Apitegromab, a Novel High-Affinity Anti-proMyostatin Monoclonal Antibody for Treating Spinal Muscular Atrophy: Results of a Phase 2 Interim Analysis

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Abstract

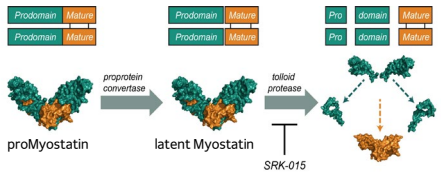
Apitegromab (SRK-015) is a fully human, high-affinity anti-proMyostatin monoclonal antibody that binds to human proMyostatin and latent myostatin and inhibits the tolloid-mediated proteolysis step for myostatin activation. As proMyostatin is the predominant form of myostatin in skeletal muscle, apitegromab inhibits myostatin activation directly in target tissues.

The primary objectives of this 52- week phase 2 trial (TOPAZ; NCT03921528)) are to assess safety and tolerability of apitegromab, administered by intravenous (IV) infusion every 4 weeks, in subjects with Type 2 and Type 3 spinal muscular atrophy (SMA) and measure changes in motor function. Secondary objectives are to characterize the pharmacokinetic (PK) and pharmacodynamic (PD) effects of apitegromab, therapeutic effects of low- (2 mg/kg) and high-dose (20 mg/kg) apitegromab, immunogenicity and other exploratory motor function measures. Subjects received apitegromab as monotherapy or with an approved SMN upregulator (nusinersen). The primary endpoint is the mean change of Hammersmith Scale scores, from baseline. Subjects in Cohort 1 (ambulatory Type 3, n=23), who received apitegromab (20 mg/kg) as monotherapy or as an adjunctive treatment to nusinersen, had a pooled mean change in baseline Revised Hammersmith Scale (RHS) scores of 0.5 (-1.1, 2.2). Cohorts 2 (n=14) and 3 (n=18) included Type 2 and non-ambulatory Type 3 subjects, who received apitegromab (Cohort 2, 20 mg/kg; Cohort 3, 2 mg/kg or 20 mg/kg) as an adjunctive treatment to nusinersen. Subjects in Cohort 2 achieved a mean change in baseline Hammersmith Functional Motor Scale Expanded (HFMSE) scores of 1.4 (0.1, 2.7). In the low-dose Cohort 3 group, the mean change in baseline HFMSE scores was 2.4 (-0.9, 5.8). In the high dose Cohort 3 group, the mean change in baseline HFMSE scores was 5.6 (2.5, 8.7). Safety and tolerability, PK/PD and responder analysis data (secondary efficacy) from the TOPAZ interim analysis will be presented.

Introduction

- Apitegromab is an investigational highly selective inhibitor of the activation of myostatin, based on *in vitro* data.
- The TOPAZ Phase 2 proof-of-concept trial enrolled 58 patients with Type 2 and Type 3 SMA across 16 study sites in the U.S. & E.U.
- The trial is evaluating the safety and efficacy of IV apitegromab dosed every four weeks (Q4W) over a 52-week treatment period.
- A pre-planned interim analysis was conducted following a six-month treatment period across all three study cohorts.*

Apitegromab: A Fully Human Antibody that Blocks Cleavage of the Myostatin Prodomain



- Activation of myostatin requires two distinct proteolysis events that generate the active mature growth factor
- Apitegromab binds to both proMyostatin and latent myostatin and inhibits tolloid-mediated cleavage of latent myostatin, thereby preventing the release of the mature, active myostatin
- Apitegromab does not bind to mature myostatin or any form of GDF11, Activin A, or other TGF-β family members

Methods

TOPAZ is a Phase 2, 52-week study of IV apitegromab treatment. Cohorts 1 and 2 are open-label while Cohort 3 was a double-blind, randomized arm (Figures 1,2).

