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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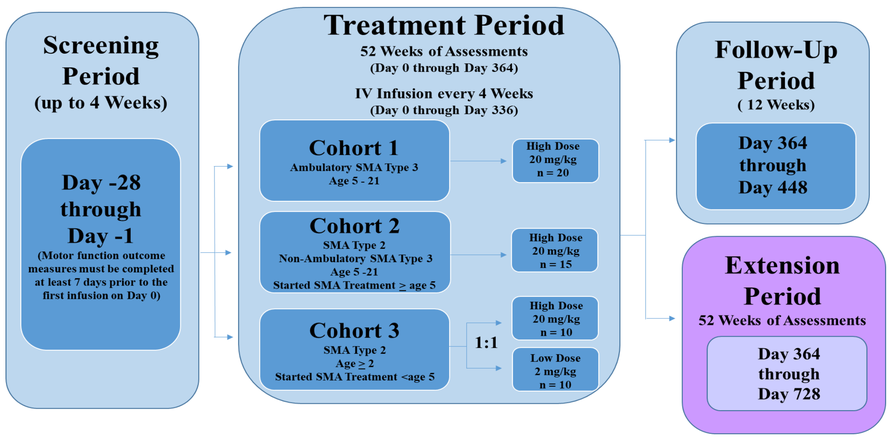
Abstract

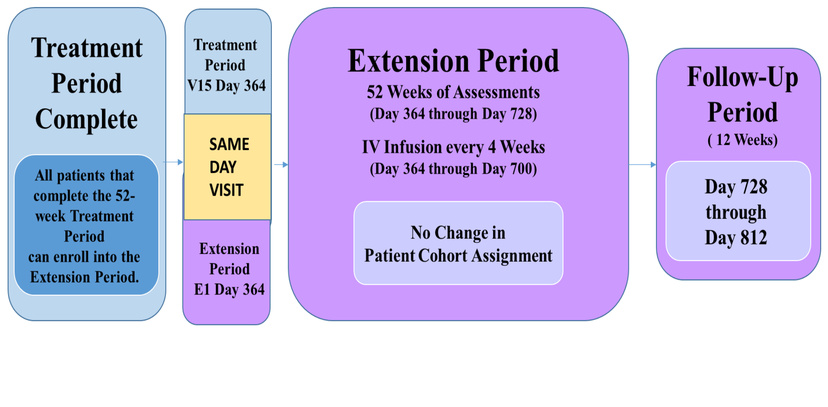
SRK-015 is a fully human anti-proMyostatin monoclonal antibody that is being developed and investigated for the treatment of SMA. This Phase 2 proof-of-concept study is being conducted in 19 study sites across the United States and Europe to evaluate the safety and efficacy of SRK-015 on motor function in later-onset SMA patients (e.g. Type 2 and Type 3 SMA patients) aged 2 through 21 years old. Fifty-eight male and female patients with later-onset SMA have been enrolled across 3 separate parallel Cohorts. Patients receive SRK-015 every 4 weeks via intravenous (IV) infusion during the 52-week treatment period, with patients in Cohorts 1 and 2 directly assigned to a 20 mg/kg SRK-015 dose and patients in Cohort 3 randomized 1:1 in a double-blind manner to either 2 mg/kg or 20 mg/kg SRK-015. Cohort 1 (N=20) enrolled ambulatory Type 3 patients, aged 5-21 years old, at least some of whom are not receiving an approved SMA treatment, as well as patients already receiving an approved SMA treatment that had been started after the patient turned 5 years old. Cohort 2 (N=15) enrolled Type 2 and non-ambulatory Type 3 patients, aged 5-21 years old, already receiving an approved SMA treatment that had been started after the patient turned 5 years old. Cohort 3 (N=20) enrolled Type 2 patients, aged ≥ 2years old, already receiving an approved SMA treatment that had been started 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). Key secondary assessments include the proportion of patients attaining various thresholds of change from baseline in RHS and change from baseline in various timed tests. The primary efficacy endpoint for Cohorts 2 and 3 is change from baseline in Hammersmith Functional Motor Scale Expanded (HFMSE). Key secondary assessments include the proportion of patients attaining various thresholds of change from baseline in HFMSE and change from baseline in Revised Upper Limb Module (RULM). Additional exploratory endpoints will be evaluated. Safety will be assessed throughout the duration of the trial and will be monitored by a Safety Surveillance Team (SST). Blood samples for the measurement of SRK-015 concentrations, circulating latent myostatin concentrations, and anti-SRK-015 antibodies will be obtained. Baseline patient characteristics and demographic data, including age range, gender, race and ethnicity as well as SMA disease history are presented.

