19 January 2022

Clinicaltrials.gov Results Posting

Re: *SRK-015-002 Results from 12-Month Treatment Period*

Sponsor:	Scholar Rock, Inc. 301 Binney Street, 3rd Floor Cambridge, MA 02142 USA
Protocol Number:	SRK-015-002
Protocol Title:	Phase 2 Active Treatment Study To Evaluate The Efficacy And Safety of SRK-015 in Patients With Later-Onset Spinal Muscular Atrophy (TOPAZ)
NCT Number:	03921528
Protocol Document Date:	3 August 2021
Statistical Analysis Plan Document Date:	24 February 2021

Thank you,
Clinical Trial Coordinator
Scholar Rock
clinicaltrials@scholarrock.com

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PROTOCOL SRK-015-002

PHASE 2 ACTIVE TREATMENT STUDY TO EVALUATE THE EFFICACY AND SAFETY OF SRK-015 IN PATIENTS WITH LATER-ONSET SPINAL MUSCULAR ATROPHY (TOPAZ)

Protocol Number:	SRK-015-002
Indication Studied:	Spinal Muscular Atrophy
Developmental Phase of Study:	2
IND Number:	136872
EudraCT Number	2018-004383-65
Description:	Fully Human Anti-proMyostatin Monoclonal Antibody
Sponsor:	Scholar Rock, Inc. 301 Binney Street, 3rd Floor Cambridge, MA 02142, USA
Sponsor Contact:	
Medical Monitor:	
Protocol Version:	5.0
Release Date:	03 August 2021

CONFIDENTIAL

SPONSOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the Principal Investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations, including, but not limited to, the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.

DocuSigned by:
George Nomikos
Signer Name: George Nomikos
Signing Reason: I approve this document
Signing Time: 11-Aug-2021 | 14:13 EDT
17FE9418529B47C781FE78CCB9DE6915

George Nomikos, MD, PhD
SVP, Medical & Clinical Research
Head of Muscle Therapeutic Area
Scholar Rock, Inc.

Date

PRINCIPAL INVESTIGATOR'S AGREEMENT

I have read and approve this protocol. My signature, in conjunction with the signature of the Sponsor, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations, including, but not limited to, the ICH Guideline for GCP, the CFR, and the ethical principles that have their origins in the Declaration of Helsinki.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

_____

Printed Name of Principal Investigator

_____

Signature of Principal Investigator

_____

Date

1. SYNOPSIS

Name of Sponsor:
Scholar Rock, Inc., 301 Binney Street, 3rd Floor, Cambridge, MA 02142, USA

Name of Investigational Product:
apitegromab (SRK-015)

Name of Active Ingredient:
apitegromab

Protocol Number:
SRK-015-002

Title of Study: Phase 2 Active Treatment Study to Evaluate the Efficacy and Safety of SRK-015 in Patients with Later-onset Spinal Muscular Atrophy (TOPAZ)

Study Centers:
Approximately 20 study sites across the United States (US) and Europe

Phase of Development: 2

Objectives for Both the Treatment Period and Extension Periods:

Primary Objectives:

- To assess safety and tolerability of SRK-015 in patients with later-onset (e.g., Type 2 and Type 3) spinal muscular atrophy (SMA)
- To assess the efficacy of SRK-015 by assessing changes in motor function outcome measures in 3 separate predefined cohorts

Secondary Objectives:

- To characterize the pharmacokinetics (PK) of SRK-015
- To evaluate the pharmacodynamic (PD) effects of SRK-015
- To evaluate time to therapeutic effect between low- and high-dose SRK-015 in a predefined cohort (Cohort 3)
- To evaluate the immunogenicity of SRK-015
- To evaluate the effect of SRK-015 on quality of life

Methodology:
This study will be conducted in approximately 20 study sites across the US and Europe to evaluate the safety and efficacy of SRK-015 in patients with later-onset SMA (e.g., patients with Type 2 and Type 3 SMA) age 2 through 21 years old. Patients may receive SRK-015 on top of an approved SMA treatment or may receive SRK-015 as monotherapy. Approximately 55 male and female patients with later-onset SMA will be enrolled across 3 separate parallel subpopulations subsequently described as cohorts. Patients will receive SRK-015 every 4 weeks during the 52-week Treatment Period, with patients in Cohorts 1 and 2 directly assigned high-dose (20 mg/kg) SRK-015 and patients in Cohort 3 randomized 1:1 double-blind between low-dose (2 mg/kg) and high-dose (20 mg/kg) SRK-015.

- Cohort 1, N=20: Ambulatory Type 3 patients, age 5 through 21 years old, approximately 10 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: Type 2 and nonambulatory Type 3 patients, age 5 through 21 years old, already receiving an approved SMA treatment that had been started after the patient turned 5 years old.
- Cohort 3, N=20: Type 2 patients, age ≥2 years old, already receiving an approved SMA treatment that had been started before the patient turned 5 years old.

During the Screening Period, all patient screening and eligibility determinations will be conducted after informed consent (and, as required by local authorities, patient informed assent) has been provided and within 28 days prior to first dose. Screening motor function outcome measures will be conducted at least 7 days prior to the first dose. All subsequent motor function outcome measures will be conducted within 96 hours prior to dosing.

During the Treatment Period, patients will be monitored at the study site through 2 hours postdose. Following each Treatment Period dose, patients will be contacted by the site within 7 days for a safety check-in-. Patients will be seen in clinic 14 days after the first Treatment Period dose. After the second dose, visits will occur every 4 weeks through the end of the study (Study Schedule of Assessments). Patients who complete the 52-week Treatment Period will have the option to enroll into an Extension Period (referred to as Extension Period A), for an additional 52-week period. There will be no interruption in dosing between the completion of the Treatment Period and the start of Extension Period A. Patients who consent to participate in Extension Period A will complete both the Treatment Period Day 364 (V15) visit and the Extension Period A Day 364 (E1) visit on the same day.

Based on the results of the prespecified 6-month safety and efficacy interim analyses, any Cohort 3 patients who were randomized to receive low-dose (2 mg/kg) SRK-015 will be re-assigned to receive high-dose (20 mg/kg) SRK-015 after completion of the Treatment Period. Due to the variability in timing of regulatory authority and/or Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approvals, the timepoint at which patients who received the low dose (2 mg/kg) will begin receiving the high dose (20 mg/kg) during Extension Period A will vary.

Patients who complete the 52-week Treatment Period and choose not to enroll into Extension Period A will be followed for a 12-week Safety Follow-up Period after Day 364 (V15).

Patients who complete Extension Period A will have the option to enroll into Extension Period B for an additional 52-week period. There will be no interruption in dosing between the completion of Extension Period A and the start of Extension Period B. Patients who consent to participate in Extension Period B will complete both the Extension Period A, Day 728 (E14) visit and the Extension Period B Day 728 (EB1) visit on the same day.

Patients who complete Extension Period A and choose not to enroll into Extension Period B will be followed for a 12-week Safety Follow-up Period after Day 728 (E14).

Patients who complete the 52-week Extension Period B will have the option to enroll into Extension Period C for an additional 52-week period. There will be no interruption in dosing between the completion of Extension Period B and the start of Extension Period C. Patients who consent to participate in Extension Period C will complete both the Extension Period B, Day 1092 (EB14) visit and the Extension Period C Day 1092 (EC1) visit on the same day.

Patients who complete Extension Period B and choose not to enroll into Extension Period C will be followed for a 12-week Safety Follow-up Period after Day 1092 (EB14).

Patients who complete the 52-week Extension Period C may be offered the option to enter a separate long-term safety extension trial at that time. Patients who complete the 52-week Extension Period C

and choose not to enroll in the separate long-term safety extension trial will be followed for a 12-week Safety Follow-up Period after Day 1456 (EC14).

Patients will be monitored throughout the Treatment Period, Extension Periods A, B, and C, and the Follow-up Period for safety. A safety surveillance team (SST) will review safety data throughout the duration of the study to assess patient safety. The SST will review safety data approximately every 6 months. Prior to Protocol Version 5.0, the SST review was approximately every 12 weeks. The SST will be blinded to all cohort-level efficacy outcomes through the completion of the predefined safety and efficacy interim analysis, and to all individual efficacy outcomes through the completion of the 52-week Treatment Period analysis. If a significant safety signal emerges at any time during the study, dosing may be suspended until the SST can evaluate the signal, recommend an appropriate course of action, and ensure the ongoing safety of all patients.

Study Stopping Rules: Dosing in the study may be suspended at any time for an emergent safety concern by the Medical Monitor in consultation with the SST until the SST can completely evaluate the event(s) and recommend an appropriate course of action. The Sponsor may terminate the study if it determines that further drug exposure would pose an undue risk to patients. The Sponsor, at its discretion, may terminate the study at any time.

If the study is terminated prematurely, Investigators, regulatory authorities, and IRBs/ IECs will be notified promptly. Patients will continue to be followed for 12 weeks after their final dose.

Individual Stopping Rules: Dosing for any individual patient may be suspended or discontinued if the patient experiences a serious adverse event (SAE) related to SRK-015 or a clinically significant nonserious adverse event (AE) related to SRK-015 that, in the assessment of the Investigator and in consultation with the Medical Monitor, warrants suspension or discontinuation from further dosing for that patient's well-being. For patients who have had their dosing suspended, dosing may resume only after their AE has resolved and only if it would be considered safe to do so in the assessment of the Investigator (and in consultation with the Medical Monitor). For patients who have discontinued dosing, the patient will continue to be followed for 12 weeks after their final dose or until the resolution of any ongoing clinically significant AE, whichever occurs later. (For the definition of AE resolution, please refer to Section 10.7.1.2 Follow-up Reports.)

Dosing of SRK-015 for an individual patient may also be suspended or discontinued for safety concerns other than those described above based on review by the SST or at the discretion of the Investigator if he/she feels the patient's safety may be threatened. The Investigator may ask for an ad hoc SST meeting to be held for any single event or combination of events that in his/her professional opinion may jeopardize the safety of the patient or the reliability of the data.

Criteria for Inclusion:

1. Age 5 through 21 years old at the time of Screening for Cohorts 1 and 2; Age ≥2 years old at the time of Screening for Cohort 3
2. Estimated life expectancy >2 years from Screening
3. Informed consent document signed by the patient if the patient is legally an adult. If the patient is legally a minor, informed consent document signed by the patient's parent or legal guardian and patient's oral or written assent obtained, if applicable and in accordance with the regulatory and legal requirements of the participating location
4. Documented diagnosis of 5q SMA
5. Diagnosed as later-onset (e.g., Type 2 or Type 3) SMA prior to receiving any treatment with therapy approved for SMA
6. Nonambulatory patients must be able to sit independently (sits up straight with head erect for at least 10 seconds; does not use arms or hands to balance body or support position) per World

Health Organization (WHO) motor milestones definition at Screening. Patients who never had the ability to walk independently will be classified as Type 2. Patients who previously had the ability to walk unaided will be classified as Type 3.

7. Ambulatory patients must have the ability to independently ambulate without aids or orthotics over 10 meters at Screening
8. For Cohort 1, Revised Hammersmith Scale (RHS) score no greater than 63 at Screening
9. For Cohorts 2 and 3, Hammersmith Functional Motor Scale Expanded (HFMSE) score no less than 10 at Screening
10. Receiving the same background SMA therapy (e.g., on an approved survival motor neuron (SMN) upregulator therapy such as nusinersen, or not on any SMA therapy) for at least 6 months prior to Screening and anticipated to remain on that therapy throughout the duration of the study
    a. If receiving the SMN upregulator therapy nusinersen, must have completed the loading regimen and initiated maintenance dosing (i.e., completed at least one maintenance dose) with at least 4 weeks after the first maintenance dose having elapsed prior to Screening
11. Nutritional status stable over the past 6 months and anticipated to be stable throughout the duration of the study
12. Have no physical limitations that would prevent the patient from undergoing motor function outcome measures throughout the duration of the study
13. Able to receive study drug infusions and provide blood samples through the use of a peripheral intravenous (IV) or a long-term IV access device that the patient has placed for reasons independent from the study (i.e., for background medical care and not for the purpose of receiving SRK-015 in the study), throughout the duration of the study
14. Able to adhere to the requirements of the protocol, including travel to the study center and completing all study procedures and study visits
15. For patients who are expected to have reached reproductive maturity by the end of the study, adhere to study-specific contraception requirements
    a. Females of childbearing potential (see Section 10.1.7.4 for definition) must have a negative pregnancy test at Screening and agree to employ highly effective contraceptive measures (failure rate of 1% or less per year when used consistently and correctly) for the duration of the study and for 18 weeks following the last dose of study drug. Effective contraception methods are restricted to combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, or sexual abstinence. In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.
    b. Male patients with female partners of childbearing potential must be abstinent or agree to employ the use of a condom with or without spermicide throughout the duration of the study and for 18 weeks following the last dose of study drug.

Criteria for Exclusion:

1. Use of tracheostomy with positive pressure
2. Use of chronic daytime noninvasive ventilatory support for >16 hours daily in the 2 weeks prior to dosing, or anticipated to regularly receive such daytime ventilator support chronically over the duration of the study
3. Any acute or comorbid condition interfering with the well-being of the patient within 14 days of Screening, including active systemic infection, the need for acute treatment or inpatient observation due to any reason
4. Severe scoliosis and/or contractures at Screening. Based on clinical judgment, any scoliosis or contractures present must be stable over the past 6 months, anticipated to be stable for the duration of the study and not prevent the patient from being evaluated on any functional outcome measures throughout the duration of the study.
5. Pregnant or breastfeeding
6. Major orthopedic or other interventional procedure, including spine or hip surgery, considered to have the potential to substantially limit the ability of the patient to be evaluated on any functional outcome measures, within 6 months prior to Screening, or anticipated for the duration of the study
7. Prior history of a hypersensitivity reaction to a monoclonal antibody (mAb) or recombinant protein bearing an Fc domain (such as a soluble receptor-Fc fusion protein), SRK-015, or excipients of SRK-015
8. Use of systemic corticosteroids within 60 days prior to Screening. Inhaled or topical steroids are allowed.
9. Treatment with investigational drugs within 3 months or 5 half-lives, whichever is longer prior to Screening.
10. Use of therapies with potentially significant muscle effects (such as androgens, insulin-like growth factor, growth hormone, systemic beta-agonist, botulinum toxin, or muscle relaxants or muscle-enhancing supplements) or potentially significant neuromuscular effects (such as acetylcholinesterase inhibitors) other than approved SMN upregulator therapy within 60 days prior to Screening.
11. Use of valproic acid within 60 days prior to Screening.
12. Patient has any other condition, which in the opinion of the Investigator may compromise safety or compliance, would preclude the patient from successful completion of the study, or interfere with the interpretation of the results

Investigational Product, Dosage, and Mode of Administration: SRK-015 is a clear to slightly opalescent, colorless to slightly yellow solution, essentially free from visible particulates, containing 50 ± 5 mg/mL human anti-proMyostatin mAb protein in 20 mM histidine, 130 mM sodium chloride, and 0.02% polysorbate 80, pH 6.0 in 1-mL solution. SRK-015 drug product is stored in a 6R clear, USP/EP Type I borosilicate glass vial with a 20 mm Flurotec®-coated, bromobutyl or chlorobutyl rubber stopper and 20 mm crimp seal with a flip-off cap. Each vial is filled to allow for a 3 mL withdrawal.

High-dose SRK-015 will be 20 mg/kg and low-dose SRK-015 will be 2 mg/kg. Doses will be diluted in normal saline and administered via IV over 2 hours +10-minute window.

All doses will be administered via peripheral IV (or via long-term IV access device such as peripherally inserted central catheter or port, if the patient has such a device for their background medical care). The placement of a new long-term IV access device is not part of this study, not required for participation, and should not be conducted if the only reason for it is to receive SRK-015. If there are no acute reactions following the first 2 doses for a patient, and if the Investigator determines that it would be safe to do so, the infusion duration can be changed to less than 2 hours but no shorter than 1 hour.

Duration of Treatment:

Treatment Period:

Total study participation for an individual patient will consist of approximately 4 weeks for Screening, 52 weeks of study visits, and, if the patient does not enroll into Extension Period A, 12 weeks of Safety Follow-up for a total duration of approximately 68 weeks (approximately 16 months).

Extension Period A:

Total study participation for an individual patient who completes both the Treatment Period and Extension Period A will consist of approximately 4 weeks for Screening, 104 weeks of study visits, and 12 weeks of Safety Follow-up for a total duration of approximately 120 weeks (approximately 28 months).

Extension Period B:

Total study participation for an individual patient who completes the Treatment Period and Extension Periods A and B will consist of approximately 4 weeks for Screening, 156 weeks of study visits, and 12 weeks of Safety Follow-up for a total duration of approximately 172 weeks (approximately 40 months).

Extension Period C:

Total study participation for an individual patient who completes the Treatment Period and Extension Periods A, B, and C will consist of approximately 4 weeks for Screening, 208 weeks of study visits, and 12 weeks of Safety Follow-up for a total duration of approximately 224 weeks (approximately 52 months).

Reference Therapy, Dosage, and Mode of Administration: Not applicable

Concomitant Treatments:

Use of the following treatments will not be permitted during the study:

- Live vaccinations within 14 days of any study visit where motor function outcome measures are conducted
- Systemic corticosteroids. Inhaled and topical steroids are allowed.
- Any therapy with potentially significant muscle effects (such as androgens, insulin-like growth factor, growth hormone, systemic beta-agonist, botulinum toxin, muscle relaxants, or muscle-

enhancing supplements) or potentially significant neuromuscular effects (such as acetylcholinesterase inhibitors) other than approved SMN upregulator therapy

- Valproic acid

SRK-015 may be administered at least 24 hours prior to a maintenance dose of nusinersen and at least 14 days after a maintenance dose of nusinersen. The dosing schedule for SRK-015, including maintaining acceptable visit windows, must be adhered to throughout the duration of the study.

Criteria for Evaluation:

Efficacy:

Cohort 1: Ambulatory Type 3 Patients

Primary Efficacy Endpoint:

- Change from Baseline in the RHS total score at Day 364 (Visit 15)

Secondary Efficacy Endpoints:

- Change from Baseline in the RHS total score at other prespecified timepoints
- Proportion of patients achieving various magnitudes of change in RHS score from Baseline
- Change from Baseline in 6-Minute Walk Test (6MWT)
- Change from Baseline in 30-Second Sit-to-Stand
- Change from Baseline in 10-Meter Walk/Run (from the RHS)
- Change from Baseline in timed rise from floor (from the RHS)

Tertiary Endpoints:

- Change from Baseline in Pediatric Evaluation of Disability Inventory Computer Adaptive Test (PEDI-CAT)
- Change from Baseline in Patient-reported Outcomes Measurement Information System (PROMIS) Fatigue Questionnaire

Cohort 2 and Cohort 3: Type 2 and Nonambulatory Type 3 Patients

Primary Efficacy Endpoint:

- Change from Baseline in HFMSE total score at Day 364 (Visit15)

Secondary Efficacy Endpoints:

- Change from Baseline in HFMSE total score at other prespecified timepoints
- Proportion of patients achieving various magnitudes of change in HFMSE score from Baseline
- Change from Baseline in Revised Upper Limb Module (RULM) total score
- Change from Baseline in number of WHO motor development milestones attained
- Proportion of patients achieving various magnitudes of change in RULM score from Baseline
- Proportion of patients who attain a new WHO motor development milestone relative to Baseline

Tertiary Endpoints:

- Change from Baseline in Time to limitation on Endurance Shuttle Nine Hole Peg Test (ESNHPT) or Endurance Shuttle Box and Block Test (ESBBT)
- Change from Baseline in PEDI-CAT
- Change from Baseline in PROMIS Fatigue Questionnaire

Additional Tertiary Endpoint for Cohort 3:

- Time to therapeutic effect (described in the statistical analysis plan [SAP]) as compared between low- and high-dose SRK-015 arms

Safety:

Safety will be evaluated based on occurrence of or changes in the following parameters:

- Treatment-emergent adverse events (TEAEs) and SAEs
- Vital signs, including blood pressure, heart rate, body temperature, and respiratory rate
- Height and weight
- Physical examinations
- Laboratory assessments (hematology, serum chemistry, coagulation, urinalysis)
- 12-lead electrocardiogram (ECG)
- Concomitant medications

Safety assessments may be revised if any important safety signals emerge from any ongoing clinical studies (including this study).

