Apitegromab in Spinal Muscular Atrophy (SMA): An Analysis of PK/PD Relationships to Efficacy in Ambulatory Patients from the TOPAZ Trial

Thomas O. Crawford[1], Basil T. Darras[2], John W. Day[3], Doreen Barrett[4], Guochen Song[4], Sanela Bilic[5], Shaun Cote[4], Janet O'Neil[4], Nily Osman[4], Nathalie Kertesz[4], George Nomikos[4,6], Yung Chyung[4]

[1]Johns Hopkins University School of Medicine, Baltimore, MD; [2]Boston Children's Hospital, Boston, MA; [3]Stanford Neuroscience Health Center, Palo Alto, CA, [4]ScholarRock Inc. Cambridge, MA; [5]Vanadro, Urbandale, IA, [6]Corresponding author; MedicalInquiry@ScholarRock.com; https://scholarrock.com

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 results from an analysis of the ambulatory cohort of our recent study of 3-cohorts of subjects with late-onset SMA, phase 2 TOPAZ study. 23 subjects received IV apitegromab 20 mg/kg Q4W for 52 weeks. The results of this analysis of this ambulatory cohort may inform future trials. The relationship of pharmacokinetics (PK) and pharmacodynamics (PD, measure of total latent myostatin in the serum) and possible confounders of efficacy in this ambulatory patient cohort will be presented (NCT03921528)[1]

Introduction

- Activation of myostatin (negative regulator of muscle mass) requires two distinct proteolysis events that generate the active mature growth factor; apitegromab is a fully human monoclonal antibody that 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, measured as part of total myostatin in circulation.[1,2]

Figure 1: TOPAZ Design & Baseline Parameters of Ambulatory Cohort[3]

Study Design	Ambulatory Patients (Revised Hammersmith Scale; RHS)
Patient Cohort	• Ambulatory Type 3 SMA 1) Subgroup receiving apitegromab monotherapy 2) Subgroup receiving background nusinersen+apitegromab
Design	• N = 23; ages 5-21 • Open-label, single-arm • 20 mg/kg apitegromab IV Q4W
Primary Objectives	• Safety • Mean change from baseline in RHS

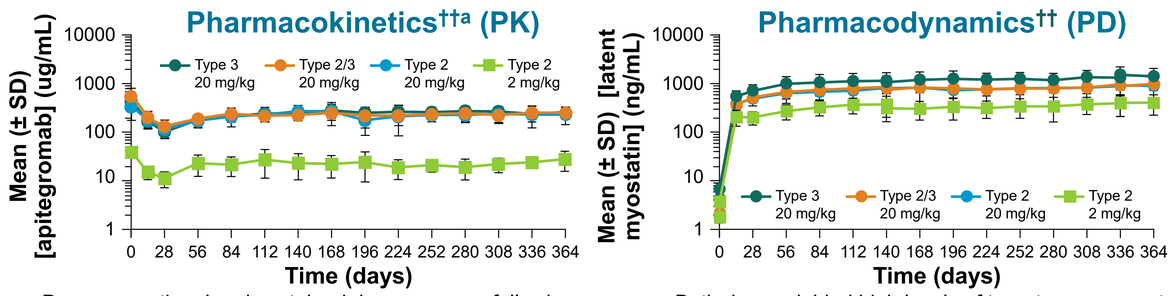
Baseline Parameters	20 mg/kg Monotherapy	20 mg/kg + Nusinersen
N (dosed)	11	12
Mean age at screening (min, max)	12.1 (7, 19)	13.1 (7, 21)
Mean age at diagnosis (min, max)	5.9 (2, 15)	4.5 (2, 15)
Female (%)	73%	58%
SMN2 Gene Copy* (#, %): 2	1 (9%)	0 (0%)
SMN2 Gene Copy* (#, %): 3	4 (36%)	9 (75%)
SMN2 Gene Copy* (#, %): 4	4 (36%)	1 (8%)
# of maintenance doses of nusinersen at baseline† (min, max)	N/A	5.6 (2, 8)
Discontinuation (s)	0	1‡
Mean RHS score (min, max)	47.6 (26, 63)	51.3 (43, 62)

