Apitegromab in SMA: An Analysis of Multiple Efficacy Endpoints in the TOPAZ Extension Study

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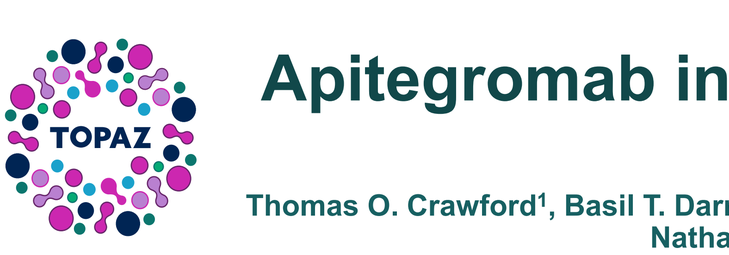
Types 2/3 SMA: SMN targeted therapies offer important benefits, but... *Substantial* unmet need remains in this era

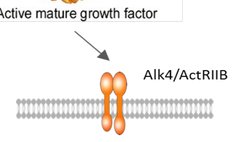
- Most patients manifest substantial functional impairment[1,2]
- The greatest improvements with SMN targeted therapies are in the youngest individuals (age < 5)[1,2]
- SMN targeted therapies address neurodegeneration, other approaches to improve motor function are needed[3-5]
- Patients with SMA experience limitations in mobility and daily activities associated with a gradual deterioration in motor function, alongside emotional difficulties, fatigue and a perceived lack of societal support; however, there has been no evidence regarding effective interventions thus far that improve QoL* measures[6-7]

Myostatin is an Important Negative Regulator of Skeletal Muscle Growth Whose Inhibition has the Potential to Lead to Improved Muscle Function in Patients With SMA[9,10]

Apitegromab: a fully human monoclonal antibody that blocks cleavage of the myostatin prodomain, thereby inhibiting myostatin activation[10]



- Two distinct proteolysis events necessary to generate active mature myostatin
- Apitegromab binds to both proMyostatin and latent myostatin and inhibits tolloid-mediated cleavage of latent myostatin
- Apitegromab bound latent myostatin is proposed to be pulled from muscle into systemic circulation and can be measured as part of total circulating myostatin.[11]



Selective Targeting of preproMyostatin, the Myostatin Precursor: Apitegromab Does Not Bind to Mature Myostatin or Any Form of GDF11, Activin A, or Other TGF-β family[10,11] Members

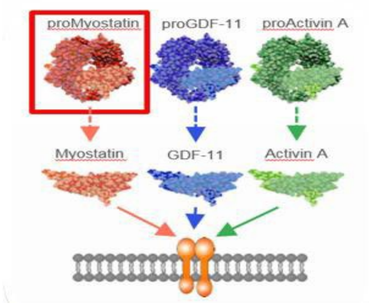


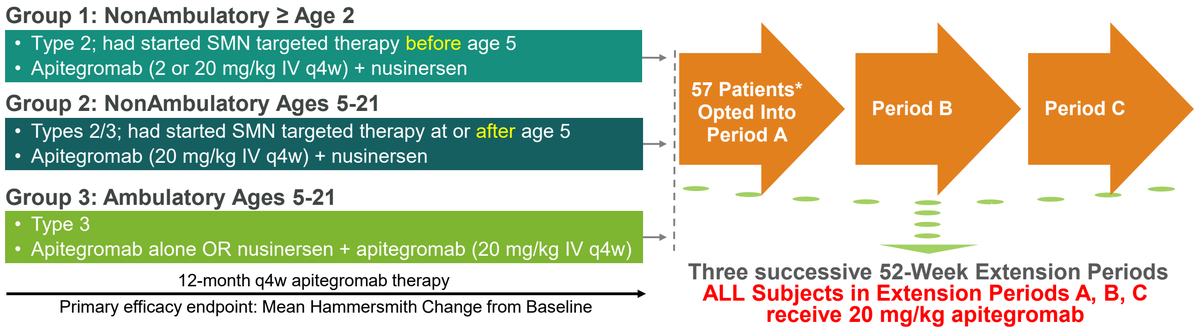
Figure 1: TOPAZ Phase 2 Trial Design, Including Open Label Extension Periods: Three Pilot Cohorts to Identify Therapeutic Opportunities

All SMA types 2/3, cohorts defined by age and ambulatory status at time of enrollment

Group 1: NonAmbulatory ≥ Age 2
- Type 2; had started SMN targeted therapy before age 5
- Apitegromab (2 or 20 mg/kg IV q4w) + nusinersen

