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

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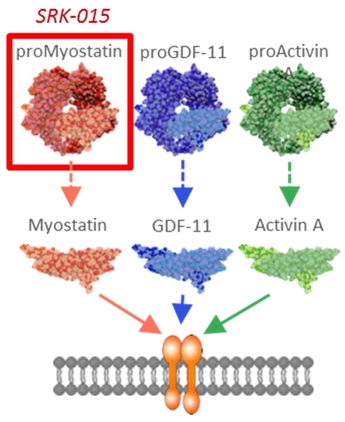
## Abstract

SRK-015 is a fully human anti-proMyostatin monoclonal antibody that's being developed and investigated for the treatment of later-onset SMA. This Phase 2 study involves approximately 25 study sites across United State and Europe. The study purpose is to evaluate the safety and efficacy of SRK-015 on motor function in SMA patients with Types 2 and 3, aged 2 through 21 years old, for 52 weeks. All patients received SRK-015 every 4 weeks via intravenous infusion. Patients in Cohorts 1 and 2 were directly assigned to a 20 mg/kg SRK-015 dose and patients in Cohort 3 were randomized 1:1 in a double-blind manner to either 2 mg/kg or 20 mg/kg SRK-015. Cohort 1 (N=23) enrolled ambulatory Type 3 patients, at least some of whom were not receiving an approved SMA up-regulator, as well as patients receiving an approved SMA treatment that was started after the patient turned 5 years old. Cohort 2 (N=15) enrolled Type 2 and non-ambulatory Type 3 patients already receiving an approved SMA up-regulator that was started after the patient turned 5 years old. Cohort 3 (N=20) enrolled Type 2 patients, who started on an approved SMA up-regulator before the patient turned 5 years old. The primary efficacy endpoint for Cohort 1 is the change from baseline in the Revised Hammersmith Scale (RHS). The primary efficacy endpoint for Cohorts 2 and 3 is change from baseline in Hammersmith Functional Motor Scale Expanded (HFMSE). Safety is being assessed throughout the trial by the Safety Surveillance Team. Blood samples for the measurement of SRK-015 concentrations, circulating latent myostatin concentrations, and anti-SRK-015 antibodies are being obtained. Demographic, baseline characteristics and preliminary PK/PD data will be presented.

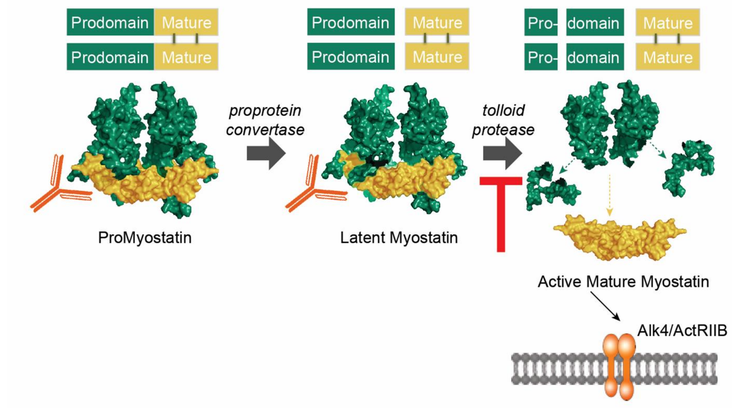
## Background

### Selective targeting of proMyostatin over other growth factors




| Analyte | SRK-015 Binding Affinity (nM) |
|---|---|
| **ProMyostatin** | **2.9** |
| **Latent Myostatin** | **2.4** |
| Myostatin | NB |
| ProGDF11 | NB |
| GDF11 | NB |
| ProActivin A | NB |
| Activin A | NB |
| BMP9 | NB |
| BMP10 | NB |
| TGFβ1 | NB |