Figure 2: TOPAZ Topline Results Demonstrate Apitegromab May Improve Motor Function in Ambulatory Patients[3]

Primary Analysis Ambulatory Cohort§	Apitegromab (Pooled)	Apitegromab Monotherapy	Apitegromab + Nusinersen
N, ITT	23	11	12
Mean ΔRHS (95% CI)	-0.3 (-2.1, 1.4)	-0.4 (-3.9, 3.1)	-0.3 (-2.0, 1.4)
# (%) ≥1-pt gain RHS	9 (39%)	4 (36%)	5 (42%)
# (%) ≥3-pt gain RHS	5 (22%)	3 (27%)	2 (17%)
Mean Δ6MWT (95% CI)	-6.3 (-23.0, 10.3)	-20.2 (-45.7, 5.3)	6.3 (-16.5, 29.2)

- Majority of patients maintained or improved RHS from baseline (57% ≥ 0-pt gain)
- Majority of patients showed stabilization (the goal of treatment where natural history suggests decline is common)[4]

Figure 3: PK and PD Data Reveal Robust and Sustained Drug Exposure and Target Engagement[5]

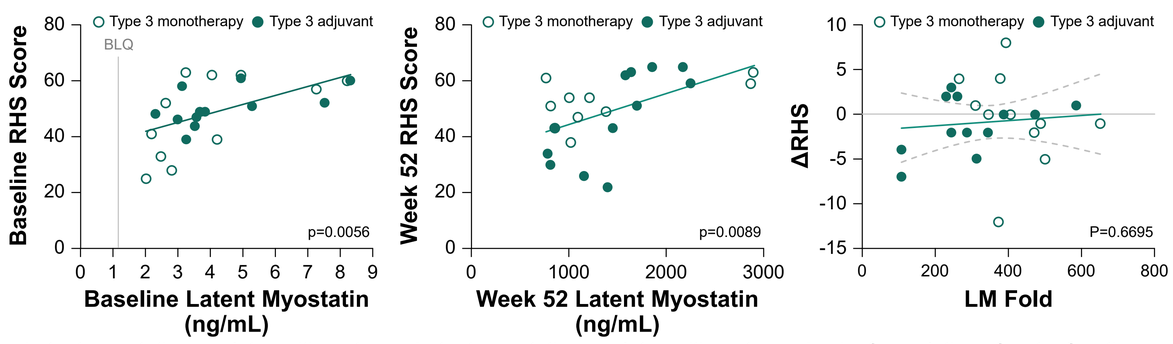


Dose-proportional and sustained drug exposure following chronic administration of apitegromab.

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

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

Figure 4: Correlations in Changes in RHS Function and Latent Myostatin in TOPAZ Ambulatory Monotherapy Group ‡‡[5]

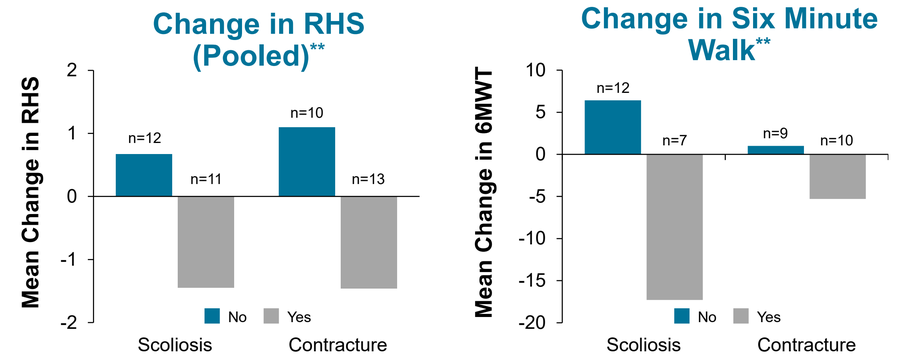


Latent myostatin correlates with motor function at baseline

Latent myostatin correlates with motor function at 52 weeks

Lack of correlation of motor function change and LM change may be due to negative confounders (see below)