Pharmacokinetics, Pharmacodynamics, and Immunogenicity:

Blood samples for the measurement of SRK-015 concentrations, circulating latent myostatin concentrations, and anti-SRK-015 antibodies will be obtained prior to dosing on Day 0 and throughout the Treatment and Extension Periods as well as the Safety Follow-up Period as indicated in the Study Schedule of Assessments.

Sample Size Rationale:

Sample sizes for each cohort were based on practical considerations. Sample sizes for Cohorts 1 (n=20) and Cohort 2 (n=15) each provide 80% power to reject the null hypothesis (expressed as means) relative to prespecified alternative hypothesis using a paired t-test with two-sided 5% Type 1 error for the mean change from Baseline for predefined cohort-specific primary efficacy endpoints. For Cohort 3 (n=20), the effect size to compare dose groups is also justified for detection with 80% power and two-sided 5% Type I error for a 1:1 randomization (high dose versus low dose) as well as the treatment-specific effect sizes that will reject the null hypothesis of no mean difference according to two-sided testing for a predefined primary efficacy endpoint.

Statistical Methods:

Safety and efficacy endpoints will be separately analyzed by cohorts and within Cohort 3, by dose groups. The safety and efficacy endpoints will also be analyzed for different cohort/dose combinations taking cohort, dose level and receiving background SMA therapy into consideration. Any changes in the analysis as specified in the protocol will be delineated in the SAP.

Vital signs and laboratory outcomes will be summarized within each treatment group within all cohorts and the 2 dose groups within Cohort 3. The incidence rate of AEs and TEAEs will be reported.

The primary efficacy endpoints will be summarized within cohorts. In addition to the primary efficacy endpoint, there are multiple secondary efficacy endpoints to help characterize the multi-dimensional aspects of each cohort and to plan subsequent clinical studies in support of approval. All continuous endpoints will be summarized within cohorts; corresponding two-sided 95% confidence intervals will be computed.

A prespecified interim analysis to evaluate the initial drug exposure (i.e., PK) and target engagement (i.e., PD) will be conducted. For Cohorts 1 and 2, this analysis will be conducted after approximately 4 patients in a cohort have received at least 2 doses of SRK-015. For Cohort 3, this analysis will be

conducted after approximately 6 patients have received at least 2 doses of SRK-015. Data from multiple cohorts may be combined as necessary. Based on the interim analysis results, and taking into consideration any available safety data, cohort-specific dose levels may be adjusted. Any adjustment in dose level will not change the frequency of dosing (i.e., every 4 weeks) and the highest dose will not exceed 30 mg/kg, as tested in the Phase 1 study.

Additionally, prespecified cohort-specific interim analyses to evaluate the initial safety and efficacy of SRK-015 in patients with SMA will be conducted after all patients complete Day 168 (Visit 8) or are terminated from the study. Interim analyses will be performed on the efficacy endpoints in addition to all safety outcomes and available PK and PD results. Safety data at all visits and efficacy endpoints at Day 168 (Visit 8) will be included in this analysis.

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
6MWT	6-Minute Walk Test
ADA	antidrug antibody
AE	adverse event
APTT	activated partial thromboplastin time
CFR	Code of Federal Regulations
CI	confidence interval
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EIU	exposure in utero
EOS	end-of-study
ESBBT	Endurance Shuttle Box and Block Test
ESNHPT	Endurance Shuttle Nine Hole Peg Test
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HFMSE	Hammersmith Functional Motor Scale Expanded
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intention-to-Treat
IV	intravenous
IWRS	Interactive Web-based Randomization System
mAb	monoclonal antibody
MAD	multiple ascending dose
NOAEL	no-observed-adverse-effect level

Abbreviation or Specialist Term	Explanation
PD	pharmacodynamic(s)
PEDI-CAT	Pediatric Evaluation of Disability Inventory Computer Adaptive Test
PK	pharmacokinetic(s)
PT/INR	prothrombin time/international normalized ratio
PROMIS	Patient-reported Outcomes Measurement Information System
QOL	quality of life
RHS	Revised Hammersmith Scale
RULM	Revised Upper Limb Module
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SMA	spinal muscular atrophy
SMN	survival motor neuron
SMN upregulator	SMN corrector
SOP	standard operating procedure
SRK-015	investigational, fully human, mAb that specifically binds to proforms of myostatin, which include proMyostatin and latent myostatin, thereby inhibiting myostatin activation
SST	Safety Surveillance Team
TEAE	treatment-emergent adverse event
Tlim	time to limitation
UNS	unscheduled
US	United States
WHO	World Health Organization

4. INTRODUCTION

4.1. SRK-015

Apitegromab (SRK-015) is an investigational, fully human, monoclonal antibody (mAb) that specifically binds to proforms of myostatin, which include proMyostatin and latent myostatin, thereby inhibiting myostatin activation. The antibody is produced in Chinese Hamster Ovary cells stably transfected with expression vectors encoding for the heavy and light chains of the antibody. SRK-015 is being developed for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients. SRK-015 is administered by intravenous (IV) infusion.

4.2. Spinal Muscular Atrophy

SMA is a rare, autosomal recessive neuromuscular disease characterized by degeneration of the motor neurons in the anterior horn of the spinal cord, resulting in atrophy of the voluntary muscles of the limbs and trunk. SMA directly results from reduced levels of survival motor neuron (SMN) protein, caused by homozygous deletions and, infrequently, mutations within the survival motor neuron 1 (*SMN1*) gene on chromosome 5q13.2. The lack of SMN protein causes the motor neurons to become dysfunctional and, eventually, to die.

Despite being a rare disorder, SMA is the most common genetic cause of infant mortality and a major cause of childhood morbidity (Pearn 1973; Sugarman 2012). The reported birth prevalence of SMA ranges from 8.5 to 10.3 per 100,000 live births (Arkblad 2009; Jedrzejowska 2013; Prior 2010; Sugarman 2012). The clinical phenotype of patients with SMA can vary significantly between patients who die soon after birth to patients who live into adulthood without symptoms. A major determinant of clinical phenotype is the number of copies present of a second gene, *SMN2*. There is a normal variance of *SMN2* gene copies in the general population where healthy individuals typically have 1 or 2 copies, and patients with SMA typically have 2 or 3 copies (Crawford 2012; Fang 2015).

Prior to the development of advanced molecular medicine techniques that allow genotyping of both *SMN1* and *SMN2* copy numbers, SMA was diagnosed based on clinical presentation and categorized phenotypically based on the maximal motor milestone achieved and the age at symptom onset. This phenotypic classification system requires subjects to be followed for enough time to determine whether a milestone will or will not be achieved. Because subjects may have been enrolled into a clinical trial before they were old enough to achieve certain motor milestones, for example sitting independently, a classification system based on age of symptom onset was used for clinical trial enrollment (Finkel 2015).

Type 0 or prenatal SMA is a rare type in which infants are born with clinical manifestations of disease, including major joint contractures and respiratory compromise, which result in a requirement for mechanical ventilation and ultimately lead to death at or shortly after birth (Dubowitz 1999; Finkel 2015; MacLeod 1999; Mercuri 2012). These patients usually have 1 copy of the *SMN2* gene.

Type 1 SMA is the most common form of SMA and represents approximately 58% of the birth prevalence (Ogino 2004). More than 90% of patients with 2 copies of *SMN2* will develop Type 1 SMA (Feldkötter 2002), and these infants usually present with hypotonia, loss of motor function, and failure to achieve new milestones within the first 6 months of life. These infants are never

able to sit without support (De Sanctis 2016; Russman 2007; Wang 2007). The major cause of morbidity and mortality in patients with Type 1 SMA is pulmonary disease due to neuromuscular weakness (Wang 2007). In the absence of respiratory support, only 1.3% of infants with Type 1 SMA survive beyond 24 months of age (Gregoretti 2013).

Type 2 SMA represents approximately 29% of the birth prevalence (Ogino 2004). Patients with Type 2 SMA usually have 3 copies of the *SMN2* gene but can vary between 2 and 4 copies. More than 80% of patients with 3 copies of *SMN2* will develop Type 2 SMA (Feldkötter 2002). Children fail to achieve motor milestones because of proximal weakness and hypotonia that typically develop within the first 18 months of life. This group is generally defined by an ability to sit independently but inability to walk unaided (Rudnik-Schöneborn 2001). However, the progressive nature of the disease means some of these patients will lose their ability to sit independently over time (Faravelli 2015; Russman 2007; Wang 2007). Orthopedic and respiratory complications are a major cause of morbidity and mortality, and only 70% of patients with Type 2 SMA are alive at 25 years of age (Faravelli 2015).

Type 3 SMA represents approximately 13% of the birth prevalence (Ogino 2004). Patients with Type 3 SMA usually have 3 or 4 copies of the *SMN2* gene. More than 80% of patients with 4 copies of *SMN2* will develop Type 3 SMA (Feldkötter 2002). Milestone achievement can vary greatly in SMA Type 3; some patients may maintain their ability to walk, while other patients have a level of functioning that more closely resembles SMA Type 2 (Finkel 2015). The distinguishing milestone for SMA Type 3 is the ability to walk unaided; however, the majority of patients lose that function over time (Rudnik-Schöneborn 2001). Ambulatory patients with Type 3 SMA commonly suffer from substantial motor functional impairment, as evidenced by abnormal Hammersmith Functional Motor Scale Expanded (HFMSE) scores and 6-Minute Walk Test (6MWT) distances (Mercuri 2016; Montes 2010). Some patients with Type 3 have orthopedic problems that are comparable to those experienced by patients with SMA Type 2, although generally with later onset and decreased severity (Haaker 2013).

Type 4 SMA is the mildest form of SMA, and its occurrence is rare (<1%). Patients with Type 4 SMA usually have 4 or more copies of the *SMN2* gene. After symptom onset, which has been reported after 10 years of age but more commonly after 20 to 30 years of age (Wang 2007), patients experience mild to moderate muscle weakness and increasing disabilities. Patients are ambulatory, and their life expectancy is normal (Faravelli 2015).

4.3. Current Therapies and Unmet Medical Need

In some countries, SPINRAZA® (nusinersen) is approved for the treatment of pediatric and adult patients with SMA, EVRYSDI™ (risdiplam) is approved for the treatment of pediatric and adult patients ≥2 months of age with SMA, and ZOLGENSMA® (onasemnogene abeparvovec-xioi) is approved for the treatment of pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the SMN1 gene. Nusinersen is an *SMN2*-directed antisense oligonucleotide and risdiplam is an *SMN2*-directed ribonucleic acid splicing modifier that are designed to treat SMA caused by mutations that lead to SMN protein deficiency. Onasemnogene abeparvovec-xioi is a recombinant adeno-associated virus vector 9-based gene therapy designed to deliver a copy of the gene encoding the human SMN protein. There are currently no approved muscle-directed therapies for the treatment of SMA. Additional medical care is supportive and focuses on respiratory support, nutritional support, and management of resulting musculotendinous

contractures and neuromuscular scoliosis through bracing, physical therapy, and surgery (Wang 2007).

SMN upregulator therapies (also referred to as SMN corrector therapies), such as nusinersen, onasemnogene abeparvovec-xioi, and other products in development (e.g., small molecule SMN upregulators) act primarily upon motor neurons to prevent further loss. While approved treatments have shown improvement in motor function in younger patients with SMA, they do not act directly on the muscle to primarily address already-existing atrophy and motor functional impairment in patients with symptomatic SMA. Consequently, there remains an unmet need for an effective muscle-directed therapy that can address muscle atrophy and motor functional impairment in patients with SMA.

4.4. Safety Rationale for SRK-015

SRK-015 has been evaluated in a single Phase 1 study (SRK-015-001). This two-part, randomized, double-blind, placebo-controlled, first-in-human trial was designed to evaluate the safety and tolerability, immunogenicity, pharmacokinetics (PK), and pharmacodynamics (PD) of intravenously administered SRK-015 in adult healthy subjects. A total of 66 subjects were enrolled, including 40 subjects in Part A, single ascending dose (SAD) and 26 subjects in Part B, multiple ascending dose (MAD). Subjects in the SAD were randomized 3:1 to receive single doses of SRK-015 or placebo across 5 dosing cohorts (1, 3, 10, 20, and 30 mg/kg), while subjects in the MAD were randomized 3:1 to receive multiple biweekly doses (on Days 0, 14, and 28) of SRK-015 or placebo across 3 dosing cohorts (10, 20, and 30 mg/kg). Both parts of the study have been completed.

Results of the study show that there were no dose-limiting toxicities (up to the highest dose tested of 30 mg/kg), deaths, subject discontinuations due to an adverse event (AE) related to SRK-015, serious adverse event (SAE) related to SRK-015, severe or life-threatening AEs related to SRK-015, or hypersensitivity reactions. The most common AE was headache in the SAD and postural dizziness in the MAD, which were observed in both the SRK-015 and placebo groups. Immunogenicity was assessed by antidrug antibody (ADA) testing, and all SRK-015 treated subjects tested negative.

Based upon PK analysis, SRK-015 displayed a well-behaved PK profile (e.g., low coefficient of variation) generally consistent with that observed with monoclonal antibodies. Drug exposure was dose proportional, and the serum half-life was 23 to 33 days across the SRK-015 dose groups in the SAD study. The findings support the investigation of a once every 4-week dosing regimen in this Phase 2 study (SRK-015-002).

No toxicologically significant findings have been observed to date for SRK-015 across the good laboratory practice (GLP) nonclinical toxicology studies. The no-observed-adverse-effect level (NOAEL) was the highest dose tested of 300 mg/kg weekly in the 26-week adult rat study and 7-week juvenile rat study. In addition, the NOAEL was the highest dose tested of 100 mg/kg weekly in the 4-week GLP nonclinical toxicology study in nonhuman primates and the 4-week GLP nonclinical toxicology study in rats. Based upon PK data from the SAD portion of the Phase 1 study, the drug exposure in this Phase 2 clinical study of monthly IV administrations of SRK-015 at the planned high-dose level of 20 mg/kg (or the maximum potential dose level of 30 mg/kg) is predicted to be substantially less than that attained and evaluated in the nonclinical toxicity studies.

For further detail on the Phase 1 clinical results and nonclinical findings, including findings that were not toxicologically significant, please refer to the SRK-015 Investigator's Brochure.

4.5. Therapeutic Rationale for SRK-015

Although progress has been made in the development of therapies addressing the SMN deficiencies, there remains an unmet medical need for a muscle-directed therapy that addresses the motor function deficits in SMA. By targeting the myostatin pathway (through the inhibition of myostatin activation), it is hypothesized that SRK-015 may address muscle atrophy and improve motor function (Han 2013).

The preclinical data, mechanistic rationale, and translational insights of SRK-015 pharmacology and muscle biology highlight the relevance of the myostatin pathway as a therapeutic target in SMA. Based upon preclinical evidence, the muscle mass and function-building effects of myostatin inhibition disproportionately impact fast-twitch fibers; in SMA, there is prominent atrophy of fast-twitch fibers and associated functional impairment. SRK-015 (or its murine version) has demonstrated the ability to substantially increase fast-twitch fiber mass across multiple animal species, including nonhuman primates. In an SMA mouse model, treatment robustly increased muscle strength (as measured by torque) (Long 2018).

Data from the Phase 1 clinical study (SRK-015-001) offer initial evidence that SRK-015 may have the pharmacologic profile necessary to suppress the myostatin pathway in humans. The PD of SRK-015 were evaluated through an assay measuring latent myostatin biomarker concentrations in the serum. These data demonstrated that SRK-015 treatment was able to successfully engage target, attain a plateau for this effect (thus, suggesting target saturation) even after a single treatment at doses of 3 mg/kg or greater, and sustain this effect for at least several months following a single dose of 20 mg/kg or greater. Relatively faster clearance of latent myostatin was observed with lower doses of SRK-015, suggesting that higher doses offer sustained target engagement. Together, these data provide evidence that systemic administration of SRK-015 at pharmacologically tractable doses in humans may successfully engage its target in the skeletal muscle, saturate this engagement, and sustain this saturation in a durable fashion.

4.6. Study Rationale

There remains an unmet need for an effective muscle-directed therapy that can address muscle atrophy and thereby improve motor function in patients with SMA despite advances in the development of SMN upregulator therapies. Through its novel mechanism, SRK-015 has the potential to produce a clinically meaningful effect on motor function in a broad population of patients with SMA who may or may not be on background SMN upregulator therapies (e.g., nusinersen). As such, SRK-015 has the potential to treat a severe disease and fulfill a significant unmet medical need for patients with SMA. Accordingly, this first study of SRK-015 in patients with Type 2 and Type 3 SMA is designed to evaluate the safety and efficacy of SRK-015 in patients who are receiving background SMN upregulator therapy (Cohorts 1, 2, and 3) and in those who are not (Cohort 1). The study will assess the effects of SRK-015 upon motor function outcome measures (e.g., HFMSE, Revised Hammersmith Scale [RHS], and Revised Upper Limb Module [RULM]) that are designed for SMA, validated in SMA, and considered clinically meaningful. In addition, the study will characterize the effect of SRK-015 upon other outcome measures relevant for neuromuscular disorders such as SMA. The sample sizes were

selected to enable meaningful assessments of the clinical effects of SRK-015 as compared to the otherwise anticipated course of disease based upon natural history as well as to characterize the safety of SRK-015.

The treatment duration necessary to attain clinical effect in patients with SMA is unknown. The increases in muscle mass and strength seen in nonclinical studies can be apparent as early as after approximately a month of dosing. Longer treatment durations may be required in patients with SMA, particularly if the goal is to attain improvements in clinically meaningful motor function outcome measures. Accordingly, a period of 52 weeks has been selected to provide a reasonable period of time to observe a clinical effect upon motor function from inhibiting the activation of myostatin. Interim analyses will explore whether clinical effects are evident earlier.

Three optional Extension Periods (52 weeks each) have been added to the study to observe the long-term safety and efficacy effects of SRK-015 and to demonstrate any potential treatment benefits for patients.

Available data and mechanistic understanding support the investigation of SRK-015 in pediatric patients. Children represent a significant proportion of the SMA population with substantial unmet medical need and have the potential to benefit from a novel therapeutic approach addressing their muscle atrophy and motor functional impairment. There is no apparent biologic basis for suspecting that pediatric patients may have any uniquely elevated safety risk from blockade of the myostatin pathway. In addition, toxicologically significant findings were not observed in the 7-week juvenile rodent study, including at the highest dose tested (300 mg/kg IV SRK-015 weekly). Data from the SAD portion of the Phase 1 study demonstrated a generally well-behaved PK profile for SRK-015, and SRK-015 dosing will be weight-based in this Phase 2 study. To initially confirm that drug exposure or target engagement in pediatric patients does not substantially differ from that observed in the Phase 1 study in adult healthy volunteers, interim PK and PD analyses will be conducted in a small number of patients in this Phase 2 study. Based upon these results, and taking into consideration any available safety data, the dose levels may be adjusted in this Phase 2 study. Any adjustment in dose level will not change the frequency of dosing (i.e., every 4 weeks) and the highest dose will not exceed 30 mg/kg, as tested in the Phase 1 study.

