# A Phase 2 Study to Evaluate the Efficacy and Safety of Apitegromab (SRK-015) in Patients with Later-Onset Spinal Muscular Atrophy (TOPAZ): Interim Analysis Results

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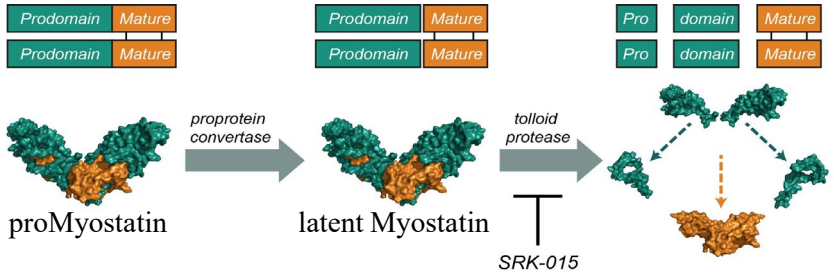
## Abstract

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.[1]

## Introduction[2]

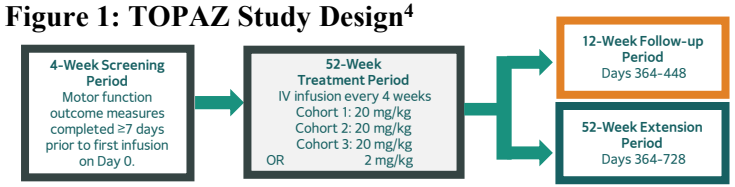



- Activation of myostatin requires two distinct proteolysis events that generate the active mature growth factor[1]
- Apitegromab does not bind to mature myostatin or any form of GDF11, Activin A, or other TGF-β family members[1]

## Methods[3]

**TOPAZ** (NCT03921528) is a Phase 2, 52-week proof-of-concept study of IV apitegromab treatment as monotherapy or with an approved SMN upregulator (nusinersen) in 58 patients across 16 study sites in the US and EU. The 52-week Treatment Period is followed by a 52-week open-label Extension Period or a 12-week Follow-Up Period. Cohorts 1 and 2 are open-label, while Cohort 3 is a double-blind, randomized arm (Fig 1). A pre-planned interim analysis was conducted following a 6-month treatment period across all three study cohorts (Fig 2; Tables 1 and 2)*.

## Figure 1: TOPAZ Study Design[4]



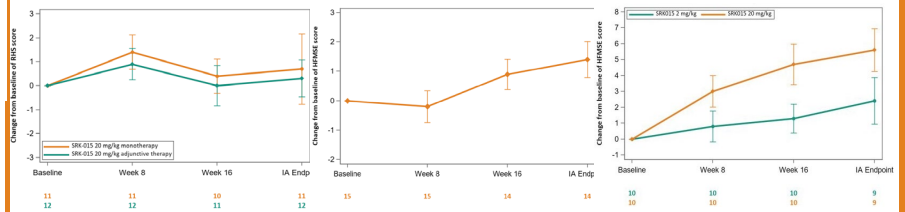

| | Cohort 1 | Cohort 2 | Cohort 3 |
|---|---|---|---|
| Design | • N= 23; ages 5-21<br>• Open-label, single-arm<br>• 20 mg/kg apitegromab IV Q4W<br>• 52-week treatment period | • N= 15; ages 5-21<br>• Open-label, single-arm<br>• 20 mg/kg apitegromab IV Q4W<br>• 52-week treatment period | • N= 20; ages ≥2<br>• Double-blind, randomized (1:1) to 2 mg/kg or 20 mg/kg apitegromab IV Q4W<br>• 52-week treatment period |
| Patients | • Ambulatory Type 3 SMA<br>• Patients receive apitegromab in combination with approved SMN up-regulator or as monotherapy | • Type 2 or non-ambulatory Type 3 SMA<br>• Receiving treatment with approved SMN up-regulator | • Type 2 SMA<br>• Initiated treatment with approved SMN up-regulator before age 5 |
| Primary Objectives | • Safety & tolerability<br>• Mean change from baseline in RHS | • Safety & tolerability<br>• Mean change from baseline in HFMSE | • Safety & tolerability<br>• Mean change from baseline in HFMSE |
| Secondary Objectives | • PK & PD effects<br>• Immunogenicity | • PK & PD effects<br>• Immunogenicity | • PK & PD effects<br>• Immunogenecity<br>• Time to therapeutic effect between low and high dose |

## Table 1: TEAEs; All cohorts: most frequently reported[4]

| 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) |

## Figure 2: TOPAZ Interim Analysis Results; change from baseline in primary efficacy endpoints [Hammersmith scores; mean (+/- 1 SE)][4]

(a) Cohort 1 (b) Cohort 2 (c) Cohort 3




## Table 2: TOPAZ Interim Analysis Results; mean improvements from baseline in HFMSE/RHS observed in each of the 3 cohorts[4]

| | 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) |

67% of total patients achieved ≥1 pnt increase in Hammersmith scores[3]
35% of total patients achieved ≥3 pnt increase in Hammersmith scores[3]

**Interim Analysis Summary:** Results support the potential of Apitegromab to be the first muscle-directed therapy for patients with SMA

- Motor function improvements were observed in the primary efficacy endpoints at 6-months
- Dose response in primary endpoint was observed at 6 months: higher improvements over BL in high dose compared to low dose arm
- Supportive PK/PD results; high dose - higher drug exposure and target engagement
- Incidence and severity of AEs were consistent with underlying patient population and background therapy
- Topline study results are due in Q2 2021

**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. Press release (October 27, 2020), available: www.scholarrock.com.; 4. Data on File, Scholar Rock, Inc. Cambridge, MA.

**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.

## Acknowledgements

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* 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); IV, intravenous; GDF11, Growth differentiation factor 11 also known as BMP11; TGF-β, Transforming growth factor β; PI, Principal Investigator; SC, study coordinator; PK, pharmacokinetic; PD, pharmacodynamic; SMN, Survival motor neuron 1; RHS, Revised Hammersmith scale; HFMSE, Hammersmith functional motor scale expanded; CI, confidence interval; SE, Standard error; SMA, spinal muscular atrophy; mg/kg, milligram/kilogram