- Primary endpoints:
  - Safety and tolerability in patients with Type 2 and Type 3 SMA
  - Efficacy assessment of change in motor function outcome measures as measured by Hammersmith scores
- Secondary endpoints:
  - PK and PD effects
  - Time to therapeutic effect between low and high dose apitegromab in Cohort 3
  - Immunogenicity
- The 52-week Treatment Period will be followed up by a 52-week open-label Extension Period or 12-week Follow-Up Period (Figure 1)

Results

Figure 1: TOPAZ Study Design

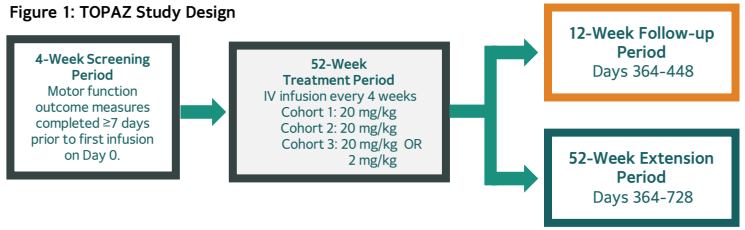


Figure 2: TOPAZ Phase 2 Active Treatment Study to Evaluate the Efficacy and Safety of Apitegromab in Patients with Later-Onset Spinal Muscular Atrophy

	Cohort 1	Cohort 2	Cohort 3
Design	• N= 23; ages 5-21 • Open-label, single-arm • 20 mg/kg apitegromab IV Q4W • 52-week treatment period	• N= 15; ages 5-21 • Open-label, single-arm • 20 mg/kg apitegromab IV Q4W • 52-week treatment period	• N= 20; ages ≥2 • Double-blind, randomized (1:1) to 2 mg/kg or 20 mg/kg apitegromab IV Q4W • 52-week treatment period
Patients	• Ambulatory Type 3 SMA • Patients receive apitegromab in combination with approved SMN up-regulator or as monotherapy	• Type 2 or non-ambulatory Type 3 SMA • Receiving treatment with approved SMN up-regulator	• Type 2 SMA • Initiated treatment with approved SMN up-regulator before age 5
Primary Objectives	• Safety • Mean change from baseline in RHS	• Safety • Mean change from baseline in HFMSE	• Safety • Mean change from baseline in HFMSE

Table 1: TOPAZ Baseline (BL) Characteristics

	Ambulatory Subjects		Non-ambulatory Subjects		
	Cohort 1		Cohort 2	Cohort 3	
	20 mg/kg Monotherapy	20 mg/kg + nusinersen	20 mg/kg + nusinersen	2 mg/kg + nusinersen	20 mg/kg + nusinersen
Dosed subjects, N	11	12	15	10	10
Mean age, years (min, max)	12.1 (7, 19)	13.1 (7, 21)	11.7 (8, 19)	4.1 (2, 6)	3.8 (2, 6)
BL nusinersen maint. dose, n	N/A	5.6	5.1	5.5	5.4
Discontinuation	0	1**	0	0	0
Mean RHS score (min, max)	47.6 (26, 63)	51.3 (43, 62)	--	--	--
Mean HFMSE score (min, max)	--	--	22.7 (13, 39)	26.1 (12, 44)	23.5 (14, 42)

**Patient who discontinued study for reasons unrelated to study drug.

Table 2: TOPAZ Interim Analysis Results; mean improvements from baseline in HFMSE/RHS observed in each of the 3 cohorts

	Ambulatory Subjects (RHS)			Non-Ambulatory Subjects (HFMSE)		
	Cohort 1			Cohort 2	Cohort 3	
	20 mg/kg pooled (n=23)	20 mg/kg monotherapy (n=11)	20 mg/kg +nusinersen (n=12)	20 mg/kg +nusinersen (n=14)	2 mg/kg +nusinersen (n=9)	20 mg/kg +nusinersen (n=9)
Mean baseline change (95% CI)	0.5 (-1.1, 2.2)	0.7 (-2.5, 4.0)	0.3 (-1.4, 2.0)	1.4 (0.1, 2.7)	2.4 (-0.9, 5.8)	5.6 (2.5, 8.7)
≥1-pt increase, n (%)	12/23 (52)	7/11 (64)	5/12 (42)	10/14 (71)	6/9 (67)	9/9 (100)
≥3-pt increase, n (%)	6/23 (26)	4/11 (36)	2/12 (17)	3/14 (21)	4/9 (44)	6/9 (67)

- Mean improvements from baseline in HFMSE/RHS observed in each of the 3 cohorts.
- Substantial proportion of patients in each cohort attained ≥3-point improvement in HFMSE/RHS.
- Dose response demonstrated in Cohort 3 (randomized, double-blind, parallel arm design).
  - Greater improvements in HFMSE scores for high dose arm across evaluated timepoints (Figure 3).
  - Supportive PK/PD results; high dose led to higher drug exposure and target engagement.