4.7. Dose Rationale

Based upon data from SRK-015-001, the first in-human study in healthy volunteers, multiple doses of up to 30 mg/kg were generally safe and well tolerated. PK results from the Phase 1 SAD study suggest that SRK-015 has a profile generally consistent with that observed of mAbs, including dose-proportionality and a low coefficient of variation. The serum half-life was 23 to 33 days across the SRK-015 dose groups. The findings support the investigation of a once every 4-week dosing regimen in this Phase 2 study.

PD results suggest that SRK-015 treatment leads to robust increases in latent myostatin concentrations in the serum above baseline and demonstrate successful target engagement in humans. Moreover, the levels of target engagement attain a plateau, suggesting that the target has been saturated even with a single treatment of SRK-015 at doses of 3 mg/kg or greater. This level of PD marker appears to be sustained for approximately 84 days following a single 20 mg/kg dose, suggesting that the PD effect is durable.

The 20 mg/kg high-dose arm is aimed at attaining target saturation rapidly (e.g., within several weeks after the first dose) and sustaining that saturation with chronic administration. Based upon PK data from the Phase 1 SAD study, the drug exposure from monthly IV administrations of SRK-015 at 20 mg/kg is predicted to be substantially less than that attained in the nonclinical toxicity studies to date. For further detail on the Phase 1 PK and PD results, please refer to the SRK-015 Investigator's Brochure.

Dose exploration will be conducted in this study by including a low-dose arm of 2 mg/kg. At this dose level, it is anticipated that target saturation will not be attained upon the first dose and thus would require additional dosing. By characterizing the time course of clinical effect from this low-dose arm and comparing it with that observed from the 20 mg/kg level, the relationship between drug exposure and therapeutic effect over time can be interrogated. Insights into the level of drug exposure necessary to initiate improvements in motor function will also be attained. Together, results from this analysis will inform the dosing regimen for future clinical studies of SRK-015 in SMA.

The results of the prespecified 6-month safety and efficacy interim analyses in this study, including greater improvements in HFMSE scores for the high-dose arm and no identification of safety signals, supported a change in dose for Cohort 3 patients from low-dose (2 mg/kg) to high-dose (20 mg/kg) SRK-015 during Extension Period A (See Section 6.2). The preliminary results of the 12-month analysis continue to support the dose change. For further details on the Phase 2 safety and efficacy analyses results please refer to the SRK-015 Investigator's Brochure.

5. TRIAL OBJECTIVES AND PURPOSE

5.1. Primary Objectives for Both the Treatment Period and Extension Periods

The primary objectives of this study are:

- To assess safety and tolerability of SRK-015 in patients with later-onset (e.g., Type 2 and Type 3) SMA
- To assess the efficacy of SRK-015 by assessing changes in motor function outcome measures in 3 separate predefined cohorts

5.2. Secondary Objectives for Both the Treatment Period and Extension Periods

The secondary objectives defined for this study are:

- To characterize the PK of SRK-015
- To evaluate the PD effects of SRK-015
- To evaluate time to therapeutic effect between low- and high-dose SRK-015 in a predefined cohort (Cohort 3)
- To evaluate the immunogenicity of SRK-015
- To evaluate the effect of SRK-015 on quality of life

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

Study SRK-015-002 is an active treatment study of SRK-015 in patients age 2 through 21 years old with later-onset SMA. Patients may receive SRK-015 as monotherapy or in addition to an SMN upregulator therapy approved for SMA.

The study will be conducted at approximately 20 study sites across the US and Europe and will enroll approximately 55 patients with SMA across 3 separate parallel subpopulations subsequently described as cohorts:

- Cohort 1, N=20: Ambulatory Type 3 patients, age 5 through 21 years old, at least 10 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: Type 2 or nonambulatory Type 3 patients, age 5 through 21 years old, already receiving an approved SMA treatment that had been started after the patient turned 5 years old.
- Cohort 3, N=20: Type 2 patients, age ≥2 years old, already receiving an approved SMA treatment that had been started before the patient turned 5 years old.

Patient participation in the study will consist of 3 parts: Screening, Treatment, and Follow-up.

1. During the Screening Period, all patient screening and eligibility determinations will be conducted after informed consent (and, as required by local authorities, patient informed assent) has been provided and within 28 days prior to first dose. Screening motor function outcome measures will be conducted at least 7 days prior to the first dose. All subsequent motor function outcome measures will be conducted within 96 hours prior to dosing.
2. During the 52-week Treatment Period, patients enrolled in Cohorts 1 and 2 will receive high-dose (20 mg/kg) SRK-015 and patients enrolled in Cohort 3 will be randomized (1:1) in a blinded manner to receive either low-dose (2 mg/kg) or high-dose (20 mg/kg) SRK-015 (Figure 1). All treatments will be administered by IV infusion over approximately 2 hours once every 4 weeks. The first dose will be administered on Day 0 and the final dose on Day 336, for a total of 13 doses. There will be a ±7-day window around each dosing visit, with a minimum of 21 days and a maximum of 35 days between doses.

   During the Treatment Period, patients will be monitored at the study site through approximately 2 hours postdose. If there are no acute reactions following the first 2 doses for a patient, and if the Investigator determines that it would be safe to do so, the infusion duration can be changed to less than 2 hours but no shorter than 1 hour.

   Following each dose, patients will be contacted by the site within 7 days as a safety check-in (in the Treatment Period only). Patients will be seen in clinic 14 days after the first dose. After the second dose, visits will occur every 4 weeks through the end of the

study (Table 2). All dosing and motor function outcome measures will be conducted at the study site during the Treatment Period.

The last Treatment Period visit will be on Day 364 (V15).

Total study participation for an individual patient who completes the Treatment Period will consist of approximately 4 weeks for Screening, 52 weeks of study visits, and, if the patient does not enroll into Extension Period A, 12 weeks of Safety Follow-up for a total duration of approximately 68 weeks (approximately 16 months).

Patients who complete the 52-week Treatment Period will have the option to enroll into Extension Period A for an additional 52-week period (Figure 2). There will be no interruption in dosing between the completion of the Treatment Period and the start of Extension Period A. The first dose in Extension Period A will be administered on Day 364 (E1), following completion of the Treatment Period at V15, and the final dose will be administered on Day 700 (E13), for a total of 13 doses.

Total study participation for an individual patient who completes both the Treatment Period and Extension Period A will consist of approximately 4 weeks for Screening, 104 weeks of study visits, and 12 weeks of Safety Follow-up for a total duration of approximately 120 weeks (approximately 28 months).

Patients who complete Extension Period A will have the option to enroll into Extension Period B for an additional 52-week period (Figure 3). There will be no interruption in dosing between the completion of Extension Period A and the start of Extension Period B. The first dose in Extension Period B will be administered on Day 728 (EB1), following completion of Extension Period A on Day 728 (E14), and the final dose will be administered on Day 1064 (EB13), for a total of 13 doses.

Total study participation for an individual patient who completes the Treatment Period and Extension Periods A and B will consist of approximately 4 weeks for Screening, 156 weeks of study visits, and 12 weeks of Safety Follow-up for a total duration of approximately 172 weeks (approximately 40 months).

Patients who complete Extension Period B will have the option to enroll into Extension Period C for an additional 52-week period (Figure 4). There will be no interruption in dosing between the completion of Extension Period B and the start of Extension Period C. The first dose in Extension Period C will be administered on Day 1092 (EC1), following completion of Extension Period B on Day 1092 (EB14), and the final dose will be administered on Day 1428 (EC13), for a total of 13 doses.

Total study participation for an individual patient who completes the Treatment Period and Extension Periods A, B, and C will consist of approximately 4 weeks for Screening, 208 weeks of study visits, and 12 weeks of Safety Follow-up for a total duration of approximately 224 weeks (approximately 52 months).

All treatments will be administered by IV infusion over 1 to 2 hours once every 4 weeks. There will be a ±7-day window around each dosing visit, with a minimum of 21 days and a maximum of 35 days between doses.

During the Extension Periods, patients will be monitored at the study site through approximately 1 hour postdose.

3. Patients who complete the 52-week Treatment Period and choose not to enroll in optional Extension Period A will be followed for a 12-week Safety Follow-up Period after Day 364 (V15). These patients will have a total of 13 doses. Patients who complete the 52-week Extension Period A and choose not to enroll in optional Extension Period B will be followed for a 12-week Safety Follow-up Period after Day 728 (E14). These patients will have a total of 26 doses. Patients who complete the 52-week Extension Period B and choose not to enroll in optional Extension Period C will be followed for a 12-week Safety Follow-up Period after Day 1092 (EB14). These patients will have a total of 39 doses. Patients who complete the 52-week Extension Period C may be offered the option to enter a separate long-term safety extension trial at that time. Patients who complete the 52-week Extension Period C and choose not to enroll in the separate long-term safety extension trial will be followed for a 12-week Safety Follow-up Period after Day 1456 (EC14). These patients will have a total of 52 doses.

6.2. Treatment Assignment

Eligible patients in Cohorts 1 and 2 will receive high-dose (20 mg/kg) SRK-015. Patients in Cohort 3 will be randomized 1:1 to low- (2 mg/kg) or high-dose (20 mg/kg) SRK-015 without stratification for the duration of the Treatment Period. Based on the results of the prespecified 6-month safety and efficacy interim analyses (data cutoff date of 20 August 2020), any Cohort 3 patients who were randomized to receive low-dose (2 mg/kg) SRK-015 will be re-assigned to receive high-dose (20 mg/kg) SRK-015 after completion of the Treatment Period. The preliminary results of the 12-month analysis (database lock date of 19 January 2021) continue to support the dose change. For further detail on the Phase 2 safety and efficacy analyses results please refer to the SRK-015 Investigator's Brochure. Due to the variability in timing of regulatory authority and/or Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approvals, the timepoint at which patients who received the low dose (2 mg/ kg) will begin receiving the high dose (20 mg/kg) during Extension Period A will vary.

Figure 1: Study Schematic: Treatment Period

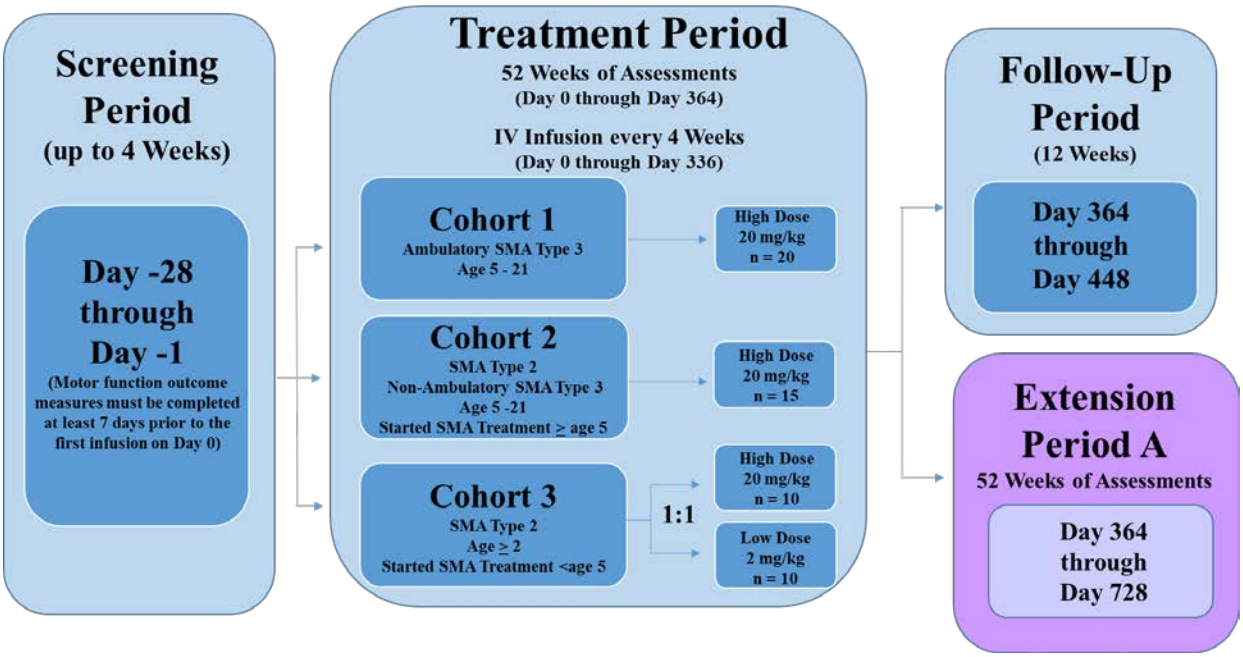

Figure 2: Study Schematic: Extension Period A

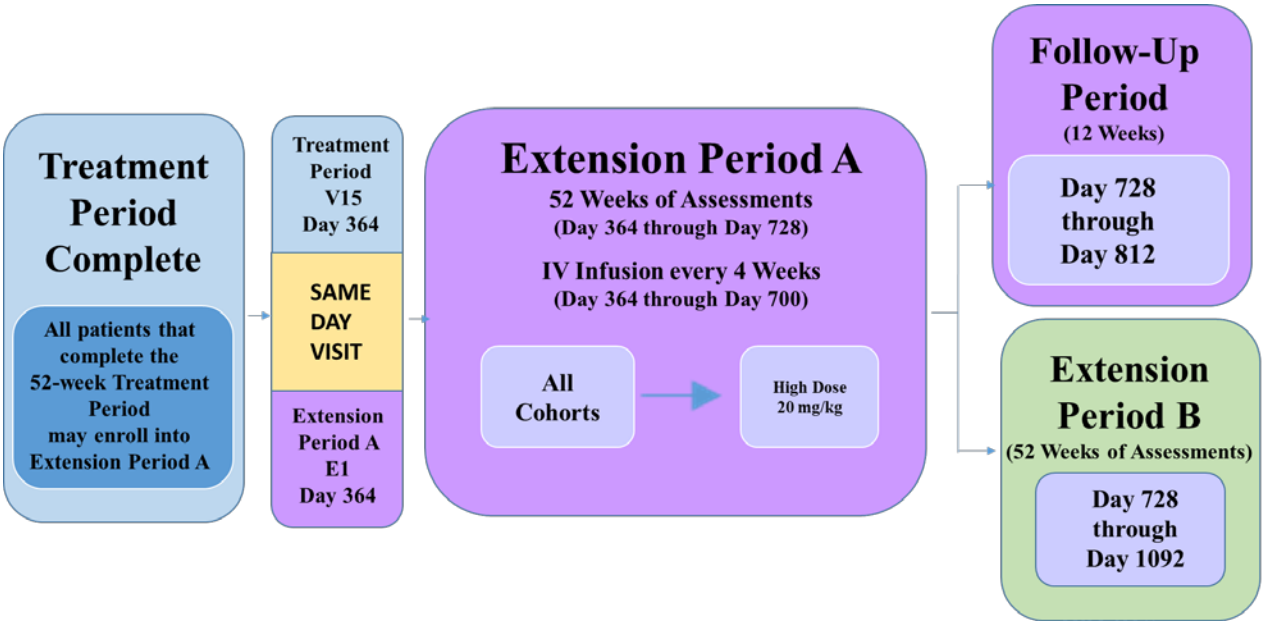

Figure 3: Study Schematic: Extension Period B

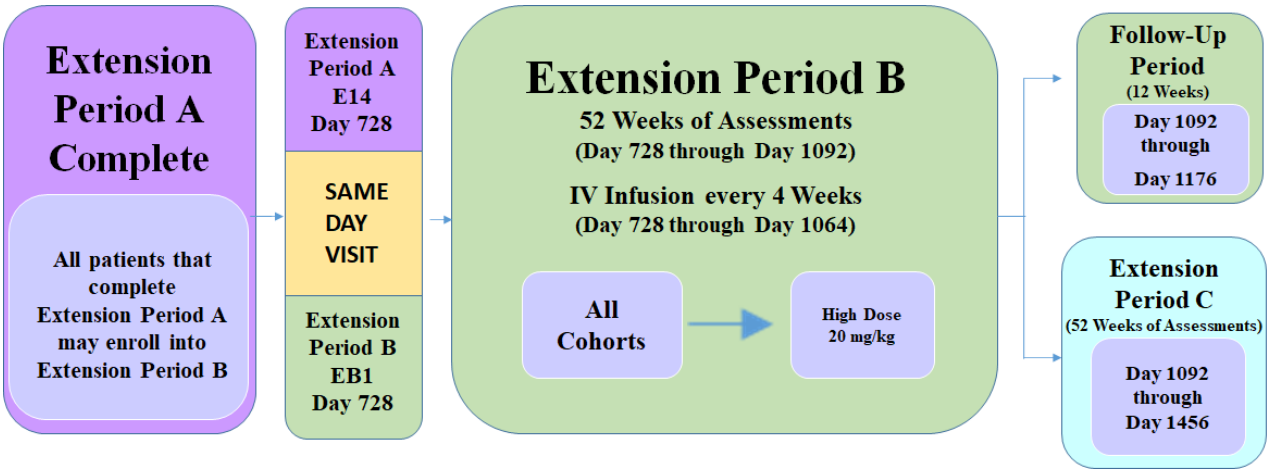

Figure 4: Study Schematic: Extension Period C

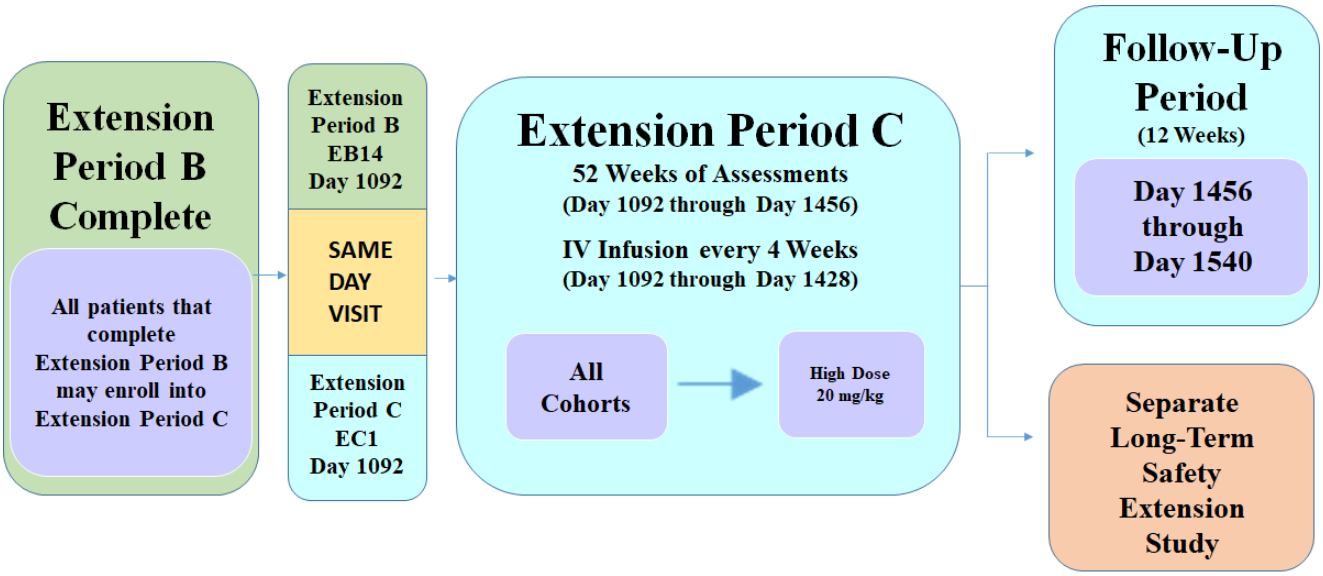

Table 2: Study Schedule of Assessments: Treatment Period

Activity/Assessment	Screening	Treatment Period																Follow-up	
Visit Time Point (Study Day[a])	-28 to -1	V1 0	V2 14	V3 28	V4 56	V5 84	V6 112	V7 140	V8 168	V9 196	V10 224	V11 252	V12 280	V13 308	V14 336	V15 364	UNS	V16 392	V17 448/EOS/ET
Informed Consent	X																		
Demographics & Medical History[c]	X																		
Inclusion/Exclusion	X																		
Pregnancy Test[d]	X	X			X				X				X						X
Weight[e]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height[f]	X	X			X		X		X		X		X			X	X	X	X
Physical Examination[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Safety Labs[i]	X	X	X	X	X		X		X		X		X		X		X	X	X
12-lead ECG[j]	X	X		X			X				X				X		X	X	X
PK and PD Sampling[k]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Antidrug Antibody Sampling[l]		X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Randomization[m]		X																	
Study Drug Administration		X		X	X	X	X	X	X	X	X	X	X	X	X				
Motor Function Outcome Measures[b,f,,n]	X	X			X		X		X		X		X			X	X	X	X
QOL[o]		X			X		X		X		X		X			X	X	X	X
Site Check-in[p]		X		X	X	X	X	X	X	X	X	X	X	X	X				
Adverse Events	*To be collected from the date that the ICF is signed through the last study visit*																		
Concomitant Therapy	*To be collected from the date that the ICF is signed through the last study visit*																		

ECG = electrocardiogram; EOS = end-of-study; ET = early termination; ICF = informed consent form; IV = intravenous; PD = pharmacodynamic; PEDI-CAT: Pediatric Evaluation of Disability Inventory Computer Adaptive Test; PK = pharmacokinetic; PROMIS = Patient-reported Outcomes Measurement Information System; QOL = quality of life; UNS = unscheduled.

