impact of these findings are being conducted. 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