Study Design

Study Schematic: Treatment Period



Study Schematic: Extension Period



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)

Study Design (Continued)

Key Efficacy Objective and Endpoints

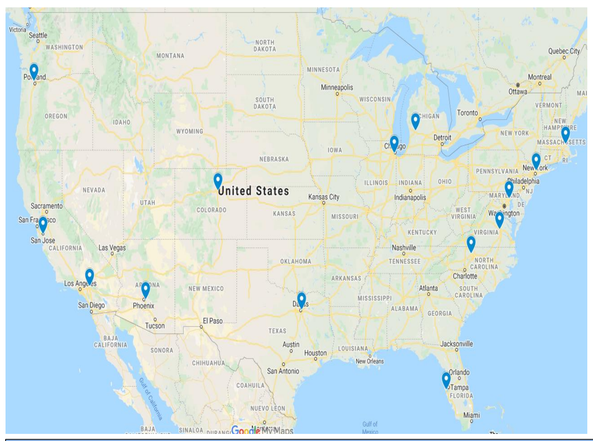
	Cohort 1	Cohorts 2 and 3
Primary:	The mean change from baseline in Revised Hammersmith Scale (RHS) over 12 months of treatment	The mean change from baseline in Hammersmith Functional Motor Scale Expanded (HFMSE) over 12 months of treatment
Key Secondary	Proportion of patients attaining various thresholds of change from baseline in RHS and change from baseline in 6-minute walk test (6MWT)	Proportion of patients attaining various thresholds of change from baseline in HFMSE and change from baseline in RULM

Additional Measurements and Endpoints

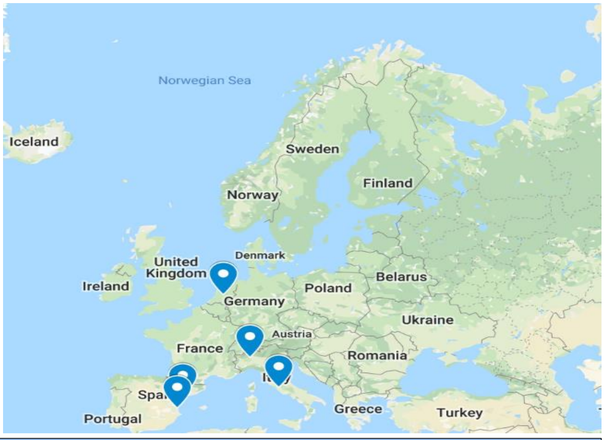
Pharmacokinetic	Pharmacodynamic: Latent Myostatin Serum Concentrations
Anti-drug Antibodies	

Study Operations

Study Sites in the United States



Study Sites in Europe:



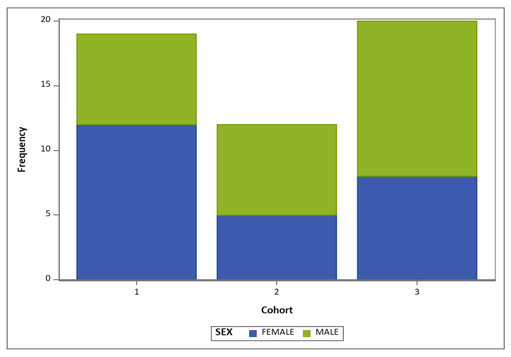
Enrollment Completed (#Dosed): Cohort 1: 23/20; Cohort 2: 15/15, Cohort 3: 20/20

Demographics*

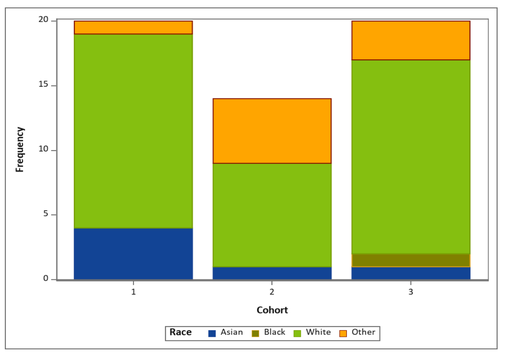
Age at Informed Consent by Cohort

Cohort	N	Mean	Std	Min	Med	Max
1	19	12.7	4.57	7	13.0	21
2	12	11.8	4.09	8	10.5	19
3	20	4.0	1.23	2	4.0	6
Total	*51*	*9.1*	*5.39*	*2*	*8.0*	*21*