[a] Study visits after Day 0 have a ±7-day window, excluding Day 14, which has a ±1-day window. Visit assessments may be conducted over multiple days within the visit window, as needed and in compliance with protocol requirements for the timing of each assessment.
[b] Screening motor function outcome measures must be completed at least 7 days prior to the first infusion on Day 0. All subsequent motor function outcome measures will be conducted within 96 hours prior to dosing.
[c] Includes history of present illness.
[d] Females of childbearing potential only. Urine or serum test is acceptable; however, positive urine tests must be confirmed with serum testing. Testing may be performed more frequently as per local requirements. The urine pregnancy test used is the Alere hCG cassette (25mIU/mL) and according to the product manufacturer, has >99% sensitivity.
[e] Weight is collected within 48 hours of each dose to calculate weight-based dosing.
[f] Height is collected at visits where the motor function outcome measures are conducted. Ulna length may be used to estimate height for patients who are nonambulatory or needs standing support.
[g] Changes in pubertal development must be assessed if not deemed physically mature at Screening. If menarche occurs during the study, the child will be deemed of childbearing potential and immediate pregnancy status will be checked. Further study drug can only be given if pregnancy status is negative. Contraception and pregnancy monitoring will be performed as outlined in the protocol.
[h] Heart rate, blood pressure, and respiratory rate are collected preinfusion, every 15 minutes (±5 minutes) during the infusion, at the end of the infusion, and 1 and 2 hours (±15 minutes) postinfusion. Body temperature will be collected preinfusion on dosing days.
[i] Clinical safety labs include serum chemistry, hematology, urinalysis, and coagulation. Labs are collected preinfusion at dosing visits.
[j] 12-lead ECGs are collected after 5 minutes of rest, in triplicate and at least 1-2 minutes apart. ECGs are collected within 2 hours prior to the start of the infusion. Unscheduled ECGs may be performed as clinically necessary.
[k] Blood samples for PK and PD are collected within 2 hours prior to the start of the infusion at dosing visits. An additional sample is collected via peripheral IV 2 hours (±1 hour) after completion of the infusion on Day 0, Day 140 (PK only), and Day 336 (PK only).
[l] Blood sample for anti-SRK-015 antibody testing is collected within 2 hours prior to the start of the infusion at dosing visits.
[m] Patients in Cohort 3 will be randomized to low- or high-dose SRK-015 within 24 hours prior to the first infusion on Day 0.
[n] See Table 6 for motor function outcome measures conducted for each cohort. Unscheduled motor function outcome measures may be performed as needed.
[o] QOL collected using the PROMIS Fatigue Questionnaire and PEDI-CAT. If the PEDI-CAT and/or PROMIS are not available in the native language, they should not be completed. Unscheduled QOL questionnaires may be performed as needed.
[p] Sites contact patients within 7 days following each infusion to collect information on adverse events and concomitant medications.

Table 3: Study Schedule of Assessments: Extension Period A (Extension A Visits 1-15)

Activity/Assessment	Extension Period A													Follow-Up/ Other	
Visit Time Point (Study Day[a])	E1 364 [c]	E2 392	E3 420	E4 448	E5 476	E6 504	E7 532	E8 560	E9 588	E10 616	E11 644	E12 672	E13 700	E14 728	E - UNS	E15 812/EOS/ ET
Informed Consent[o]	X															
Pregnancy Test[d]	For patients who enroll into Extension Period A, assessments will merge between Treatment Period Day 364 (V15) and Extension Period A Day 364 (E1). Study drug administration and PK/PD/ADA Sampling will only be performed for patients who enroll into Extension Period A.		X				X				X					X
Weight[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height[f]					X				X					X	X	X
Physical Examination[g]		X		X		X		X		X		X		X	X	X
Vital Signs[h]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Safety Labs[i]		X			X			X			X		X		X	X
12-lead ECG[j]		X			X			X			X		X		X	X
PK and PD Sampling[k]	X	X			X			X			X		X	X	X	X
Antidrug Antibody Sampling[l]	X	X			X			X			X		X	X	X	X
Study Drug Administration	X	X	X	X	X	X	X	X	X	X	X	X	X			
Motor Function Outcome Measures [b,f,m]					X				X					X	X	X
QOL[n]					X				X					X	X	X
Adverse Events	*To be collected from the date that the ICF is signed through the last study visit*															
Concomitant Therapy	*To be collected from the date that the ICF is signed through the last study visit*															

ECG = electrocardiogram; EOS = end-of-study; ET = early termination; ICF = informed consent form; IV = intravenous; PD = pharmacodynamic; PEDI-CAT: Pediatric Evaluation of Disability Inventory Computer Adaptive Test; PK = pharmacokinetic; PROMIS = Patient-reported Outcomes Measurement Information System; QOL = quality of life; UNS = unscheduled.

[a] Study visits have a ±7-day window. Visit assessments may be conducted over multiple days within the visit window, as needed and in compliance with protocol requirements for the timing of each assessment.

[b] All motor function outcome measures will be conducted within 96 hours prior to dosing.
[c] Treatment Period Day 364 (Visit 15) and Extension Period A Day 364 (E1) occur on the same day. Treatment Period V15 will serve as the last Treatment Period visit and Extension Period A E1 will serve as the first visit for Extension Period A. There will not be any duplicate assessments performed.
[d] Females of childbearing potential only. Urine or serum test is acceptable; however, positive urine tests must be confirmed with serum testing. Testing may be performed more frequently as per local requirements. The urine pregnancy test used is the Alere hCG cassette (25mIU/mL) and according to the product manufacturer, has >99% sensitivity.
[e] Weight is collected within 48 hours of each dose to calculate weight-based dosing.
[f] Height is collected at visits where the motor function outcome measures are conducted. Ulna length may be used to estimate height for patients who are nonambulatory or not able to stand independently.
[g] Changes in pubertal development must be assessed if not deemed physically mature during Treatment Period. If menarche occurs during the study, the child will be deemed of childbearing potential and immediate pregnancy status will be checked. Further study drug can only be given if pregnancy status is negative. Contraception and pregnancy monitoring will be performed as outlined in the protocol.
[h] Heart rate, blood pressure, and respiratory rate are collected preinfusion, every 15 minutes (±5 minutes) during the infusion, at the end of the infusion, and 1 hour (±15 minutes) postinfusion. Body temperature will be collected preinfusion on dosing days.
[i] Clinical safety labs include serum chemistry, hematology, urinalysis, and coagulation. Labs are collected preinfusion at dosing visits.
[j] 12-lead ECGs are collected after 5 minutes of rest, in triplicate and at least 1-2 minutes apart. ECGs are collected within 2 hours prior to the start of the infusion. Unscheduled ECGs may be performed as clinically necessary.
[k] Blood samples for PK and PD are collected within 2 hours prior to the start of the infusion at dosing visits. An additional sample is collected via peripheral IV 1 hour (+ 30-minute window) after completion of the infusion on Day 700 (PK only).
[l] Blood sample for anti-SRK-015 antibody testing is collected within 2 hours prior to the start of the infusion at dosing visits.
[m] See Table 6 for motor function outcome measures conducted for each cohort. Unscheduled motor function outcome measures may be performed as needed.
[n] QOL collected using the PROMIS Fatigue Questionnaire and PEDI-CAT. If the PEDI-CAT and/or PROMIS are not available in the native language, they should not be completed. Unscheduled QOL questionnaires may be performed as needed.
[o] Patients may consent to participate in Extension Period A at any time prior to V15/E1 or at V15/E1.

Table 4: Study Schedule of Assessments: Extension Period B (Extension B Visits 1-15)

Activity/Assessment	**Extension Period B**														**Follow-Up/ Other**	
Visit Time Point (Study Day[a])	**EB1[o] 728**	**EB2 756**	**EB3 784**	**EB4 812**	**EB5 840**	**EB6 868**	**EB7 896**	**EB8 924**	**EB9 952**	**EB10 980**	**EB11 1008**	**EB12 1036**	**EB13 1064**	**EB14 1092**	**EB - UNS**	**EB15 1176 /EOS/ET**
Informed Consent[n]	X															
Pregnancy Test[c]	X		X				X				X					X
Weight[d]	For patients who enroll into Extension Period B, assessments will merge between Extension Period A Day 728 (E14) and Extension Period B Day 728 (EB1). Study drug administration will only be performed for patients who enroll into Extension Period B.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height[e]					X				X					X	X	X
Physical Examination[f]		X		X		X		X		X		X		X	X	X
Vital Signs[g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Safety Labs[h]		X			X			X			X		X		X	X
12-lead ECG[i]		X			X			X			X				X	X
PK and PD Sampling[j]	X	X			X			X			X		X		X	X
Antidrug Antibody Sampling[k]	X	X			X			X			X		X		X	X
Study Drug Administration	X	X	X	X	X	X	X	X	X	X	X	X	X			
Motor Function Outcome Measures[b,e,l]					X				X					X	X	X
QOL[m]					X				X					X	X	X
Adverse Events	*To be collected from the date that the ICF is signed through the last study visit*															
Concomitant Therapy	*To be collected from the date that the ICF is signed through the last study visit*															

ECG = electrocardiogram; EOS = end-of-study; ET = early termination; ICF = informed consent form; IV = intravenous; PD = pharmacodynamic; PEDI-CAT: Pediatric Evaluation of Disability Inventory Computer Adaptive Test; PK = pharmacokinetic; PROMIS = Patient-reported Outcomes Measurement Information System; QOL = quality of life; UNS = unscheduled.

[a] Study visits have a ±7-day window. Visit assessments may be conducted over multiple days within the visit window, as needed and in compliance with protocol requirements for the timing of each assessment.

[b] All motor function outcome measures will be conducted within 96 hours prior to dosing.

[c] Females of childbearing potential only. Urine or serum test is acceptable; however, positive urine tests must be confirmed with serum testing. Testing may be performed more frequently as per local requirements. The urine pregnancy test used is the Alere hCG cassette (25mIU/mL) and according to the product manufacturer, has >99% sensitivity.

[d] Weight is collected within 48 hours of each dose to calculate weight-based dosing.

[e] Height is collected at visits where the motor function outcome measures are conducted. Ulna length may be used to estimate height for patients who are nonambulatory or not able to stand independently.

[f] Changes in pubertal development must be assessed if not deemed physically mature during Extension Period A. If menarche occurs during the study, the child will be deemed of childbearing potential and immediate pregnancy status will be checked. Further study drug can only be given if pregnancy status is negative. Contraception and pregnancy monitoring will be performed as outlined in the protocol.

[g] Heart rate, blood pressure, and respiratory rate are collected preinfusion, every 15 minutes (±5 minutes) during the infusion, at the end of the infusion, and 1 hour (±15 minutes) postinfusion. Body temperature will be collected preinfusion on dosing days.

[h] Clinical safety labs include serum chemistry, hematology, urinalysis, and coagulation. Labs are collected preinfusion at dosing visits.

[i] 12-lead ECGs are collected after 5 minutes of rest, in triplicate and at least 1-2 minutes apart. ECGs are collected within 2 hours prior to the start of the infusion. Unscheduled ECGs may be performed as clinically necessary.

[j] Blood samples for PK and PD are collected within 2 hours prior to the start of the infusion at dosing visits. An additional sample is collected via peripheral IV 1 hour (+ 30-minute window) after completion of the infusion on Day 1008 (PK only).

[k] Blood sample for anti-SRK-015 antibody testing is collected within 2 hours prior to the start of the infusion at dosing visits.

[l] See Table 6 for motor function outcome measures conducted for each cohort. Unscheduled motor function outcome measures may be performed as needed.

[m] QOL collected using the PROMIS Fatigue Questionnaire and PEDI-CAT. If the PEDI-CAT and/or PROMIS are not available in the native language, they should not be completed. Unscheduled QOL questionnaires may be performed as needed.

[n] Patients may consent to participate in Extension Period B at any time prior to E14/EB1 or at E14/EB1.

[o] Extension Period A Day 728 (E14) and Extension Period B Day 728 (EB1) occur on the same day. Extension Period A E14 will serve as the last Extension Period A visit and Extension Period B EB1 will serve as the first visit for Extension Period B. There will not be any duplicate assessments performed.

Table 5: Study Schedule of Assessments: Extension Period C (Extension C Visits 1-15)

Activity/Assessment	Extension Period C														Follow-Up/Other	
Visit Time Point (Study Day[a])	EC1[o] 1092	EC2 1120	EC3 1148	EC4 1176	EC5 1204	EC6 1232	EC7 1260	EC8 1288	EC9 1316	EC10 1344	EC11 1372	EC12 1400	EC13 1428	EC14 1456	EC - UNS	EC15 1540 /EOS/ET
Informed Consent[n]	X															
Pregnancy Test[c]	X		X				X				X					X
Weight[d]	For patients who enroll into Extension Period C, assessments will merge between Extension Period B Day 1092 (EB14) and Extension Period C Day 1092 (EC1). Study drug administration will only be performed for patients who enroll into Extension Period C.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height[e]					X				X					X	X	X
Physical Examination[f]		X		X		X		X		X		X		X	X	X
Vital Signs[g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Safety Labs[h]		X			X		X				X		X		X	X
12-lead ECG[i]	X						X						X		X	X
PK and PD Sampling[j]	X						X						X		X[p]	X
Antidrug Antibody Sampling[k]	X						X						X		X[p]	X
Study Drug Administration	X	X	X	X	X	X	X	X	X	X	X	X	X			
Motor Function Outcome Measures[b,e,l]					X				X					X	X	X
QOL[m]					X				X					X	X	X
Adverse Events	*To be collected from the date that the ICF is signed through the last study visit*															
Concomitant Therapy	*To be collected from the date that the ICF is signed through the last study visit*															

ECG = electrocardiogram; EOS = end-of-study; ET = early termination; ICF = informed consent form; IV = intravenous; PD = pharmacodynamic; PEDI-CAT: Pediatric Evaluation of Disability Inventory Computer Adaptive Test; PK = pharmacokinetic; PROMIS = Patient-reported Outcomes Measurement Information System; QOL = quality of life; UNS = unscheduled.

[a] Study visits have a ±7-day window. Visit assessments may be conducted over multiple days within the visit window, as needed and in compliance with protocol requirements for the timing of each assessment.

[b] All motor function outcome measures will be conducted within 96 hours prior to dosing.

[c] Females of childbearing potential only. Urine or serum test is acceptable; however, positive urine tests must be confirmed with serum testing. Testing may be performed more frequently as per local requirements. The urine pregnancy test used is the Alere hCG cassette (25mIU/mL) and according to the product manufacturer, has >99% sensitivity.

[d] Weight is collected within 48 hours of each dose to calculate weight-based dosing.

[e] Height is collected at visits where the motor function outcome measures are conducted. Ulna length may be used to estimate height for patients who are nonambulatory or not able to stand independently.

[f] Changes in pubertal development must be assessed if not deemed physically mature during Extension Period B. If menarche occurs during the study, the child will be deemed of childbearing potential and immediate pregnancy status will be checked. Further study drug can only be given if pregnancy status is negative. Contraception and pregnancy monitoring will be performed as outlined in the protocol.

[g] Heart rate, blood pressure, and respiratory rate are collected preinfusion, every 15 minutes (±5 minutes) during the infusion, at the end of the infusion, and 1 hour (±15 minutes) postinfusion. Body temperature will be collected preinfusion on dosing days.

[h] Clinical safety labs include serum chemistry, hematology, urinalysis, and coagulation. Labs are collected preinfusion at dosing visits.

[i] 12-lead ECGs are collected after 5 minutes of rest, in triplicate and at least 1-2 minutes apart. ECGs are collected within 2 hours prior to the start of the infusion and within 1 hour after the end of infusion at Visit EC1 and EC13. Unscheduled ECGs may be performed as clinically necessary.

[j] Blood samples for PK and PD are collected within 2 hours prior to the start of the infusion at dosing visits. An additional sample is collected via peripheral IV 1 hour (+ 30-minute window) after completion of the infusion at Visit EC1 (Day 1092) and EC13 (Day 1428) (PK only).

[k] Blood sample for anti-SRK-015 antibody testing is collected within 2 hours prior to the start of the infusion at dosing visits.

[l] See Table 6 for motor function outcome measures conducted for each cohort. Unscheduled motor function outcome measures may be performed as needed.

[m] QOL collected using the PROMIS Fatigue Questionnaire and PEDI-CAT. If the PEDI-CAT and/or PROMIS are not available in the native language, they should not be completed. Unscheduled QOL questionnaires may be performed as needed.

[n] Patients may consent to participate in Extension Period C at any time prior to EB14/EC1 or at EB14/EC1.

[o] Extension Period B Day 1092 (EB14) and Extension Period C Day 1092 (EC1) occur on the same day. Extension Period B EB14 will serve as the last Extension Period B visit and Extension Period C EC1 will serve as the first visit for Extension Period C. There will not be any duplicate assessments performed.

[p] PK/PD/ADA samples will only be collected at unscheduled visits when SRK-015 is administered on the same day. Please refer to footnotes j and k for sample collection details.

Table 6: Motor Function Outcome Measures

Cohort 1	Cohorts 2 and 3
• Revised Hammersmith Scale (RHS) • 6-Minute Walk Test (6MWT) • 30-Second Sit-to-Stand • 10-Meter Walk/Run (from RHS) • Timed Rise from Floor (from RHS)	• Hammersmith Functional Motor Scale Expanded (HFMSE) • World Health Organization (WHO) Motor Development Milestones • Revised Upper Limb Module (RULM) • Endurance Shuttle Nine Hole Peg Test (ESNHPT) or Endurance Shuttle Box and Block Test (ESBBT)[a]

[a] Patients who score ≤3 on Item A of the RULM at Screening will perform the ESNHPT at Screening and all subsequent assessments, while patients who score >3 on Item A of the RULM at Screening will perform the ESBBT at Screening and all subsequent assessments. If patient maxes out of an endurance test, the PT Advisory Board will be consulted to potentially change assessment designation. [b] The motor function outcome measures will be videotaped for educational and training purposes to ensure that they are being conducted properly and consistently by the physical therapists, upon consent.