Figure 3: TOPAZ Interim Analysis Results; change from baseline in primary efficacy endpoints [Hammersmith scale scores; mean (+/- 1 SE)]

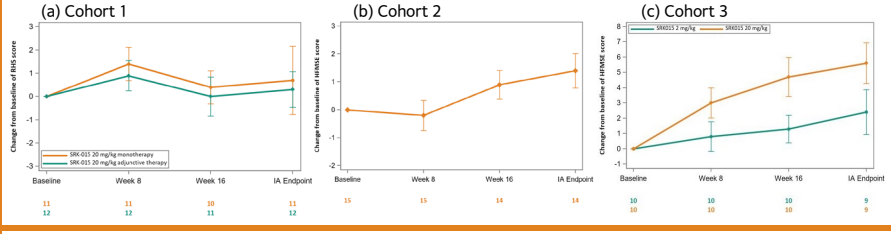


Table 3: Treatment Emergent Adverse Events (TEAEs; All cohorts: most frequently reported)

TEAEs ≥ 5	Cohort 1			Cohort 2	Cohort 3		
Preferred Term (PT)	20 mg/kg, monotherapy (n=11)	20 mg/kg, adjunctive therapy (n=12)	Total (n=23)	20 mg/kg (n=15)	2 mg/kg (n=10)	20 mg/kg (n=10)	Total (n=20)
Subjects with any TEAE	10 (90.9)	9 (75.0)	19 (82.6)	13 (86.7)	9 (90.0)	8 (80.0)	17 (85.0)
Headache	5 (45.5)	3 (25.0)	8 (34.8)	3 (20.0)	2 (20.0)	1 (10.0)	3 (15.0)
Upper respiratory tract infection	3 (27.3)	2 (16.7)	5 (21.7)	2 (13.3)	3 (30.0)	3 (30.0)	6 (30.0)
Pyrexia	1 (9.1)	0	1 (4.3)	2 (13.3)	3 (30.0)	5 (50.0)	8 (40.0)
Nasopharyngitis	1 (9.1)	1 (8.3)	2 (8.7)	2 (13.3)	2 (20.0)	3 (30.0)	5 (25.0)
Cough	1 (9.1)	2 (16.7)	3 (13.0)	1 (6.7)	2 (20.0)	3 (30.0)	5 (25.0)
Vomiting	0	1 (8.3)	1 (4.3)	1 (6.7)	3 (30.0)	3 (30.0)	6 (30.0)

Summary

- Motor function improvements were observed for all three treatment cohorts in the primary efficacy endpoints (Hammersmith scale scores) at 6-months
  - 67% of total patients achieved ≥1 point improvement in Hammersmith scores.
  - 35% of total patients achieved ≥3 point increase in Hammersmith scores
- Dose response in primary efficacy endpoint was observed in the randomized, double-blind cohort (Cohort 3), with high dose attaining a 5.6 point mean improvement over baseline at 6-months compared to low dose (2.4 point mean)
- Incidence and severity of adverse events were consistent with underlying patient population and background therapy
- First clinical data showing the potential therapeutic benefits of Scholar Rock's innovative scientific platform of inhibiting the activation of latent myostatin
- **Apitegromab has the potential to be the first muscle-directed therapy for patients with SMA**

TOPAZ Timelines

- Interim analysis: 6-month treatment period
- Topline results: 52-week treatment period
  - **Anticipated in the second quarter of 2021**
- **Results from TOPAZ trial may inform future studies in SMA**

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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 and apitegromab has not been approved by the FDA or any other regulatory authority.

* Three patients (one in Cohort 2 and two in Cohort 3) each missed three doses of apitegromab and the six-month interim analysis timepoint due to COVID-19-related site access restrictions; the six-month timepoint from these patients was not included in the interim analysis. TEAE, treatment emergent adverse events (defined as AEs that started after the first dose of study drug or started prior to the administration of study drug and worsen in severity/grade or relationship to investigational medication after the administration of study drug); GDF11, Growth differentiation factor 11 also known as BMP11; TGF-β, Transforming growth factor β; PI, Principal Investigator; SC, study coordinator; 2H, 2nd half; SMN, Survival motor neuron 1; RHS, Revised Hammersmith scale; HFMSE, Hammersmith functional motor scale expanded; CI, confidence interval; SE, Standard error; mg/kg, milligram/kilogram

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