### SRK-015: A fully human antibody that blocks cleavage of the Myostatin prodomain

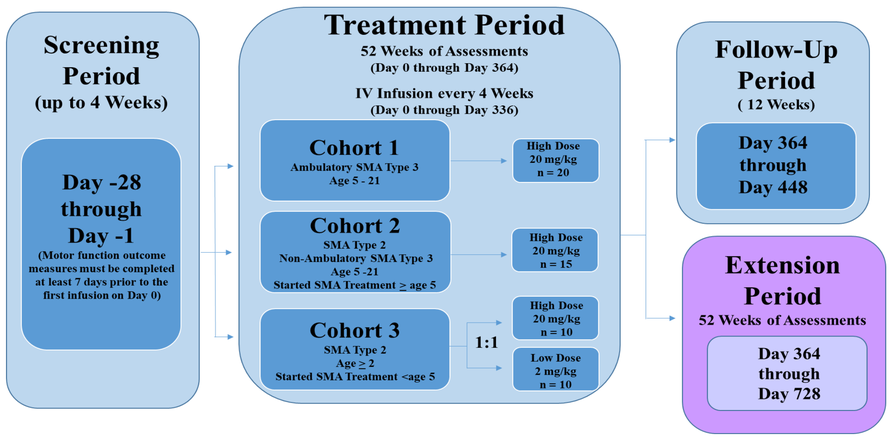



### Phase 2 TOPAZ Clinical Trial Design

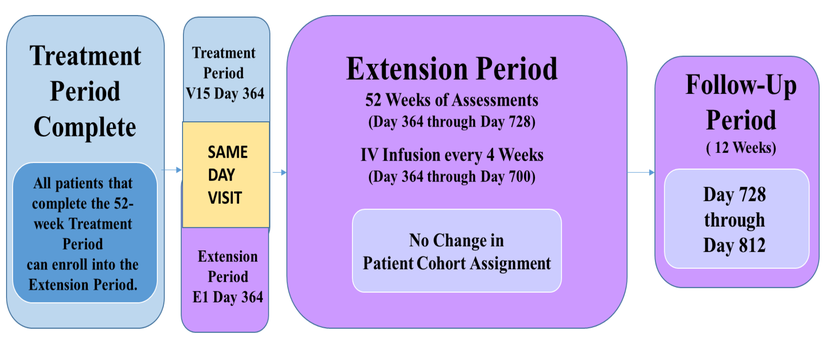
| | Cohort 1 | Cohort 2 | Cohort 3 |
|---|---|---|---|
| Design | • N= 20; ages 5-21<br>• Open-label, single-arm<br>• 20 mg/kg SRK-015 IV Q4W<br>• 12-month treatment period | • N= 15; ages 5-21<br>• Open-label, single-arm<br>• 20 mg/kg SRK-015 IV Q4W<br>• 12-month treatment period | • N= 20; ages ≥2<br>• Double-blind, randomized (1:1) to 2 mg/kg or 20 mg/kg SRK-015 IV Q4W<br>• 12-month treatment period |
| Patients | • Ambulatory Type 3 SMA<br>• Receiving treatment with approved SMN upregulator or as monotherapy | • Type 2 or non-ambulatory Type 3 SMA<br>• Receiving treatment with approved SMN upregulator | • Type 2 SMA<br>• Initiated treatment with approved SMN upregulator before age 5 |
| Primary Objectives | • Safety<br>• Mean change from baseline in RHS | • Safety<br>• Mean change from baseline in HFMSE | • Safety<br>• Mean change from baseline in HFMSE |

## Study Design (Continued)

### Study Schematic: Treatment Period




### Study Schematic: Extension Period




### Additional Measurements and Safety Endpoints

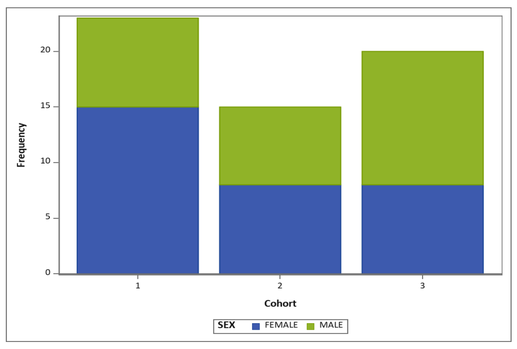
| | |
|---|---|
| Treatment-emergent adverse events (TEAEs) and SAEs | Concomitant medications |
| Vital signs: blood pressure, heart rate, body temperature, and respiratory rate | Physical examinations, including height and weight |
| 12-Lead ECG | Laboratory assessments (hematology and coagulation, serum chemistry, urinalysis) |
| Pharmacokinetics (PK) | Pharmacodynamics (PD): Serum Latent Myostatin Concentrations |
| Anti-drug antibodies | |