6.3. Safety Oversight and Stopping Rules

6.3.1. Safety Surveillance Team

A safety surveillance team (SST) will review safety data throughout the duration of the study (inclusive of Treatment, Extension and Safety Follow-up Periods) to assess patient safety. The SST will review safety data approximately every 6 months, and on an ad hoc basis as needed. Prior to Protocol Version 5.0, the SST review was approximately every 12 weeks. Safety reviews prepared by the independent Clinical Research Organization will be provided to a core team comprised of the Scholar Rock Medical Director, the Scholar Rock Product Safety Lead, the Medical Monitor, an independent biostatistician, and a physician not participating as an Investigator in the study. To further assist in the safety assessments, the core SST may request that other individuals such as SMA experts or others within their organizations review the data and participate in the discussions. Data tables and listings will be provided to the SST by a biostatistician as will be described in the statistical analysis plan (SAP). The SST reviews will not include any efficacy data. The responsibilities and actions of the SST will be governed by a separate SST charter outside of this protocol.

6.3.2. Pharmacokinetic Criteria for Dose Adjustment

The SST will review PK and PD data for each cohort as part of a prespecified interim analysis (refer to Section 11.4). Drug exposure and target engagement levels in patients with SMA will be evaluated to compare them to the levels seen in the Phase 1 healthy adult study. Data from multiple cohorts may be combined as necessary and will be provided by a biostatistician. Based on these results, and taking into consideration any available safety data, cohort-specific dose levels may be adjusted. Any adjustment in dose level will not change the frequency of dosing (i.e., every 4 weeks) and the highest dose will not exceed 30 mg/kg, as tested in the Phase 1 study.

6.3.3. Study Stopping Rules

Dosing in the study may be suspended at any time for an emergent safety concern by the Medical Monitor in consultation with the other core SST members until the SST can completely evaluate the event(s) and recommend an appropriate course of action.

The SST may make recommendations to restart dosing and continue the study with no changes, continue the study with changes to the protocol, terminate the study, or require more data, input, and deliberation prior to making a decision. Criteria for study termination are based on the assessment of safety concerns that may arise during the conduct of the study or from data from the SRK-015 preclinical and clinical program. The study may be discontinued at any time at the Sponsor's discretion, or if the SST determines that further drug exposure would pose an undue risk to patients.

If the study is terminated prematurely, all Investigators, regulatory authorities and IRBs/ IECs will be notified promptly. Patients will continue to be followed for 12 weeks after their final dose.

6.3.4. Individual Stopping Rules

Dosing for any individual patient may be suspended or discontinued if the patient experiences an SAE related to SRK-015 or a clinically significant non-serious AE related to SRK-015, that in the assessment of the Investigator and in consultation with the Medical Monitor, warrants suspension or discontinuation from further dosing for that patient's well-being. For patients who have had their dosing suspended, dosing may resume only after their AE has resolved and only if it would be considered safe to do so in the assessment of the Investigator (and in consultation with the Medical Monitor). For patients who have discontinued dosing, the patient will continue to be followed for 12 weeks after their final dose or until the resolution of any ongoing clinically significant AE, whichever occurs later. (For the definition of AE resolution, please refer to Section 10.2.1.)

Dosing of SRK-015 for an individual patient may also be suspended or discontinued for safety concerns other than those described above based on review by the SST or at the discretion of the Investigator if he/she feels the patient's safety may be threatened. The Investigator may ask for an ad hoc SST meeting to be held for any single event or combination of events that in his/her professional opinion may jeopardize the safety of the patient or the reliability of the data.

Patients who develop either an SAE or other toxicity meeting the individual stopping criteria will be carefully monitored, which may include the following at the discretion of the Investigator:

- Additional clinical laboratory tests and/or other clinical investigations
- Additional visits or extended duration of follow-up
- Obtaining a specialist consultation

7. SELECTION AND WITHDRAWAL OF PATIENTS

7.1. Patient Inclusion Criteria

1. Age 5 through 21 years old at the time of Screening for Cohorts 1 and 2; Age ≥2 years old at the time of Screening for Cohort 3
2. Estimated life expectancy >2 years from Screening
3. Informed consent document signed by the patient if the patient is legally an adult. If the patient is legally a minor, informed consent document signed by the patient's parent or legal guardian and patient's oral or written assent obtained, if applicable and in accordance with the regulatory and legal requirements of the participating location
4. Documented diagnosis of 5q SMA
5. Diagnosed as later-onset (e.g., Type 2 or Type 3) SMA prior to receiving any treatment with therapy approved for SMA
6. Nonambulatory patients must be able to sit independently (sits up straight with head erect for at least 10 seconds; does not use arms or hands to balance body or support position) per World Health Organization (WHO) motor milestones definition at Screening. Patients who never had the ability to walk independently will be classified as Type 2. Patients who previously had the ability to walk unaided will be classified as Type 3.
7. Ambulatory patients must have the ability to independently ambulate without aids or orthotics over 10 meters at Screening
8. For Cohort 1, RHS score no greater than 63 at Screening
9. For Cohorts 2 and 3, HFMSE score no less than 10 at Screening
10. Receiving the same background SMA therapy (e.g., on an approved SMN upregulator therapy such as nusinersen, or not on any SMA therapy) for at least 6 months prior to Screening and anticipated to remain on that therapy throughout the duration of the study
    a. If receiving the SMN upregulator therapy nusinersen, must have completed the loading regimen and initiated maintenance dosing (i.e., completed at least one maintenance dose) with at least 4 weeks after the first maintenance dose having elapsed prior to Screening
11. Nutritional status stable over the past 6 months and anticipated to be stable throughout the duration of the study
12. Have no physical limitations that would prevent the patient from undergoing motor function outcome measures throughout the duration of the study
13. Able to receive study drug infusions and provide blood samples through the use of a peripheral IV, or a long-term IV access device that the patient has placed for reasons independent from the study (i.e., for background medical care and not for the purpose of receiving SRK-015 in the study), throughout the duration of the study
14. Able to adhere to the requirements of the protocol, including travel to the study center and completing all study procedures and study visits

15. For patients who are expected to have reached reproductive maturity by the end of the study, adhere to study specific contraception requirements:
    a. Females of childbearing potential (see Section 10.1.7.4 for definition) must have a negative pregnancy test at Screening and agree to employ highly effective contraceptive measures (failure rate of 1% or less per year when used consistently and correctly) for the duration of the study and for 18 weeks following the last dose of study drug. Effective contraception methods are restricted to combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner, or sexual abstinence. In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.
    b. Male patients with female partners of childbearing potential must be abstinent or agree to employ the use of a condom with or without spermicide throughout the duration of the study and for 18 weeks following the last dose of study drug.

7.2. Patient Exclusion Criteria

1. Use of tracheostomy with positive pressure
2. Use of chronic daytime noninvasive ventilatory support for >16 hours daily in the 2 weeks prior to dosing, or anticipated to regularly receive such daytime ventilator support chronically over the duration of the study
3. Any acute or comorbid condition interfering with the well-being of the patient within 14 days of Screening, including active systemic infection, the need for acute treatment or inpatient observation due to any reason
4. Severe scoliosis and/or contractures at Screening. Based on clinical judgment, any scoliosis or contractures present must be stable over the past 6 months, anticipated to be stable for the duration of the study and not prevent the patient from being evaluated on any functional outcome measures throughout the duration of the study.
5. Pregnant or breastfeeding
6. Major orthopedic or other interventional procedure, including spine or hip surgery, considered to have the potential to substantially limit the ability of the patient to be evaluated on any functional outcome measures, within 6 months prior to Screening, or anticipated for the duration of the study
7. Prior history of a hypersensitivity reaction to a mAb or recombinant protein bearing an Fc domain (such as a soluble receptor-Fc fusion protein), SRK-015, or excipients of SRK-015
8. Use of systemic corticosteroids within 60 days prior to Screening. Inhaled or topical steroids are allowed.

9. Treatment with investigational drugs within 3 months or 5 half-lives, whichever is longer prior to Screening
10. Use of therapies with potentially significant muscle effects (such as androgens, insulin-like growth factor, growth hormone, systemic beta-agonist, botulinum toxin, or muscle relaxants or muscle-enhancing supplements) or potentially significant neuromuscular effects (such as acetylcholinesterase inhibitors) other than approved SMN upregulator therapy within 60 days prior to Screening
11. Use of valproic acid within 60 days prior to Screening
12. Patient has any other condition, which in the opinion of the Investigator may compromise safety or compliance, would preclude the patient from successful completion of the study, or interfere with the interpretation of the results

7.3. Patient Withdrawal Criteria

Patients may withdraw consent at any time. Participation in the study may be terminated at any time without the patient's consent as determined by the Investigator. The Investigator may withdraw a patient from the study for any of the following reasons:

- Protocol violation
- Serious or intolerable AE (see Section 6.3.4)
- Clinically significant change in a laboratory parameter (see Section 6.3.4)
- Sponsor or Investigator decision
- Patient and/or parent or guardian request

7.4. Patient Rescreening, Replacement, and Over-enrollment

A patient who is determined to be eligible based on screening assessments and experiences an acute or comorbid condition that causes a delay in their Baseline visit and first infusion (Day 0) may remain eligible up to an additional 14 days after the end of the Screening Period without having to rescreen. The patient may proceed with entering the Treatment Period after the resolution of the event and if deemed safe to do so by the Investigator. Screening patients who experience an acute clinical event that results in a delay of more than 14 days outside of the Screening Period must rescreen to determine eligibility.

Patients who withdraw from the study for reasons that are not related to safety before receiving 4 doses of SRK-015 and undergoing 2 postdose HFMSE or RHS assessments may be replaced at the discretion of the Sponsor.

Patients who are in the Screening Period at the time a cohort has enrolled its required number of patients may continue to be enrolled after they are determined to be eligible.

To preserve the robustness of the analyses, the Sponsor may enroll additional patients into a cohort as a result of patients in that cohort who significantly change their background approved SMA treatment while on study (e.g., a patient discontinues nusinersen or begins a new approved treatment as part of standard of care for their SMA).

7.5. Patient Enrollment into the Optional Extension Periods

Patients who choose to enroll into Extension Period A should review and sign the informed consent form (ICF) prior to performing any assessments being conducted on Day 364 (V15). A patient is determined to be eligible for enrollment into Extension Period A after completion of the 52-week Treatment Period. Patients may consent to participate in Extension Period A at any time prior to V15/E1 or at V15/E1.

Patients who choose to enroll into Extension Period B should review and sign the ICF prior to performing any assessments being conducted on Day 728 (EB1). A patient is determined to be eligible for enrollment into Extension Period B after completion of the 52-week Extension Period A. Patients may consent to participate in Extension Period B at any time prior to E14/EB1 or at E14/EB1.

Patients who choose to enroll into Extension Period C should review and sign the ICF prior to performing any assessments being conducted on Day 1092 (EC1). A patient is determined to be eligible for enrollment into Extension Period C after completion of the 52-week Extension Period B. Patients may consent to participate in Extension Period C at any time prior to EB14/EC1 or at EB14/EC1.

8. STUDY TREATMENT

8.1. Study Drug Description

SRK-015 drug product is a clear to slightly opalescent, colorless to slightly yellow solution, essentially free from visible particulates, containing 50 ± 5 mg/mL fully human anti-proMyostatin mAb protein in 20 mM histidine, 130 mM sodium chloride, 0.02% polysorbate 80, at pH 6.0 in 1-mL solution. The drug product formulation does not contain novel excipients or excipients of animal origin.

SRK-015 is a sterile, preservative-free liquid stored in a 6R clear, USP/EP Type I borosilicate glass vial with a 20 mm Flurotec®-coated, bromobutyl or chlorobutyl rubber stopper, and 20 mm crimp seal with a flip-off cap. SRK-015 is sterile filtered and filled to provide sufficient volume for withdrawal. Each vial is intended for single use administration only. SRK-015 is stable at 2 to 8ºC.

8.2. Study Drug Preparation and Administration

Instructions for preparation of each IV dose of study drug will be provided to the Pharmacist. Preparation and dispensing of the study drug will be handled by the site pharmacy. Instructions for safe handling of the study drug are provided in the Pharmacy Manual.

SRK-015 will be administered to patients at one of two dose levels: 20 mg/kg and 2 mg/kg, according to the cohort assignments. Doses will be diluted in normal saline and administered by IV over 2 hours (+10-minute window). If there are no acute reactions following the first 2 doses for a patient, and if the Investigator determines that it would be safe to do so, the infusion duration can be changed to less than 2 hours but no shorter than 1 hour.

All doses will be administered via peripheral IV (or via long-term IV access device such as a peripherally inserted central catheter or port, if the patient has such a device for their background medical care). The placement of a new long-term IV access device is not part of this study, not required for participation, and should not be conducted if the only reason for it is to receive SRK-015.

If an acute reaction occurs, further dosing will be suspended and the Investigator, in consultation with the Medical Monitor if needed, will evaluate the risk represented by the acute reaction. Such an evaluation will incorporate consideration of the nature of the event, relatedness to the drug, and seriousness and severity of the event.

Intervention for patients who experience an acute infusion reaction should be performed in accordance with standard procedures and may include restarting the infusion at a slower rate, terminating the infusion, administration of medications, or other medically supportive measures, as necessary.

8.3. Randomization and Blinding

Cohorts 1 and 2 are directly assigned to the 20 mg/kg dose of SRK-015 while Cohort 3 patients will be randomized (1:1) in a double-blind manner to receive either 2 mg/kg or 20 mg/kg SRK-015 via an Interactive Web-based Randomization System (IWRS). Use of the IWRS will be outlined in the Study Operations Manual and in the IWRS quick reference guide.

The Sponsor, patients, caregivers, Investigators, and site personnel, with the exception of the Pharmacist, will be blinded to Cohort 3 SRK-015 dose level assignments as specified here. The site Pharmacist will remain unblinded throughout the duration of the study. The Sponsor will be blinded to individual efficacy data until prespecified interim analyses are performed (see Section 11.4). The Sponsor will remain blinded to efficacy data not included as part of the interim analyses until the Treatment Period database lock or deemed necessary by the SST. Select personnel of the Sponsor (e.g., Lead Clinical Research Associate and auditors) will have access to efficacy data to ensure study oversight.

For unblinding procedures refer to Section 10.7.1.5. Based on interim analysis at 6 months (Day 168), which was supported by the 12-month analysis (Day 364), any Cohort 3 patients who were randomized to receive low-dose (2 mg/kg) SRK-015 will be re-assigned to receive high-dose (20 mg/kg) SRK-015 after completion of the Treatment Period (see Section 6.2).

Original blind designation will be maintained. In accordance with Section 6.3.1, the SST reviews will not include any efficacy data.

8.4. Study Drug Compliance

Study drug will be administered under the supervision of the Investigator or qualified site personnel. The study site is required to adhere to all applicable laws, regulations, and guidelines including, but not limited to, the United States (US) Code of Federal Regulations (CFR), the International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, the Health Insurance Portability and Accountability Act of 1996, as well as any applicable local and federal regulations.

8.5. Study Drug Packaging and Labeling

Study drug will be supplied by Scholar Rock and packaged and labeled according to applicable local and regulatory requirements for investigational studies.

8.6. Study Drug Storage and Accountability

All supplies of SRK-015 must be stored refrigerated (2ºC to 8ºC/36ºF to 46ºF) in the carton and protected from light, in a securely locked area, and accessible to authorized persons only, until needed for dose preparation.

The Investigator (or designee) is responsible for maintaining accurate accountability records of the investigational product throughout the clinical study. The site Pharmacist will inventory the investigational product received and will maintain records of disposition of the drug, including dates, quantity, and use. All dispensing and accountability records will be available for Sponsor review. Study drug accountability will be verified during on-site monitoring visits. At the end of the study, Study Monitors or designees will conduct a final accountability of all study drugs.

8.7. Study Drug Disposal and Return

Following accountability of study drug by a Study Monitor, used vials may be destroyed at the site according to local standard operating procedures (SOPs) containing well-documented destruction procedures. Unused vials should be returned to Scholar Rock, or its designated storage location, for final disposition.

8.8. Concomitant Treatment

Concomitant treatment or interventional procedures that are medically indicated for any AEs the patient experiences during the study or that are provided as part of standard supportive care for the patient, is permitted at the discretion of the Investigator and supersedes any of the restrictions outlined in this protocol.

Patients may receive an approved SMA treatment in accordance with the cohort they are enrolled into (Section 6.2). Patients are expected to remain on the same background SMA therapy (e.g., on an SMN upregulator therapy such as nusinersen, or not on any SMA therapy) for at least 6 months prior to the first dose of study drug and throughout the duration of the study. Investigators who contemplate changing a patient's standard of care treatment for their SMA are encouraged to discuss this with the Medical Monitor in advance.

Patients that receive the SMN upregulator treatment, nusinersen, must receive their maintenance doses at least 24 hours after receiving SRK-015, or at least 14 days prior to any scheduled SRK-015 study drug administration visit. Any change in the timing of the patient's nusinersen treatment that would fall within 14 days prior to the scheduled SRK-015 administration should be discussed with the Medical Monitor in advance.

Investigational therapies are not permitted 3 months (or 5 half-lives, whichever is longer) prior to Screening and throughout the duration of the study.

The concomitant use of the following drugs or products has the potential to interfere with the assessment of treatment effect in this study. Accordingly, the use of the following is prohibited from Screening through the final visit.

- Live vaccinations within 14 days of any study visit where motor function outcome measures are conducted
- Systemic corticosteroids. Inhaled and topical steroids are allowed.
- Any therapy with potentially significant muscle effects (such as androgens, insulin-like growth factor, growth hormone, systemic beta-agonist, botulinum toxin, muscle relaxants or muscle-enhancing supplements) or potentially significant neuromuscular effects (such as acetylcholinesterase inhibitors) other than approved SMN upregulator therapy
- Valproic acid

9. ASSESSMENT OF EFFICACY, PHARMACOKINETICS, AND PHARMACODYNAMICS

9.1. Efficacy Endpoints

Primary, secondary, and tertiary efficacy endpoints will be assessed at the times indicated in Table 2, Table 3, Table 4, and Table 5. The efficacy endpoints for each cohort are outlined in Table 7. Functional outcome measures (e.g., HFMSE/RHS, 6MWT, WHO Motor Milestones, RULM, 30-Second Sit-to-Stand, Endurance Shuttle Nine Hole Peg Test [ESNHPT], or Endurance Shuttle Box and Block Test [ESBBT]) will be conducted and assessed by the Physical Therapist. Requirements for the order of assessments, duration of assessments, and rest periods between assessments will be outlined in a separate Physical Therapist training manual.

Study procedures will not be conducted for patients who develop an AE (e.g., musculoskeletal injury) during the study, irrespective of relatedness to study drug, that the Investigator considers would make it unsafe to perform a functional outcome assessment. Upon resolution of the AE, and if the Investigator assesses it would be safe to do so, performance of that study procedure will be resumed at the next scheduled assessment as indicated in Table 2, Table 3, Table 4, and Table 5.