Group 2: NonAmbulatory Ages 5-21
- Types 2/3; had started SMN targeted therapy at or after age 5
- Apitegromab (20 mg/kg IV q4w) + nusinersen

Group 3: Ambulatory Ages 5-21
- Type 3
- Apitegromab alone OR nusinersen + apitegromab (20 mg/kg IV q4w)



*Excludes one patient from Cohort 1 who discontinued from the trial; 57/58 Completed Treatment Period and Enrolled in Extension Period A; 2 Withdrew Consent in Extension Period A; 55 Completed Extension Period A and Enrolled into Extension Period B; Place A, et al. *Eu J Neurol.* 2021;28(Suppl1) 207–334:(EPR-184).

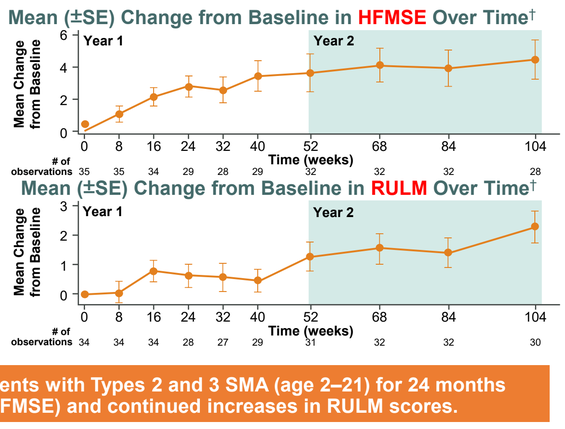
Figure 2: TOPAZ Subject Disposition, Demographics and Baseline Characteristics[12]

		Age ≥ 2 Type 2		Age 5-21 Type 2/3		Age 5-21 Type 3	
		2 mg/kg + nusinersen	20 mg/kg + nusinersen	20 mg/kg + nusinersen		20 mg/kg monotherapy	20 mg/kg + nusinersen
N (dosed)	NonAmbulatory Patients	10	10	15	Ambulatory Patients	11	12
Mean age at screening (min, max)		4.1 (2, 6)	3.8 (2, 6)	11.7 (8, 19)		12.1 (7, 19)	13.1 (7, 21)
Mean age at SMA diagnosis (min, max)		1.2 (1, 2)	1.2 (1, 3)	3.1 (1, 16)		5.9 (2, 15)	4.5 (2, 15)
Female (%)		30	50	53		73	58
SMN2 Gene Copy* (#, %)							
2		1 (10)	1 (10)			1 (9)	0 (0)
3		8 (80)	8 (80)	11 (73)		4 (36)	9 (75)
4		1 (10)	0 (0)	2 (13)		4 (36)	1 (8)
Months of prior treatment of nusinersen at baseline (min, max)		26.6 (12,36)		25.2 (12, 39)		N/A	26.0 (9, 40)
Discontinuation(s)		0	0	1†		0	2†
Scoliosis (#, %)		4 (40)	3 (30)	11 (73.3)		7 (63.6)	4 (33.3)
Contracture(s) (#, %)		8 (80)	4 (40)	13 (86.7)		6 (54.5)	7 (58.3)
Mean RHS score (min, max)						47.6 (26, 63)	51.3 (43, 62)
Mean HFMSE score (min, max)		26.1 (12, 44)	23.5 (14, 42)	22.7 (13, 39)			

*1 patient answered 3-4, 1 patient answered >4, both patients are in Cohort 1 treated with 20 mg/kg + nusinersen; data not available for all patients. †1 cohort 1 patient discontinued study in 12M Treatment Period, 1 cohort 1 patient and 1 cohort 2 patient discontinued during 24M Extension Period A. All discontinuations were for reasons unrelated to study drug.

Figure 3: NonAmbulatory Patients Continue to Improve in Motor Function Over 24 Months of Apitegromab Treatment[12]