## Demographics*

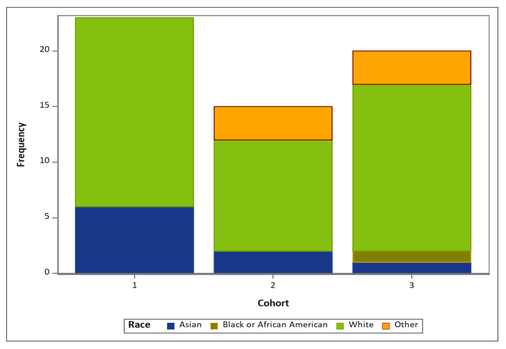
### Age at Informed Consent by Cohort

| Cohort | N | Mean | Std | Min | Med | Max |
|---|---|---|---|---|---|---|
| 1 | 23 | 12.6 | 4.53 | 7 | 13.0 | 21 |
| 2 | 15 | 11.7 | 3.94 | 8 | 10.0 | 19 |
| 3 | 20 | 4.0 | 1.23 | 2 | 4.0 | 6 |
| *Total* | *58* | *9.4* | *5.31* | *2* | *8.0* | *21* |

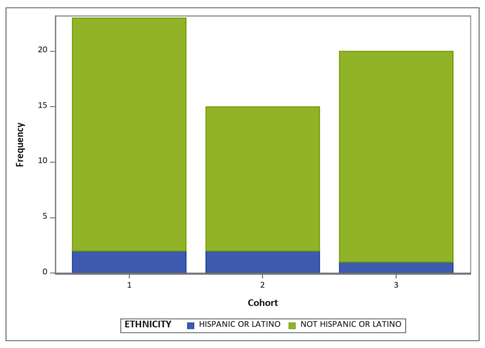
### Sex Distribution by Cohort




### Race Distribution by Cohort

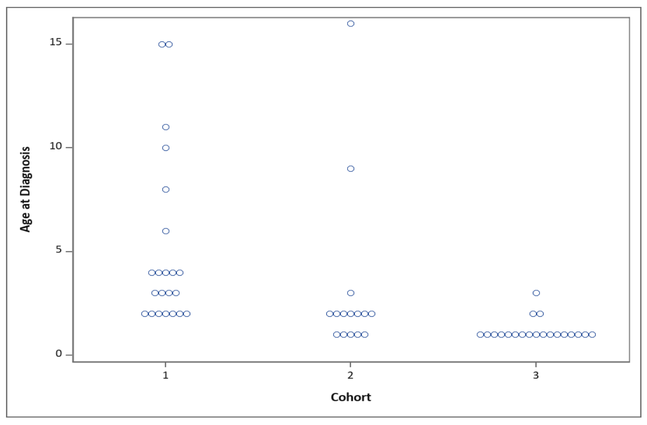



### Ethnicity Distribution by Cohort

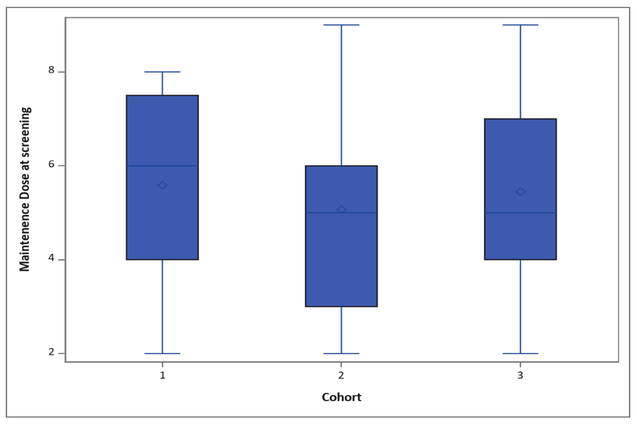



## Disease History*

### Age at Diagnosis by Cohort



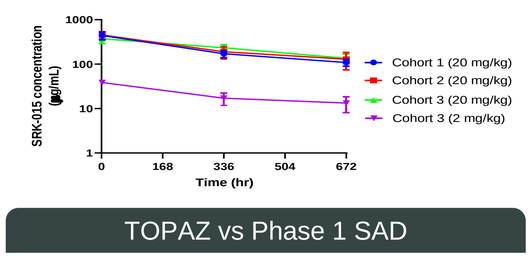

### Maintenance Dose of Nusinersen at Screening†



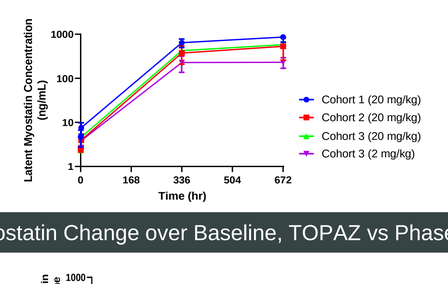

†Excluded Cohort 1 patients who are not on Nusinersen

## Preliminary Pharmacokinetic (PK)/Pharmacodynamic (PD)**

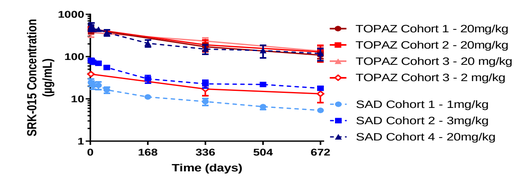
### Preliminary TOPAZ PK Data



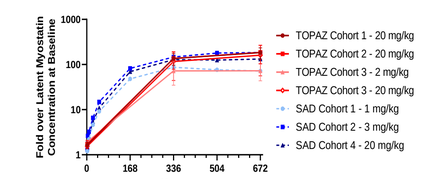

### Preliminary TOPAZ PD Data




### TOPAZ vs Phase 1 SAD




### Latent Myostatin Change over Baseline, TOPAZ vs Phase 1




## Functional Motor Skills at Screening*

### RHS Score at Screening, Cohort 1

| | N | Mean | Std | Min | Med | Max |
|---|---|---|---|---|---|---|
| RHS Score | 23 | 49.0 | 11.00 | 25 | 49 | 63 |

### 6 Minutes Walk at Screening‡, Cohort 1

| | N | Mean | Std | Min | Med | Max |
|---|---|---|---|---|---|---|
| Distance Walked(m) | 20 | 260.1 | 166.85 | 11 | 341.0 | 514 |

‡Only including patients who are ambulatory and completed the test

### HFMSE at Screening, Cohort 2 and 3

| Cohort | N | Mean | Std | Min | Med | Max |
|---|---|---|---|---|---|---|