Table 7: Efficacy Endpoints by Cohort

	Cohort 1	Cohorts 2 and 3
Primary:	Change from Baseline in the RHS total score at Day 364 (V15)	Change from Baseline in the HFMSE total score at Day 364 (V15)
Secondary:	• Change from Baseline in the RHS total score at other prespecified timepoints • Proportion of patients achieving various magnitudes of change in RHS score from Baseline • Change from Baseline in the 6MWT • Change from Baseline in the 30-Second Sit-to-Stand • Change from Baseline in the 10-Meter Walk/Run (from the RHS) • Change from Baseline in the timed rise from floor (from the RHS)	• Change from Baseline in the HFMSE total score at other prespecified timepoints • Proportion of patients achieving various magnitudes of change in HFMSE score from Baseline • Change from Baseline in the RULM total score • Proportion of patients achieving various magnitudes of change in RULM from Baseline • Change from Baseline in the number of WHO motor development milestones attained • Proportion of patients who attain a new WHO motor development milestone relative to Baseline

	Cohort 1	Cohorts 2 and 3
Tertiary:	• Change from Baseline in the PEDI-CAT • Change from Baseline in the PROMIS Fatigue Questionnaire	• Change from Baseline in time to limitation on the ESNHPT or ESBBT • Change from Baseline in the PEDI-CAT • Change from Baseline in the PROMIS Fatigue Questionnaire **Cohort 3 only:** • Time to therapeutic effect (delineated in the SAP) as compared between low- and high-dose SRK-015

6MWT = 6-Minute Walk Test; ESBBT = Endurance Shuttle Box and Block Test; ESNHPT = Endurance Shuttle Nine Hole Peg Test; HFMSE = Hammersmith Functional Motor Scale Expanded; PEDI-CAT = Pediatric Evaluation of Disability Inventory Computer Adaptive Test; PROMIS = Patient-reported Outcomes Measurement Information System; RHS = Revised Hammersmith Scale; RULM = Revised Upper Limb Module; SAP = statistical analysis plan; WHO = World Health Organization.

9.1.1. Efficacy Parameters

9.1.1.1. Revised Hammersmith Scale

The RHS will be performed for the ambulatory patient subgroup (Cohort 1). Administration of the RHS includes the timed rise from floor and 10-Meter Walk/Run tests. The RHS is a 36-item clinical assessment for physical abilities of patients with Type 2 SMA, and ambulatory and nonambulatory patients with Type 3 SMA. The RHS includes 33 items that are graded on a scale of 0, 1, 2, where 0 denotes the lowest level of ability/function and 2 denotes the highest level of ability (Ramsey 2017). The remaining 3 items are scored 0, 1, where 0 denotes an inability and 1 denotes an ability to achieve. The maximum achievable score is 69.

9.1.1.2. 10-Meter Walk/Run

The 10-Meter Walk/Run test is an enhanced function of the RHS used for ambulant patients with Type 3 SMA. It is a measure of the time taken to walk/run 10 meters.

9.1.1.3. Timed Rise from Floor

The timed rise from floor test is an enhanced function of the RHS used for ambulant patients with Type 3 SMA. It is a measure of the time taken to rise to standing from the floor.

9.1.1.4. 6-Minute Walk Test

The 6MWT is an assessment of exercise capacity and fatigue that has been used in clinical studies of ambulatory patients with later-onset SMA (Young 2016) Ambulant patients in Cohort 1 will complete the 6MWT. Patients are directed to walk along a 25-meter course as fast as possible over 6 minutes. The minute distances and total distance walked over 6 minutes is measured.

9.1.1.5. 30-Second Sit-to-Stand

The 30-Second Sit-to-Stand Test is used by researchers and clinicians as an assessment of functional lower limb strength (Jones 1999). The test was modified for ambulatory SMA population based on recent research of the modified 30-Second Sit-to-Stand being a reliable, feasible tool for use in a general geriatric population with a lower level of function (McAllister 2019) and was related to fall risk in institutionalized veterans (Applebaum 2017, Le Berre 2016). The test measures the maximal number of times the patient can transition from sitting to standing in 30 seconds.

9.1.1.6. Hammersmith Functional Motor Scale Expanded

The HFMSE assesses the physical abilities of patients with Type 2 and Type 3 SMA (O'Hagen 2007; Glanzman 2011) and will be performed for nonambulatory patient subgroups (Cohorts 2 and 3). It consists of 33 items graded on a scale of 0, 1, 2, where 0 denotes unable, 1 denotes performed with modification or adaptation, and 2 denotes without modification or adaptation.

9.1.1.7. Revised Upper Limb Module

The RULM is a 20-item assessment of upper limb function in nonambulatory patients with SMA (young children as well as adults) (Mazzone 2017). The 19 scored items test functions that relate to everyday life, such as placing hands from lap, pressing a button, and picking up a token. The items are scored 0, 1, 2, where 0 denotes unable, 1 denotes able with modification, and 2 denotes able with no difficulty. The maximum score achievable is 37. Nonambulant patient subgroups (Cohorts 2 and 3) will perform the RULM. The RULM will be completed by patients who are 30 months of age or older at the time of the baseline assessment.

9.1.1.8. WHO Motor Development Milestones

The WHO Multicentre Growth Reference Study performance criteria is being utilized to assess motor development milestones of patients with Type 2 and nonambulatory Type 3 SMA enrolled in Cohort 2 and Cohort 3.

9.1.1.9. Endurance Shuttle Nine Hole Peg Test

The ESNHPT is an endurance test for severely affected patients with SMA. Patients are instructed to repeatedly perform the original 9 Hole Peg Test at 75% of their individual maximum speed. The shuttles refer to the set speed marked by auditory cues, with the test ending when the patient missed 2 consecutive beeps. The primary outcome parameter is “time to limitation (Tlim),” which is defined as the time a task can be maintained at the pre-set intensity. Maximum test duration is 20 minutes (Stam 2018). Nonambulant patients who score ≤3 on Item A of the RULM at Screening will perform the ESNHPT at Screening and all subsequent assessments. The ESNHPT will be completed by patients who are or will turn 8 years of age or older during the study. Patients who turn 8 years of age in Extension Periods A, B, or C who score ≤3 on Item A of the RULM at Screening should perform the ESNHPT as early as possible (preferred to begin at E1) and at all subsequent assessments until the end of the study.

9.1.1.10. Endurance Shuttle Box and Block Test

ESBBT is an endurance test for moderately affected patients with SMA. Patients are instructed to repeatedly perform the original Box and Block Test at 75% of their individual maximum speed. The shuttles refer to the set speed marked by auditory cues, with the test ending when the patient missed 2 consecutive beeps. The primary outcome parameter is Tlim. Maximal test duration is 20 minutes (Stam 2018). Nonambulant patients who score >3 on Item A of the RULM at Screening will perform the ESBBT at Screening and all subsequent assessments. The ESBBT will be completed by patients who are or will turn 8 years of age or older during the study. Patients who turn 8 years of age in Extension Periods A, B, or C who score >3 on Item A of the RULM at Screening should perform the ESBBT as early as possible (preferred to begin at E1) and at all subsequent assessments until the end of the study.

9.1.1.11. Pediatric Evaluation of Disability Inventory Computer Adaptive Test

A caregiver (who may or may not be a parent and/or legal guardian) must complete the PEDI-CAT Assessment. The PEDI-CAT Assessment should not be administered if a caregiver is not present. The PEDI-CAT Assessment should not be administered to the patient. The PEDI-CAT is a questionnaire completed by the caregiver that assesses the patient's ability to perform daily functions (Haley 2005). The PEDI-CAT is filled out by the caregiver in a location where they are not watching the patient perform any functional assessment tests. The same caregiver must fill out the assessment throughout the study duration. The answers are scored on a 4-point scale (unable to easy). The test is suitable to assess function in newborns to 21-year-olds; this questionnaire should be completed throughout the duration of the study (regardless of age). Properties of the PEDI-CAT have been studied in the SMA population. A Rasch analysis with results published in 2016 revealed that the distribution of abilities for the Mobility and Daily Activities domains of the PEDI-CAT are best represented in the Type 2 and Type 3 populations (Pasternak 2016). As the PEDI-CAT is an age-dependent questionnaire, a patient's full date of birth is required for accurate assessment.

9.1.1.12. Patient-reported Outcomes Measurement Information System

The Patient-reported Outcomes Measurement Information System (PROMIS) is a person-centered measure intended to be completed by the patient or parent proxy without help from anyone (Ader 2007). The fatigue profile domain measures a range of symptoms, from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion. The self-report measures are suitable for children 8-17 years old and the parent proxy report measures are suited for children 5-17 years old. If a caregiver completes this form, the same caregiver must complete the form throughout the study duration. Patients age 18 through 21 years old will complete an adult form of PROMIS. The PROMIS will be completed by patients who are or will turn 5 years of age or older at the time of the baseline assessment; the same questionnaire used at Screening should be used throughout the duration of the study (regardless of age).

9.2. Pharmacokinetics Blood Sample Collection

Blood samples for the measurement of SRK-015 concentrations will be obtained prior to study drug infusion as indicated in the schedule of assessments in Table 2, Table 3, Table 4, and

Table 5. In the Treatment Period, the 2-hour (± 1 hour) postdose (from the stop of the infusion) sample collection on Day 0, Day 140, and Day 336 must be collected via peripheral venipuncture. In Extension Periods A, B, and C, the 1-hour (+30-minute window) postdose (from the stop of the infusion) sample collection on Day 700, Day 1008, Day 1092, and Day 1428 must be collected via peripheral venipuncture.

Each collected sample will be split into approximately equal volume sample sets to allow for retesting, if required. Aliquots from the PK blood samples may be used for biomarker testing (Extension Period C only) or additional PD or immunogenicity testing as appropriate, and Baseline and postbaseline samples may be used to support PK, PD, and/or ADA assay validation.

9.3. Pharmacodynamics Blood Sample Collection

Blood samples will be collected for the measurement of latent myostatin levels. These blood samples will be obtained prior to infusion as indicated in the schedule of assessments in Table 2, Table 3, Table 4, and Table 5. The 2-hour (+30-minute window) postdose (from stop of infusion) sample collection on Day 0 must be collected via peripheral venipuncture. Each collected sample will be split into approximately equal volume sample sets to allow for retesting, if required. Aliquots from the PD blood samples may be used for biomarker testing (Extension Period C only) or additional PK or immunogenicity testing as appropriate, and Baseline and postbaseline samples may be used to support PK, PD, and/or ADA assay validation.

9.4. Immunogenicity Blood Sample Collection

Blood samples for the measurement of anti-SRK-015 antibodies will be obtained prior to infusion as indicated in the schedule of assessments in Table 2, Table 3, Table 4, and Table 5.

Each collected sample will be split into approximately equal volume sample sets to allow for retesting, if required. Aliquots from the immunogenicity samples may be used for biomarker testing (Extension Period C only) or additional PK or PD testing as appropriate, and Baseline and postbaseline samples may be used to support PK, PD, and/or ADA assay validation.

9.5. Biomarkers (Extension Period C Only)

Aliquots from PK, PD, and ADA serum samples collected during Extension Period C will be stored and may be used for exploratory biomarker testing. These samples may be used for research to develop methods, assays, prognostics, and/or companion diagnostics related to discovering and/or evaluating effects of SRK-015. Additional blood samples will not be collected for the purposes of biomarker testing.

10. ASSESSMENT OF SAFETY

10.1. Safety Parameters

10.1.1. Demographic/Medical History

Patient demographics and medical history will be recorded on the source document and electronic case report form (eCRF). Demographic characteristics include age, sex, race, and ethnicity. Medical history will capture the patient's SMA history as well as current and past relevant medical status (surgeries, allergies, and concomitant medications).

10.1.2. Vital Signs

Vital signs will be performed by the Investigator or his/her qualified designee according to the schedule of assessments provided in Table 2, Table 3, Table 4, and Table 5. Routine vital sign assessments will include heart rate, blood pressure, and respiratory rate to be collected in the Treatment Period at preinfusion, every 15 minutes (±5 minutes) during the infusion from the start of the infusion, at the end of the infusion, and 1 and 2 hours (±15 minutes) postinfusion. In Extension Periods A, B, and C, vital sign assessments will be collected at preinfusion, every 15 minutes (±5 minutes) during the infusion (from the start of the infusion), at the end of the infusion, and 1 hour (±15 minutes) postinfusion. Body temperature will be collected preinfusion.

10.1.3. Weight and Height

Weight and height will be collected according to the schedule of assessments provided in Table 2, Table 3, Table 4, and Table 5. Weight will be collected within 48 hours of each dose to calculate weight-based dosing and height will be collected at visits where the motor function outcome measures are conducted. Standing height will be collected for all individuals who are able to independently stand. Surrogate height may be estimated using ulna length if the patient is nonambulatory or needs standing support.

10.1.4. Physical Examination

A complete physical examination will be performed by the Investigator or a qualified designee according to the schedule of assessments provided in Table 2, Table 3, Table 4, and Table 5. The findings of each examination will be recorded on the source documents and eCRF. The physical examination will include an assessment of the following: general appearance, skin, lymph nodes, head-eyes-ears-nose-throat, neck, abdomen, extremities, and the respiratory, cardiovascular, musculoskeletal, and neurologic body systems.

10.1.5. Electrocardiogram

A 12-lead electrocardiogram (ECG) will be collected at the times indicated in Table 2, Table 3, Table 4, and Table 5. ECGs are to be performed with the patient having rested for at least 5 minutes before each reading. ECGs are to be performed in triplicate, each at least 1 to 2 minutes apart. On infusion days, ECG will be collected within 2 hours prior to the start of the infusion and within 1 hour after the end of infusion at Visits EC1 and EC13. ECGs will be sent to a central reading vendor for assessment.

10.1.6. Concomitant Medications

All concomitant medications will be collected from the time the patient signs the ICF through 12 weeks after the final dose.

10.1.7. Laboratory Assessments

Laboratory testing (eligibility screening, serum chemistry, hematology, urinalysis, and coagulation, PK and PD sample draw, and ADA testing) will be performed using established methods at the times indicated in Table 2, Table 3, Table 4, and Table 5. When multiple sample collection types are performed at the same assessment time point, the samples will be drawn in the following order (depending on what sample types are to be collected at that time point): laboratory safety samples (hematology, coagulation, serum chemistry, urinalysis), PK, PD, ADAs. Aliquots from the PK, PD, and ADA samples may be retained as back-up for retesting if necessary. The total blood draw for each patient who completes the 52-week Treatment Period, will be approximately 158 mL. Patients who do not enroll into Extension Period A and complete the 12-week Safety Follow-up Period will have approximately 25 mL of additional blood drawn.

The total blood draw for each patient who completes the 52-week Extension Period A, will be approximately 82 mL. Patients who do not enroll into Extension Period B and complete the 12-week Safety Follow-up Period will have approximately 13 mL of additional blood drawn.

The total blood draw for each patient who completes the 52-week Extension Period B will be approximately 77 mL. Patients who do not enroll into Extension Period C and complete the 12-week Safety Follow-up Period will have approximately 13 mL of additional blood drawn.

The total blood draw for each patient who completes the 52-week Extension Period C will be approximately 57 mL. Patients who do not enroll into the separate long-term safety extension and complete the 12-week Safety Follow-up Period will have approximately 13 mL of additional blood drawn.

Please refer to the Laboratory Manual for more information.

10.1.7.1. Hematology and Coagulation

The following hematology and coagulation parameters will be assessed:

- Hemoglobin
- Red blood cell count
- Hematocrit
- White blood cell count with differential
- Absolute platelet count
- Mean corpuscular hemoglobin
- Mean corpuscular hemoglobin concentration
- Mean corpuscular volume
- Activated partial thromboplastin time (APTT)
- Prothrombin time/international normalized ratio (PT/INR)

10.1.7.2. Blood Chemistry

The following blood chemistry parameters will be assessed:

- Albumin
- Alanine aminotransferase
- Alkaline phosphatase
- Aspartate aminotransferase
- Bilirubin (total and direct)
- Blood urea nitrogen
- Calcium
- Carbon dioxide
- Chloride
- Creatinine
- Creatine phosphokinase
- Gamma-glutamyl transferase
- Glucose
- Pregnancy (females only)
- Lactate dehydrogenase
- Magnesium
- Phosphate
- Potassium
- Sodium
- Total cholesterol
- Total protein
- Triglycerides
- Uric acid

10.1.7.3. Urinalysis

The following urinalysis parameters will be assessed:

- Bilirubin
- Blood microscopy (if urinalysis is abnormal)
- Glucose
- Ketones
- Nitrite
- pH
- Protein
- Specific gravity

10.1.7.4. Pregnancy Testing

A female is considered of childbearing potential, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Pregnancy testing will be conducted for females of childbearing potential at the times indicated in Table 2, Table 3, Table 4, and Table 5. A urine or serum test is acceptable however, positive urine tests must be confirmed with serum testing.

Patients who become pregnant during the study should not receive further study drug and should be followed according to the procedures outlined in Section 10.7.1.3.

10.2. Adverse and Serious Adverse Events

10.2.1. Definition of Adverse Events

10.2.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient or clinical study patient administered a pharmaceutical product that does not necessarily have to have a causal relationship with the treatment administered. An AE can, therefore, be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

- AEs may be new events or may be preexisting conditions that have become aggravated or have worsened in severity, seriousness, or frequency from Baseline at any time during the study.
- AEs may be clinically significant changes from Baseline in physical examination, laboratory tests, or other diagnostic investigation.

Any medical condition already present at Screening should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present changes in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an AE.

10.2.1.2. Serious Adverse Event

An SAE is any adverse experience occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening experience; Note: “Life-threatening” refers to a situation in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that might have caused death if it were more severe.
- Inpatient hospitalization or prolongation of existing hospitalization. The following are excluded as per this criterion:
  - Emergency room visits/hospital admissions for AEs less than 24 hours in duration do not meet SAE criterion unless they meet any of the other SAE criteria in this list.
  - A scheduled or elective hospitalization for medical/surgical procedure planned prior to informed consent for a preexisting condition that has not worsened from Baseline during participation in the study. However unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.
- Persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions

- Congenital anomaly or birth defect
- Is considered to be an important medical event: Important medical events are those that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

10.2.1.3. Dosing Errors

All dosing errors (including, but not limited to, route of administration and wrong dose) must be reported as protocol deviations. A brief description should be provided in the deviation report, including information about whether the patient was symptomatic or not. Dosing details should be captured in the eCRF.

An overdose is defined as a significant variation from the recommended/scheduled dosage for a product. The dosing for this study will be conducted in a controlled clinical setting and an overdose is not anticipated. However, in the event of an accident, for this study, an overdose of SRK-015 is considered a dose that is at least 2-fold higher than 20 mg/kg.

Overdoses are not considered AEs and should not be recorded as an AE in the eCRF unless an AE or an SAE occurs. All overdoses (regardless of whether or not they result in an AE) must be recorded in the eCRF. If an overdose results in an SAE, the SAE form must be completed and faxed to Scholar Rock or designee (e.g., PPD). Should an overdose occur, the Investigator or designee must contact the Medical Monitor within 24 hours.

10.2.1.4. Pregnancy

Pregnancy is not an AE; however, if a female patient or female partner of a male study patient becomes pregnant during the conduct of the study, the Investigator must notify PPD according to the procedures provided in Section 10.7.1.3. A patient becoming pregnant while on study drug will immediately be withdrawn from further dosing and will be followed according to the procedures provided in Section 10.7.1.3.

10.2.1.5. Treatment-Emergent Adverse Event

An AE is treatment emergent if the onset time is after administration of the first dose of study drug through the final follow-up visit or, in the event that onset time precedes study drug administration, the AE increases in severity during the Safety Follow-up Period.

10.3. Adverse Event Monitoring

Each patient will be monitored for the occurrence of AEs, including SAEs, from the signing of the ICF through the final follow-up visit.