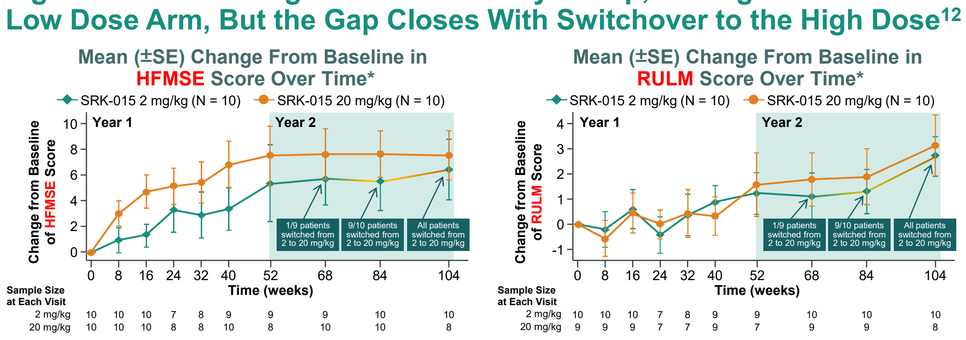
	At 12 months*	At 24 months†
Mean Change in HFMSE (95% CI):	Increase of 3.6 (1.2, 6.0)	Increase of 4.4 (2.0, 6.9)
≥3 pt point change in HFMSE:	Achieved in 42% (13/32) of patients	Achieved in 46% (13/28) of patients
Mean Change in RULM score (95% CI):	Increase of 1.3 (0.2, 2.3)	Increase of 2.3 (1.2, 3.4)
≥2 pt point change in RULM:	Achieved in 40% (12/31) of patients	Achieved in 50% (15/30) of patients



Apitegromab + SMN targeted treatment in nonambulatory patients with Types 2 and 3 SMA (age 2–21) for 24 months demonstrated durable improvement in motor function (HFMSE) and continued increases in RULM scores.

*Observed Case (OC) Analysis includes all patients who had a valid measurement at E14 (Day 728). OC analysis included patients treated with 2 as well as 20 mg/kg of apitegromab. This analysis does not exclude any patients who missed doses due to COVID-19 related site access restrictions. †24-month Sensitivity Analysis excludes from the OC Analysis any HFMSE data following scoliosis surgery in TOPAZ. Of the three non-ambulatory patients who had scoliosis surgery, data from one was excluded and the other two did not have valid HFMSE assessments. Error bars represent SEM.

Figure 4: In the Younger NonAmbulatory Group, the High Dose Arm Outperformed the Low Dose Arm, But the Gap Closes With Switchover to the High Dose[12]



Dose Response Observed Over 24 Months

*24-month Sensitivity Analysis excludes from the OC Analysis any HFMSE data following scoliosis surgery in TOPAZ. Of the three nonambulatory patients who had scoliosis surgery, data from one was excluded and the other two did not have valid HFMSE assessments. Error bars represent SEM.

Figure 5: Ambulatory Patients Receiving Both Apitegromab + SMN Targeted Treatment Stabilized Over 24 Months[12]

	Mean Change in RHS Score (95% CI)	Any Point Change in RHS Score
12 Months Group 3: Ambulatory Type 3*	Decline of -0.3 (-2.0,1.4)	17% (2/12) of patients achieved ≥3 pt RHS change from baseline
24 Months Group 3: Ambulatory Type 3*	Decline of -0.7 (-3.1,1.7)	20% (2/10) of patients achieved ≥3 pt RHS change from baseline

*Observed Case (OC) Analysis includes all patients who had a valid measurement at E14 (Day 728); Inclusive of data from 3 patients in monotherapy who lost ability to ambulate. This analysis does not exclude any patients who missed doses due to COVID-19 related site access restrictions.

Figure 6: Patients Receiving Both Treatments Manifest Improvements in Activities of Daily Living Over 24 Months[12]

PEDI-CAT mean change (tertiary endpoints) – measure of activities of daily living: higher scores reflect improved abilities[13]

4-point scale **(1=unable to 4=easy)** assessment of various activities. PEDI-CAT has been validated in SMA[14].

	Improvements in ADL at 12 Months	Improvements in ADL at 24 Months
Group 1: NonAmbulatory type 2 (≥2 years) – nusinersen before 5 years of age (95% CI)	Increase of 1.9 (–0.3, 4.1) (n=11)	Increase of 3.0 (1.8, 4.1) (n=14)
Group 2: NonAmbulatory type 2/3 (5-21 years) – nusinersen after 5 years of age (95% CI)	Increase of 0.9 (–1.4, 3.2) (n=12)	Increase of 0.7 (–1.8, 3.2) (n=8)
Group 3: Ambulatory type 3 (5-21 years) (95% CI)	Increase of 2.8 (1.6, 4.0) (n=9)	Increase of 1.8 (–11.2, 14.9) (n=3)

Apitegromab treatment resulted in patients improving in patient-reported outcomes related to self-sufficiency but requires further analysis due to small sample size.

Completed without assistance by a patient or a given parent proxy that was completed by patients who were 5 years of age or older at the time of the baseline assessment.