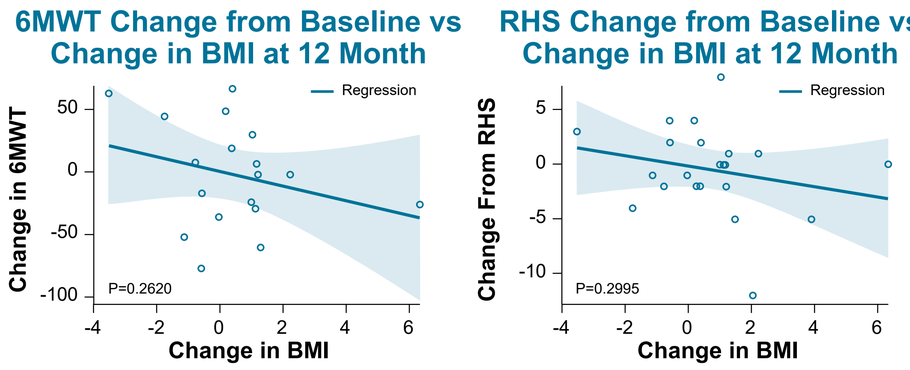
Figure 5: The Presence of Scoliosis and Contractures may be Negative Confounders of Motor Function Improvements (ΔRHS or Δ6MWT) in TOPAZ Ambulatory Subjects‡‡[5b]



Exploratory Analysis: Negative correlations between improvements in Δ6MWT or ΔRHS measures and presence of scoliosis and contractures‡‡[5]

[b]4 patients excluded from 6MWT analysis; 3 due to loss of mobility in the ambulatory subset, 1 had an invalid measure at visit 15

Figure 6: In-Study Increase in BMI may be Associated Negatively with Δ6MWT or ΔRHS Assessments of Motor Function in TOPAZ Ambulatory Subjects (Pooled Subsets)‡‡[5c]



Exploratory Analysis: Negative trends between improvements in Δ6MWT measures and ΔBMI or ΔRHS and ΔBMI‡‡[5]

[c]5 patients excluded from BMI analysis; 3 due to loss of mobility in the ambulatory subset, 1 had an invalid measure at visit 15, 1 patient excluded due to early withdrawal

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.

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.** Data on File, Scholar Rock.

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

Summary

- Motor function improvements were observed in the primary and secondary efficacy endpoints in all cohorts in the Phase 2 TOPAZ clinical trial.
- PK: Dose-proportional & sustained drug exposure; PD: Dose-dependent & sustained increase in serum latent myostatin, used as proxy for target engagement.
- Substantial correlations between magnitude of target engagement (PD, serum latent myostatin) and of motor function measures in ambulatory subjects.
- Ambulatory cohort exhibited overall mean stabilization of motor function, compared to natural history data for this ambulatory Type 3 population suggesting decline is common.
- No correlation of motor function change and LM change that may be due to presence of negative confounders such as increased BMI, presence of scoliosis and contractures and may explain declines in motor function and on target effect.
- Apitegromab has the potential to be the first muscle-directed therapy to address motor function impairment in patients with SMA.

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. *1 patient answered 3–4, 1 patient answered >4, both patients are in the ambulatory cohort, treated with 20 mg/kg + nusinersen; data not available for all patients; †Patients on average received ~2 years of nusinersen treatment at baseline and ~3 years of nusinersen treatment by the end of the TOPAZ study (12-months); ‡Patient who discontinued study for reasons unrelated to study drug. §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; ††4 patients (1 in Nonambulatory Type 2/3 and 3 in Nonambulatory Type 2) 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; Visit 15 (Day 365) of TOPAZ trial ambulant Type 3 SMA; LM Fold, latent myostatin at Day 365/value at predose; ‡‡Similar correlations were not found in the nonambulatory subjects. Additional post hoc analyses to understand the impact of these findings are being conducted. ¶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; CI, confidence interval; GDF11, Growth differentiation factor 11 also known as BMP11; 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; TGF-β, transforming growth factor β; URTI, upper respiratory tract infection; 6MWT, Six minute walk test

Copyright © 2022 Scholar Rock