- Patients will be questioned and/or examined by the Investigator or a qualified designee for evidence of AEs. The questioning of patients with regard to the possible occurrence of AEs will be generalized such as, "How have you been feeling since your last visit?" The presence or absence of specific AEs should not be elicited from patients.
- Patients having AEs will be monitored until resolution or stabilization (in the case of persistent impairment), or until the event becomes chronic in nature, or the patient dies.
- AEs, actions taken as a result of AEs, and follow-up results must be recorded in the eCRF as well as in the patient's source documentation. Follow-up laboratory results should be filed with the patient's source documentation.

For any SAEs or AEs that require the patient to be discontinued from dosing, relevant clinical assessments and laboratory tests will be repeated as clinically appropriate, until final resolution or stabilization of the event(s). Patients will continue to be followed through 12 weeks after the final dose.

All safety laboratory analyses will be performed at a central laboratory. The clinical laboratory values will be reported to the Investigator who will review them for clinical significance and consideration of abnormal values as potential AEs.

10.3.1. Relationship to Study Drug (Causality Assessment)

A medically qualified Investigator must assess the relationship of any AE (including SAEs) to the use of the investigational product, as related or not related, based on clinical judgment and using all available information, and may include consideration of the following factors:

- The temporal sequence from study drug administration
- Underlying, concomitant, intercurrent diseases
- Concomitant use of other drugs
- Whether the manifestations of the AE are consistent with known actions or toxicity of the investigational product
- Exposure to physical and/or mental stresses
- The pharmacology and PK of the study drug
- The AE resolved or improved with decreasing the dose or stopping the use of the investigational product (dechallenge). Judgment should be used if multiple products are discontinued at the same time.

The causal relationship between the study drug and the AE will be assessed using one of the following categories:

- Not Related: Factors consistent with an assessment of Not Related may include:
  - Temporal relationship is lacking (e.g., the event did not occur within a reasonable time frame following administration of the study drug); or

  - Other causative factors more likely explain the event (e.g., a preexisting condition, other concomitant medications)
- Related: Factors consistent with an assessment of Related may include:
  - There is a positive temporal relationship (e.g., the event occurred within a reasonable time frame following administration of study drug)
  - The AE is more likely explained by the investigational product than by another cause (e.g., the AE shows a pattern consistent with previous knowledge of the investigational product or the class of the investigational product).

10.4. Assessment of Expectedness

As part of the regulatory reporting requirements, the Sponsor must perform an assessment of expectedness (expected/unexpected from the perspective of previously observed, not on the basis of what might be anticipated from the pharmacological properties of a medicinal product) for AEs. Adverse reactions will be considered unexpected if the nature, seriousness, severity or outcome of the reaction(s) is not consistent with the reference safety information section of the Investigator's Brochure.

10.5. Common Terminology Criteria for Adverse Events

Clinical and laboratory AEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe nausea). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning.

10.6. Recording Adverse Events

Each patient will be monitored for the occurrence of AEs, including SAEs, from the signing of the ICF through the final follow-up visit. Patients and/or their legal guardians will be questioned, and the patients may be examined by the Investigator or a qualified designee for evidence of AEs. Patients having AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the Investigator.

For each AE, the Investigator will evaluate and record the requested information in the eCRF and the patient's source documentation.

10.6.1. Instructions for Recording AEs in eCRF

10.6.1.1. Recording Diagnosis Versus Signs and Symptoms

If a patient reports signs and symptoms that represent a medical diagnosis/syndrome, the final diagnosis/syndrome should be recorded in the eCRF rather than each sign and symptom (e.g., cough, runny nose, fever = upper respiratory infection). However, if a medical diagnosis cannot be made, then each sign or symptom should be recorded as an individual SAE or AE, as appropriate.

10.6.1.2. Abnormal Laboratory Values or Vital Signs

Protocol defined laboratory values and vital signs should not be reported as AEs unless the abnormal laboratory value or vital sign meets at least one of the following:

- Requires an adjustment in the study drug(s) or discontinuation of treatment;
- Requires medical or surgical intervention;
- Is associated with accompanying signs/symptoms that are not considered part of a preexisting diagnosis or syndrome (or if considered part of a preexisting diagnosis or syndrome, is associated with disease worsening); or
- Is considered clinically significant by the Investigator,

10.7. Reporting Serious Adverse Events

10.7.1. Serious Adverse Event Reporting

10.7.1.1. Initial Reports

All SAEs occurring from the time of informed consent through the final study visit must be reported to PPD within 24 hours of the awareness of the occurrence (this refers to any AE that meets any of the aforementioned serious criteria). (Note: The change in reporting from Medpace to PPD became effective on 20 May 2021). All SAEs that the Investigator considers related to study drug occurring after the study must be reported to the Sponsor.

To report the SAE, the SAE form will be completed electronically in the electronic data capture (EDC) system for the study. When the form is completed, PPD Safety personnel will be notified electronically and will retrieve the form. Any supporting documentation (e.g., discharge summary, diagnostic results) must be redacted by the site and emailed or faxed to PPD (contact information below).

If the EDC system cannot be accessed for technical reasons and the event meets serious criteria, complete the back-up paper SAE form and send via email or fax to PPD (contact information below) or call the PPD SAE reporting line (phone number listed below). When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Safety Contact Information: PPD

PPD SAE reporting line – USA/Canada:

Telephone: +1.888.483.7729

Fax: +1.888.529.3580

PPD SAE Hotline – Europe:

Telephone: +44 122 337 4240

Fax: +44 122 337 4102

Email: RTPSafety@ppd.com

10.7.1.2. Follow-up Reports

The Investigator is required to follow SAEs until resolution, stabilization (in the case of persistent impairment), or until the event becomes chronic in nature, or the patient dies. SAE resolution is defined as:

- Resolved with or without residual effects
- A return to Baseline for a preexisting condition
- Laboratory values have returned to Baseline or stabilized
- The Investigator does not expect any further improvement or worsening of the event
- Fatal outcome - if an autopsy is performed, the autopsy report should be provided to the Sponsor as soon as it is available.

Within 24 hours of receipt or awareness of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., patient discharge summary or autopsy reports) to PPD\ via fax or email. All supporting patient documentation must be redacted for personal details as per Good Clinical Practice (GCP). If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

10.7.1.3. Reporting Pregnancies

If a female patient or the female partner of a male patient becomes pregnant during the course of the study, the Investigator must report the pregnancy to PPD within 24 hours of awareness of the event. PPD will then forward the paper exposure in utero (EIU) form to the Investigator/site for completion. The Investigator/site must complete the EIU form and fax/email it back to PPD within 24 hours. The Investigator/site must obtain consent to collect pregnancy information (including the status of the newborn, if applicable).

The patient or partner should be followed by the Investigator until completion of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the follow-up EIU form should be completed and faxed/emailed to PPD within 24 hours. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

Refer to Section 10.7.1.1 for Safety Contact Information.

10.7.1.4. Reporting to Institutional Review Board/Independent Ethics Committee by Investigator

The Investigator is responsible to report any expedited reports to their local IRB or IEC, per local reporting regulations.

10.7.1.5. Unblinding a Patient's Treatment During the Study

Treatment Period:

In the event of a drug-related, serious, unexpected AE, Scholar Rock will provide the Cohort 3 patient's dose level for the purpose of regulatory authority agency reporting, if appropriate. Because all patients in the study receive SRK-015, unblinding of a Cohort 3 patient's dose level (i.e., high vs. low dose) by the Investigator is discouraged. In the event of a drug-related SAE, the Investigator may, if deemed medically necessary to provide patient care, and after consultation with the Medical Monitor, obtain the patient's dose level from the IWRS system.

Extension Periods:

Any Cohort 3 patients who were randomized to receive low-dose (2 mg/kg) SRK-015 will be re-assigned to receive high-dose (20 mg/kg) SRK-015 after completion of the Treatment Period (see Section 6.2). As of Protocol Version 5.0, unblinding is no longer applicable because all Cohort 3 patients randomized to the low dose who enrolled in Extension Period A have switched to the high dose.

10.7.2. Expedited Reporting by the Sponsor to a Regulatory Health Authority

The Sponsor/designee will manage the expedited reporting of relevant safety information to concerned health authorities in accordance with local laws and regulations. The Sponsor/designee will also inform all Investigators as required per local regulation.

11. STATISTICS

11.1. General Methodology

All analyses will be performed under GCP standards using a prospective SAP. Analyses will be conducted using Statistical Analysis System (Version 9.4 or later, Cary, North Carolina).

The study is regarded as 3 separate cohorts; therefore, no Type I error is allocated towards separate cohort testing. No formal statistical testing will be applied for the interim analysis and no alpha spending will be applied. Two-sided 95% confidence intervals (CIs) will be reported.

There will be an interim analysis conducted when prespecified enrollment (see below) and treatment duration have been reached for all 3 cohorts (see Section 11.4); the final analysis will be conducted once each cohort completes the 52-week Treatment Period. Biostatistics Data Review Meetings will be held for the final analyses to distinguish between major and minor protocol violations. Both Per-Protocol and Intention-to-Treat (ITT) populations will be analyzed, with the ITT population being the primary analysis population.

Any changes in the analysis as specified in the protocol will be delineated in the SAP.

11.2. Analysis Strategy

All prespecified safety and efficacy endpoints will be analyzed by cohort and by dose group for Cohort 3. All patients with any postbaseline data will be included in the interim and primary analyses. In addition, safety and efficacy data for the high dose will be analyzed for different cohort/dose combinations taking cohort, dose level, and receiving background SMA therapy into consideration. For the change from Baseline analyses (to utilize the patient as their own control for response analyses), the last observation before the first dose will be used as the Baseline. Cohort 3 low- vs high-dose treatment outcomes will also be evaluated for the time to response as a descriptive outcome.

11.2.1. Safety Analyses

Safety data will be evaluated for vital signs, laboratory outcomes, concomitant medications, ECGs, and AEs. Clinically significant outcomes will be noted. Vital signs and laboratory outcomes will be summarized within each treatment group within all cohorts and the 2 dose groups within Cohort 3. AEs will be coded in the Medical Dictionary for Regulatory Activities; the emphasis will be on treatment-emergent adverse events (TEAEs); the TEAE type, incidence, severity, relationship, onset and resolution time will be displayed descriptively. The incidence rate of AEs and TEAEs will be reported.

11.2.2. Efficacy Analyses

Efficacy data will be evaluated for multiple measures with continuous endpoints (e.g., HFMSE score, RHS score, RULM score, etc.) at time points specified in Table 2, Table 3, Table 4, and Table 5. The primary endpoints and other efficacy continuous endpoints will be summarized within cohorts and by dose groups for Cohort 3; corresponding two-sided 95% CIs will be computed as well. Similar analyses for different cohort/dose combinations will be explored. The HFMSE, RHS, and WHO motor development endpoints will be further categorized to assess the

specific distributions of the change from Baseline (waterfall displays of unit changes from Baseline) and the proportion of patients reaching certain milestones.

Waterfall charts will be generated to display the distribution of improvement from Baseline for HFMSE, RHS, RULM, and other unit-based measures at postbaseline milestones in support of efficacy and future study planning.

Time to outcome improvement will be assessed using Kaplan-Meier lifetables to characterize time to efficacy for Cohort 3 low dose versus high dose.

11.2.3. Pharmacokinetic and Pharmacodynamic Analysis

All patients who receive at least 1 dose of study drug and have at least 1 quantifiable PK result will be included in the population PK analysis. The data from this study may be combined with other Sponsor SMA studies for both population PK analysis and exposure-response analysis, if data permit. SRK-015 concentrations and circulating latent myostatin concentrations will be determined using blood samples collected before and after dosing through the final follow-up visit. SRK-015 concentrations will be listed and summarized in tabular formats using descriptive statistics and will be plotted against time points by cohort, and dose and schedule. The latent myostatin concentrations will be listed for each patient and summarized by cohort.

11.2.4. Anti-SRK-015 Antibody Analysis

All patients who receive at least 1 dose of study drug and have at least 1 ADA result will be included in the immunogenicity evaluation. The ADA population is defined as patients who receive at least 1 dose of study drug and have a pretreatment result and at least 1 posttreatment result from the ADA sample collection. Immunogenicity will be evaluated through a 3-tier ADA assay (screening, confirmatory, and titer) and a neutralizing antibody assay. The number and percent of patients who become positive for ADAs and who develop neutralizing antibodies will be listed and summarized in tabular format using descriptive statistics by cohort, visit, dose and schedule, and overall.

11.3. Sample Size Rationale

Sample sizes for each cohort were based on practical considerations. Sample sizes of 15 to 20 patients for each cohort will provide 80% power to reject the null hypothesis involving mean changes from Baseline within each treatment group relative to prespecified alternative hypothesis using a paired t-test with two-sided 5% Type 1 error. Table 8 presents the effect sizes within dose groups that can be detected with 80% power and two-sided 5% Type I error as well as the effect sizes that will reject the null hypothesis of no difference according to two-sided p=0.05. As illustration, assuming a 2.5-unit standard deviation (SD) for the change from Baseline for HFMSE, a mean 1.7-unit improvement for HFMSE (n=20) and a mean 2-unit improvement for HFMSE (n=15) can be detected with 80% power while a mean 1.2-unit improvement in HFMSE (n=20) and a mean 1.3-unit improvement in HFMSE reaches two-sided p=0.05 (rules out a 0 as the two-sided 95% CI for the change from Baseline).

Table 8: Paired T-test: Reject Null Hypothesis No Mean Change from Baseline

	80% Power		Two-sided p=0.05	
Test significance level, α	0.05	0.05	0.05	0.05
Effect size, e = $\|\Delta_1 - \Delta_2\| / s$	0.66	0.778	0.462	0.543
n (after losses)	20	15	20	15

In addition, the total sample size for Cohort 3 (n= 20) provides 80% power to reject the null hypothesis of no mean change from Baseline against the prespecified difference between doses for a clinically meaningful improvement at a two-sided 5% Type I error for a 1:1 randomization (high dose vs. low dose).

Table 9 presents the effect size which could be detected with 80% power and a two-sided 5% Type 1 error as well as the effect sizes required to reject the null hypothesis of no change from Baseline for comparing Cohort 3 low vs. high dose. If the SD of the change from Baseline is 2.5 units for HFMSE, then a mean 2.4-unit difference between low and high dose will reach two-sided p=0.05 (rules out 0 as the lower two-sided 95% CI as the mean difference between dose groups).

Table 9: Unpaired T-test: Reject Null Hypothesis: No Mean Difference from Baseline

	80% Power	Two-sided p=0.05
Two-sided significance level, α	0.05	0.05
Effect size, e = $\|\Delta_A - \Delta_0\| / s$	1.325	0.926
n per group (after losses)	10	10

11.4. Interim Analyses

11.4.1. Pharmacokinetic and Pharmacodynamic Interim Analysis

Prespecified interim analyses to initially evaluate drug exposure (i.e., PK) and target engagement (i.e., PD) in patients with SMA will be conducted. For Cohorts 1 and 2, these analyses will be conducted after approximately 4 patients in each cohort have received at least 2 doses of SRK-015. For Cohort 3, these analyses will be conducted after approximately 6 patients have received at least 2 doses of SRK-015. Data from multiple cohorts may be combined as necessary. Enrollment will continue while the interim analysis is ongoing. Based on these results, and taking into consideration any available safety data, the cohort-specific dose levels may be adjusted. Any adjustment in dose level will not change the frequency of dosing (i.e., every 4 weeks) and the highest dose will not exceed 30 mg/kg, as tested in the Phase 1 study.

11.4.2. Safety and Efficacy Interim Analyses

Prespecified interim analyses to evaluate the initial safety and efficacy of SRK-015 in patients with SMA will be conducted when all enrolled patients complete Day 168 (Visit 8) or are terminated from the study. Interim analyses will be performed on the efficacy endpoints in addition to all safety outcomes and available PK and PD results. Safety data at all visits and efficacy endpoints at Day 168 (Visit 8) will be included in this analysis.

These interim analyses are being conducted to explore the possibility that clinically meaningful effects may be observed early in the course of SRK-015 treatment. Based on the interim results, these insights may inform and expedite the planning of future clinical studies in SMA.

12. STUDY ADMINISTRATION

The study administration structure is provided in Table 10.

Table 10: Study Administrative Structure

Sponsor Contact:	Mara Sadanowicz Phone: +1.617.386.6842 Email: msadanowicz@scholarrock.com
Sponsor Medical Director:	George Nomikos, MD, PhD Phone: +1.857.598.4874 Email: gnomikos@scholarrock.com
Medical Monitor:	Nancy Campbell, MD Mobile phone: +1.513.978.2506 Email: n.campbell@medpace.com
Study Monitoring (US and EU):	Medpace 5375 Medpace Way Cincinnati, OH 45227 Phone (Main): +1.513.579.9911
Safety Laboratory (US and EU):	Medpace Reference Laboratories 5365 Medpace Way Cincinnati, OH 45227 Phone (Main): +1.513.579.9911
Central ECG Laboratory (US and EU):	Medpace Core Laboratories 5365 Medpace Way Cincinnati, OH 45227 Phone (Main): +1.513.579.9911

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

13.1. Study Monitoring

This study will be performed in accordance with regulatory requirements outlined in Food and Drug Administration (FDA) 21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, 21 CFR Part 312 and 21 CFR Part 11, as well as the ICH GCP E6 Guidelines. A Study Monitor designated by the Sponsor will carefully monitor all aspects of the study for compliance with GCP, SOPs, and applicable government regulations. The Study Monitor will meet with the Investigator and staff shortly before the start of the study to review the procedures for study conduct and documentation. During the study, the Study Monitor will visit the site to verify record keeping and adherence to the protocol.

The Investigator must prepare and maintain adequate and accurate records of all observations and other data pertinent to the clinical study for each study patient. Frequent communication between the clinical site and the Sponsor/designee is essential to ensure that the safety of the study is monitored adequately. The Investigator will make all appropriate safety assessments on an ongoing basis. The Sponsor's medical representative may review safety information as it becomes available throughout the study.

13.2. Audits and Inspections

The Investigator should immediately notify the Sponsor representative of any announced or unannounced regulatory agency inspections. An auditing inspection may also be conducted by the Sponsor representative.

The Investigator will allow Sponsor representatives, contract designees, authorized regulatory authority inspectors, and the IRB/IEC to have direct access to all documents pertaining to the study.

13.3. Institutional Review Board/Independent Ethics Committee

The Investigator must obtain IRB/IEC approval for the investigation. Initial IRB/IEC approval and all materials approved by the IRB/IEC for this study, including the patient consent form and recruitment materials, must be maintained by the Investigator and made available for inspection.

14. QUALITY CONTROL AND QUALITY ASSURANCE

An electronic data system will be used to ensure quality assurance and facilitate data capture during the study. The system is fully CFR 21 Part 11-compliant and provides for control and capture of study operations performance in real time.

The Investigator or a qualified designee will prepare and maintain adequate and accurate study documents (medical records, ECGs, AE and concomitant medication reporting, raw data collection forms, etc.) designed to record all observations and other pertinent data for each patient receiving randomized study drug. The Investigator will ensure the accuracy, completeness, and timeliness of the data reported to the Sponsor and will cooperate with the Sponsor's representative(s) for the periodic review of study documents to ensure the accuracy and completeness of the data capture system at each scheduled monitoring visit. Access to all source documentation will be made available for monitoring and audit purposes. Monitors will conduct 100% source document verification by comparing the eCRFs with the source documents to ensure consistency. Edit check programs, other forms of electronic validation, manual listings, and a query process will be executed to verify the accuracy of the database. The EDC system will maintain a full audit trail of electronic data changes. This information will be provided to the site by means of electronic or manual queries. Only enrolled patients will be entered into the database.