Figure 7: Patients Receiving Both Treatments Report Less Fatigue Over 24 Months[12]

Mean change in PROMIS (tertiary endpoints: fatigue) – measure of patient fatigue: lower scores reflect less fatigue[8,15]

Measures mild subjective feelings of tiredness to debilitating and sustained feelings of exhaustion. Has been used to assess fatigue and fatigability in the Cure SMA database, but has not been fully validated in SMA[8]

	Fatigue at 12 Months	Fatigue at 24 Months
Group 1: NonAmbulatory type 2 (≥2 years) – nusinersen before 5 years of age (95% CI)	Decrease of –5.5 (–10.1, –0.9) (n=4)	Decrease of –5.0 (–8.9, –1.1) (n=10)
Group 2: NonAmbulatory type 2/3 (5-21 years) – nusinersen after 5 years of age (95% CI)	Decrease of –0.6 (–5.9, 4.7) (n=10)	Decrease of –1.3 (–6.7, 4.0) (n=9)
Group 3: Ambulatory type 3 (5-21 years) (95% CI)	Decrease of –5.0 (–13.3, 3.3) (n=6)	Decrease of –5.8 (–15.4, 3.9) (n=4)

Apitegromab treatment resulted in patients reporting less fatigue but requires further analysis due to small sample size.

Completed without assistance by a patient or a given parent proxy that was completed by patients who were 5 years of age or older at the time of the baseline assessment. The parent proxy report utilized for children aged 5 to 17 years.

Figure 8: No New Safety Risks Identified Over 2 Years of Treatment[12]

Treatment-Emergent Adverse Events (TEAEs)*	Apitegromab 2 mg/kg dose (N=10) n (%)	Apitegromab 20 mg/kg dose (N=48) n (%)	Total (N=58) n (%)
Any TEAE	10 (100)	45 (93.8)	55 (94.8)
Any serious TEAE	3 (30)	11 (22.9)	14 (24.1)
Any TEAE leading to study drug discontinuation	0 (0.0)	1 (2.1)	1 (1.7)
Any grade 3 (severe) or higher TEAE	2 (20)	9 (18.8)	11(19)

- The incidence and types of TEAEs were consistent with the underlying disease or nusinersen therapy
- The 5 most common TEAEs were headache, pyrexia, upper respiratory tract infection, cough, and nasopharyngitis
- No deaths or suspected unexpected serious adverse reactions (SUSARs) reported
- Adverse events continue to be reported as mostly mild to moderate in severity, as observed during the 12-month analysis

*Notes: % = 100 x n/N
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.

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Summary of TOPAZ Extension Period: 24-Month Data

- The pilot TOPAZ experience has shaped the Phase 3 randomized, double-blinded SAPPHIRE trial now in progress
- NonAmbulatory Types 2/3 SMA: motor function gains with apitegromab treatment show durability at 24 months
  - Sustained increases in motor function (HFMSE & RULM) over 2 years
  - Continued improvements in RULM throughout 2 years
  - High dose outperforms low dose in HFMSE & RULM, but switchover to high dose closes the gap
  - Stabilization or improvements in Activities of Daily Living and Fatigue endpoints
- Stabilization of motor function over 2 years in ambulatory subjects with apitegromab + nusinersen
  - Potential motor function gains in subgroups
  - Stabilization or improvements in Activities of Daily Living and Fatigue endpoints
- **QoL data in this small sample suggests sustained improvement over 24 months in contrast to a recent systematic review of SMA natural history in which QoL deteriorated despite treatment with SMN up-regulators alone[7]**
- No new safety risks identified over 2 years of apitegromab treatment
- **Many thanks to all the patients who participate in these studies, caregivers/families, healthcare professionals & patient advocacy groups**

The TOPAZ trial is sponsored by Scholar Rock, a biopharmaceutical company developing and investigating apitegromab in a clinical development program for the treatment of Spinal Muscular Atrophy (SMA). 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.

*QoL, Quality of Life=outcomes that are meaningful from the patient perspective, and which measure the impact of therapies on other dimensions of life other than assessing survival or significant changes in motor milestones such as activities of daily living, work productivity, and fatigue.[8]

CI=Confidence Interval; ESBBT=endurance shuttle box and block test; HFMSE=Hammersmith Functional Motor Scale Expanded; HRQoL=health-related quality of life; PEDI-CAT=the Pediatric Evaluation of Disability Inventory computer adaptive test; PROMIS=Patient-Reported Outcome Measurement Information System; PRO(s)=patient-reported outcome(s); RHS=Revised Hammersmith Scale; SMA=spinal muscular atrophy; WHO=World Health Organization.

ClinicalTrials.gov identifier: NCT03921528.

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