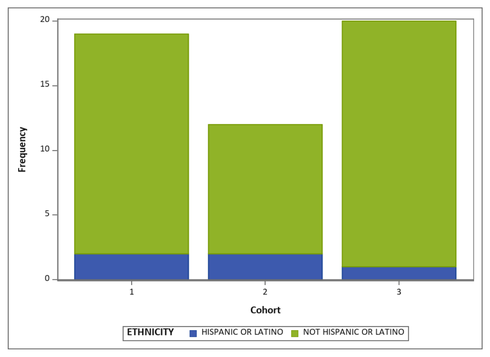
Sex Distribution by Cohort



Race Distribution by Cohort

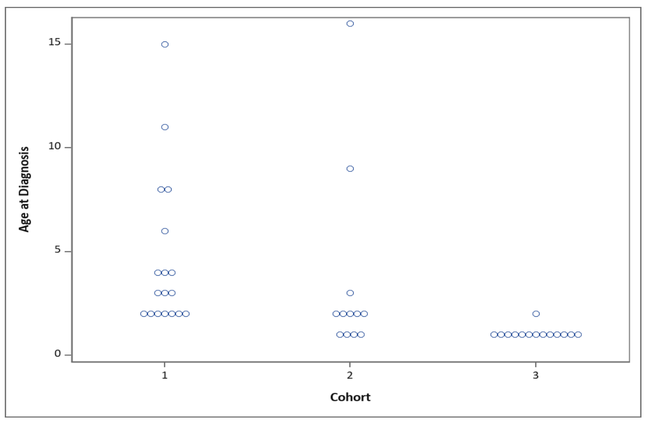


Ethnicity Distribution by Cohort

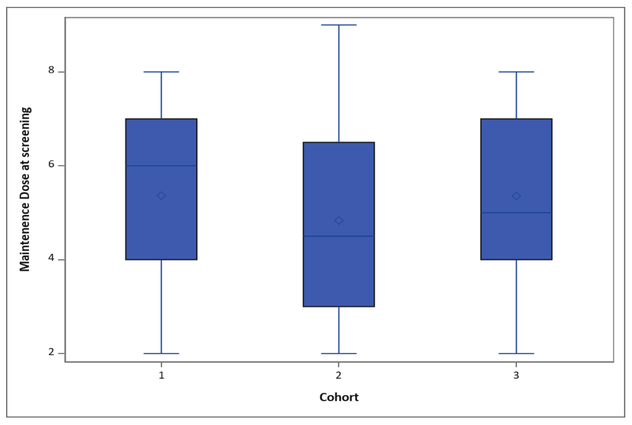


Disease History*

Age at Diagnosis by Cohort



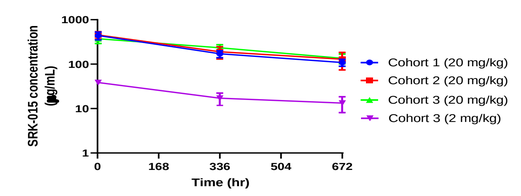
Maintenance Dose of Nusinersen at Screening†



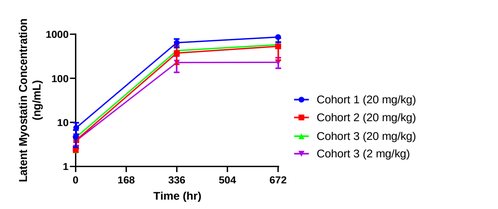
†Excluded Cohort 1 patients who are not on Nusinersen

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

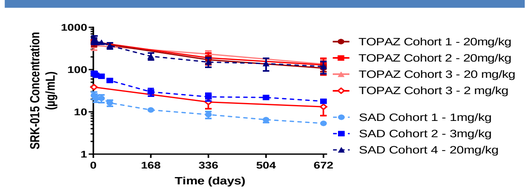
Preliminary TOPAZ PK Data



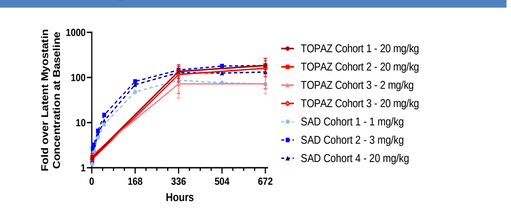
Preliminary TOPAZ PD Data



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	10	47.4	10.12	27	49	62

6 Minutes Walk at Screening‡, Cohort 1

	N	Mean	Std	Min	Med	Max
Distance Walked(m)	15	284.9	149.33	32	350.0	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	12	22.5	8.39	12	20.0	35
3	16	24.8	8.92	14	22.0	44
Total	*28*	*23.8*	*8.62*	*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; no clinically significant safety signals have been observed as of the most recent data cutoff (Nov 2019); press release (link)

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 Jan 08, 2020. **PK/PD analyses were performed as part of a planned data cutoff in Nov 2019 and include data from 29 patients.