| 2 | 15 | 22.3 | 8.98 | 12 | 19.0 | 37 |
| 3 | 19 | 25.0 | 9.58 | 12 | 22.0 | 44 |
| *Total* | *34* | *23.8* | *9.28* | *12* | *21.5* | *44* |

## Summary

### Summary

- Study Enrollment has been completed
- Preliminary demographic and baseline characteristics data are in line with published data with nusinersen (e.g., Mercuri 2018, Darras 2019), and ensure appropriate inclusion of subjects with Type 2 and 3 SMA
- As of planned data cutoff in November 2019 (N=29), preliminary PK data show that SRK-015 exposure in patients with SMA is consistent with that in healthy volunteers; preliminary PD (latent myostatin in serum) data provide first demonstration of target engagement in patients with SMA (data on file); no clinically significant safety signals have been observed as of the most recent meeting of the Safety Surveillance Team (Jan 2020)

**Acknowledgments:** The authors thank the Phase 2 patients, the Phase 2 PIs, SCs and site staff, SRK-015 preclinical and clinical teams, Medpace (Phase 2 CRO), the SMA Foundation, Cure SMA, and the SMA community.

**References:**
1. Darras BT et al. Neurology. 2019; 92(21)
2. Mercuri E et al. N Engl J Med. 2018 378(7) 625-635

**Disclaimer:** SRK-015 is an investigational drug candidate being developed and studied for SMA and other indications. The effectiveness and safety of SRK-015 have not been established and SRK-015 has not been approved by the FDA or other regulatory agency.

*Demographics, baseline and SMA disease history data presented were based on data entered and source verified as of Feb 20, 2020. **PK/PD analyses were performed as part of a planned data cutoff in Nov 2019 and include data from 29 patients.