15. ETHICS

15.1. Ethics Review

The protocol and all protocol amendments must be signed and dated by the Investigator and approved in writing by the IRB/IEC in accordance with GCP prior to implementation. In addition, the IRB/IEC must approve the written informed consent and assent forms, any consent or assent form updates, patient recruitment procedures (e.g., advertisements), and any written information to be provided to patients prior to implementation. The Investigator must provide updates to the IRB/IEC with progress reports at appropriate intervals and a Study Progress Report following the completion, termination, or discontinuation of the Investigator's participation in the study.

15.2. Ethical Conduct of the Study

The procedures set out in this clinical study protocol are designed to ensure that the Sponsor and the Investigator abide by the principles of the ICH guidelines on GCP and the Declaration of Helsinki (Version 2013). The clinical study will also be carried out in keeping with national and local legal requirements (in accordance with US Investigational New Drug regulations [21 CFR 56]).

15.3. Written Informed Consent and Assent

Written informed consent will be obtained from each patient if the patient is legally an adult. If the patient is legally a minor, informed consent document will be signed by the patient's parent or legal guardian and patient's oral or written assent obtained, if applicable and in accordance with regulatory and legal requirements of the participating location, before study procedures are conducted. As part of this procedure, the Investigator must explain orally and in writing, the nature, duration, and purpose of the study, and the action of the drug in such a manner that the patient and/or their parent or legal guardian is aware of the potential risks, inconveniences, or AEs that may occur. Patients and/or their parents or legal guardians should be informed that they are free to withdraw from the study at any time and that they will receive all information that is required by federal regulations and ICH guidelines. The Principal Investigator or a qualified designee will provide the Sponsor with a copy of the IRB/IEC-approved ICF prior to the start of the study.

15.4. Patient Confidentiality

The anonymity of participating patients must be maintained. Patients will be identified on study documents by their Patient number and birth date (if allowed based on local data protection regulations), not by name. Documents that identify the patient (e.g., the signed informed consent document) must be maintained in confidence by the Investigator. The Investigator agrees not to use or disclose protected health information other than as permitted or required by the patient authorization or as required by law.

16. DATA PROTECTION

16.1. Organizational and Technical Arrangements to Avoid Unauthorized Access, Disclosure, Dissemination, Alteration, or Loss of Information and Personal Data Processed

The conduct of this study and the processing of any personal data collected from each patient (or from a patient's healthcare professional or other relevant third-party sources) by the Sponsor or designee, the site and the Investigator for use in the study will fully adhere to the requirements set out in applicable data protection and medical privacy laws or regulations, including, without limitation, the General Data Protection Regulation (GDPR) EU 2016/679. Sponsor or designee shall ensure that at all times it has an appropriate legal basis for processing personal data under applicable data protection law. Measures will be implemented in case of data security breach.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

Regulatory agencies may request access to all study records, including source documents, for inspection and copying, in keeping with country regulations. The Investigator will permit the designated Sponsor representatives and regulatory bodies to have direct access to the source documents to verify data represented in the eCRF.

17.2. Retention of Records

All source documents (e.g., ICFs, laboratory reports, imaging scans, progress notes, medical histories, physical and diagnostic findings, diagnosis and pharmacy records, and study drug dispensing/disposition records) that support data in the eCRFs of each study patient must be retained in the files of the responsible Investigator.

According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational medicinal product. However, these documents should be retained for a longer period if required by the applicable legal requirements.

If the responsible Investigator retires, relocates, or for any other reason withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor representative must be notified in writing of the name and address of the new custodian, prior to the transfer.

18. PUBLICATION POLICY

All information concerning SRK-015, including but not limited to, Sponsor operations, patent applications, formulas, manufacturing processes, scientific data, and formulation information, supplied to the Investigator by a Sponsor representative and not previously published, is considered confidential and remains the sole property of the Sponsor. The Investigator must agree to use this information solely for the purposes of carrying out this study and must not use it for other purposes without the Sponsor's advanced written consent.

The information developed in this study will be used by the Sponsor in connection with the continued development of SRK-015 and thus may be disclosed to other clinical Investigators or government regulatory agencies. The Investigator is obligated to provide the Sponsor with all data obtained in the study.

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STATISTICAL ANALYSIS PLAN

Protocol Title:	Phase 2 Active Treatment Study to Evaluate the Efficacy and Safety of SRK-015 in Patients with Later-onset Spinal Muscular Atrophy (TOPAZ)
Protocol Number:	SRK-015-002
Protocol Version/Date:	4.0 / 13 November 2020
Investigational Product:	SRK-015
Sponsor:	Scholar Rock, Inc. 301 Binney Street, 3rd Floor Cambridge, MA 02142
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CONFIDENTIAL

SIGNATURE PAGE

Protocol Title: Phase 2 Active Treatment Study to Evaluate the Efficacy and Safety of SRK-015 in Patients with Later-onset Spinal Muscular Atrophy (TOPAZ)

Protocol Number: SRK-015-002

SAP Version/Date: 3.0 / 24 February 2021

We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

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VERSION HISTORY

Version	Version Date	Description
1.0	31JUL2020	Version 1.0 signed
2.0	05OCT2020	Version 2.0 updated for Interim Analysis in Q4 2020
3.0	24FEB2021	Version 3.0 updated for Protocol Version 4.0

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LIST OF ABBREVIATIONS

Abbreviation	Definition
6MWT	6-minute Walk Test
AE	Adverse Event
ADaM	Analysis Data Model
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ESNHPT	Endurance Shuttle Nine Hole Peg Test
ESBBT	Endurance Shuttle Box and Block Test
ET	Early Termination
HFMSE	Hammersmith Functional Motor Scale Expanded
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ITT	Intention-to-Treat
IV	Intravenous
IWRS	Interactive Web-based Randomization System
LOCF	Last Observation Carried Forward
LSMEANS	Least Square Means
MAD	Multiple Ascending Dose
MedDRA	Medical Dictionary for Regulatory Activities
MGRS	Multicentre Growth Reference Study
MMRM	Mixed-effects Model for Repeated Measures
PD	Pharmacodynamics
PEDI-CAT	Pediatric Evaluation of Disability Inventory Computer Adaptive Test
PK	Pharmacokinetic(s)
PP	Per Protocol
PROMIS	Patient-Reported Outcomes Measurement Information System
RHS	Revised Hammersmith Scale
RULM	Revised Upper Limb Module
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
SMA	Spinal Muscular Atrophy
SMN	Survival Motor Neuron
SST	Safety Surveillance Team
TEAE	Treatment-emergent Adverse Event
TE-SAE	Treatment-emergent Serious Adverse Event
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods and procedures to be implemented for the analysis of data from Scholar Rock, Inc. protocol number SRK-015-002, "Phase 2 Active Treatment Study to Evaluate the Efficacy and Safety of SRK-015 in Patients with Later-onset Spinal Muscular Atrophy (TOPAZ)". If circumstances arise during the study such that more appropriate analytic procedures become available, the SAP may be revised. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

The primary objectives of this study are:

- To assess safety and tolerability of SRK-015 in patients with later-onset (e.g., Type 2 and Type 3) spinal muscular atrophy (SMA), and
- To assess the efficacy of SRK-015 by assessing changes in motor function outcome measures in 3 separate predefined cohorts.

2.1.2 Secondary Objectives

The secondary objectives of this study are:

- To characterize the pharmacokinetics (PK) of SRK-015,
- To evaluate the pharmacodynamic (PD) effects of SRK-015,
- To evaluate time to therapeutic effect between low- and high-dose SRK-015 in a predefined cohort (Cohort 3),
- To evaluate the immunogenicity of SRK-015, and
- To evaluate the effect of SRK-015 on quality of life.

2.2 Study Design

2.2.1 Overview

Study SRK-015-002 (TOPAZ) is an active treatment study to evaluate the efficacy and safety of SRK-015 in patients age 2 through 21 years old with later-onset (e.g., Type 2 and Type 3) SMA. Patients may receive SRK-015 as monotherapy or in addition to a survival motor neuron (SMN) upregulator therapy approved for SMA.

This study will be conducted in approximately 20 study sites across the United States and Europe. Approximately 55 male and female patients with later-onset SMA will be enrolled across 3 separate parallel subpopulations subsequently described as cohorts.

- Cohort 1, N=20: Ambulatory Type 3 patients, age 5 through 21 years old, approximately 10 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: Type 2 and nonambulatory Type 3 patients, age 5 through 21 years old, already receiving an approved SMA treatment that had been started after the patient turned 5 years old.
- Cohort 3, N=20: Type 2 patients, age ≥2 years old, already receiving an approved SMA treatment that had been started before the patient turned 5 years old.

Patient participation in the study will consist of 3 parts: Screening, Treatment, and Follow-up. Screening motor function outcome measures will be conducted at least 7 days prior to the first dose. All subsequent motor function outcome measures will be conducted within 96 hours prior to dosing. During the 52-week Treatment Period, patients enrolled in Cohorts 1 and 2 will receive high-dose (20 mg/kg) SRK-015 and patients enrolled in Cohort 3 will be randomized (1:1) in a blinded manner to receive either low-dose (2 mg/kg) or high-dose (20 mg/kg) SRK-015.

All treatments will be administered by intravenous (IV) infusion over approximately 2 hours once every 4 weeks. The first dose will be administered on Day 0 and the final dose on Day 336, for a total of 13 doses. During the Treatment Period, patients will be monitored at the study site through approximately 2 hours postdose. If there are no acute reactions following the first 2 doses for a patient, and if the Investigator determines that it would be safe to do so, the infusion duration can be changed to less than 2 hours but no shorter than 1 hour.

Patients will be seen in clinic 14 days after the first dose. After the second dose, visits will occur every 4 weeks through the end of the study. All dosing and motor function outcome measures will be conducted at the study site during the Treatment Period. The last Treatment Period visit will be on Day 364 (V15).

The total duration of the Treatment Period for an individual patient will consist of approximately 4 weeks for Screening, 52 weeks of study visits, and, if the patient does not enroll into Extension Period A, 12 weeks of Safety Follow-up for a total duration of approximately 68 weeks (approximately 16 months).

Patients who complete the 52-week Treatment Period will have the option to enroll into Extension Period A for an additional 52-week period. There will be no interruption in dosing between the completion of the Treatment Period and the start of Extension Period A. The first dose in Extension Period A will be administered on Day 364 (E1), following completion of the Treatment Period at V15, and the final dose will be administered on Day 700 (E13), for a total of 13 doses. The total duration of Extension Period A for an individual patient who completes both the Treatment Period and Extension Period A will consist of approximately 4 weeks for Screening, 104 weeks of study visits, and 12 weeks of Safety Follow-up for a total duration of approximately 120 weeks (approximately 28 months).

Patients who complete Extension Period A will have the option to enroll into Extension Period B for an additional 52-week period. There will be no interruption in dosing between the completion of Extension Period A and the start of Extension Period B. The first dose in Extension Period B will be administered on Day 728 (EB1), following completion of Extension Period A on Day 728 (E14), and the final dose will be administered on Day 1064 (EB13), for a total of 13 doses. The total duration of Extension Period B for an individual patient who completes the Treatment Period and Extension Periods A and B will consist of approximately 4 weeks for Screening, 156 weeks of study visits, and 12 weeks of Safety Follow-up for a total duration of approximately 172 weeks (approximately 40 months).

Patients who complete the 52-week Treatment Period and choose not to enroll in optional Extension Period A will be followed for a 12-week Safety Follow-up Period after Day 364 (V15). These patients will have a total of 13 doses. Patients who complete the 52-week Extension Period A and choose not to enroll in optional Extension Period B will be followed for a 12-week Safety Follow-up Period after Day 728 (E14). These patients will have a total of 26 doses. Patients who complete the 52-week Extension Period B will be followed for a 12-week Safety Follow-up Period after Day 1092 (EB14). These patients will have a total of 39 doses.

Based on the results of the prespecified 6-month safety and efficacy interim analyses, any Cohort 3 patients who were randomized to receive low-dose (2 mg/kg) SRK-015 will be re-assigned to receive high-dose (20 mg/kg) SRK-015 after completion of the Treatment Period. Due to the variability in timing of regulatory authority and/or Institutional Review Board/Independent Ethics Committee approvals, the timepoint at which patients who received the low dose (2 mg/ kg) will begin receiving the high dose (20 mg/kg) during Extension Period A or B will vary.

A study schema is depicted in Figure1, Figure 2, and Figure 3.

Figure 1: Study Schematic: Treatment Period

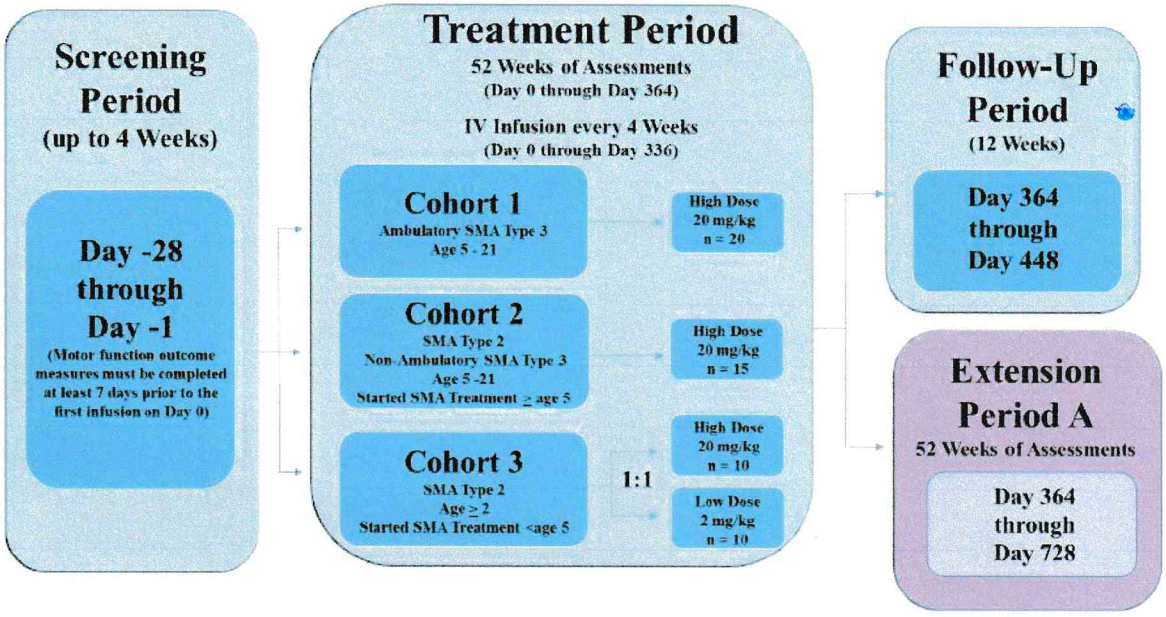


Figure 2: Study Schematic: Extension Period A

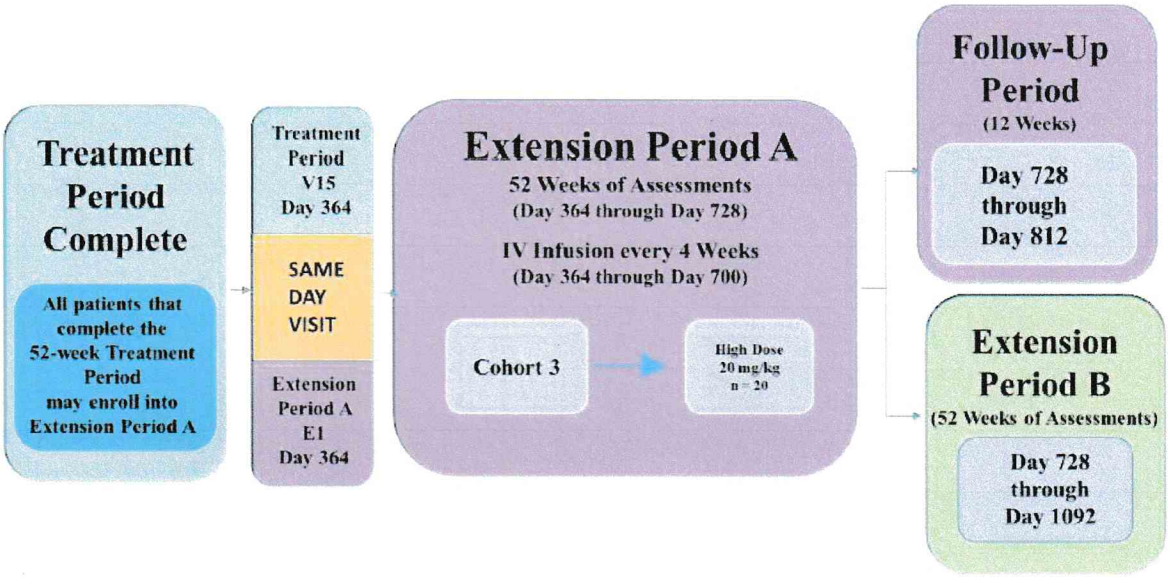
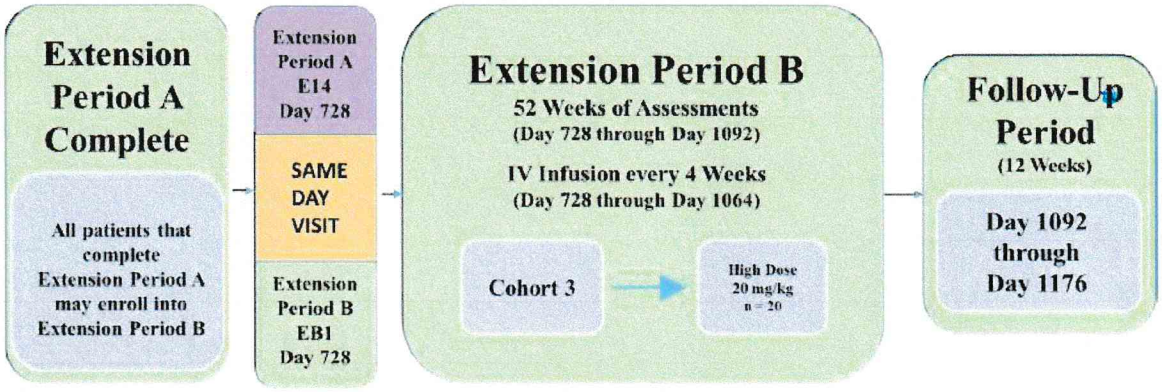


Figure 3: Study Schematic: Extension Period B



2.2.2 Randomization and Blinding

Patients in Cohorts 1 and 2 are directly assigned to the 20 mg/kg dose of SRK-015 while Cohort 3 patients will be randomized (1:1) without stratification in a double-blind manner to receive either 2 mg/kg or 20 mg/kg SRK-015 via an Interactive Web-based Randomization System (IWRS). Use of the IWRS will be outlined in the Study Operations Manual and in the IWRS quick reference guide.

The Sponsor, patients, caregivers, Investigators and site personnel, with the exception of the Pharmacist, will be blinded to Cohort 3 SRK-015 dose level assignments. The site Pharmacist will remain unblinded throughout the duration of the study. The Sponsor will be blinded to individual efficacy data and cohort-level efficacy results until prespecified interim analyses are performed and will only be unblinded to the cohort-level efficacy results at the safety and efficacy interim analysis. The Sponsor will remain blinded to individual efficacy data until the Treatment Period

database lock or deemed necessary by the Safety Surveillance Team (SST). A list of personnel who may be granted access to the efficacy data from the Sponsor side to perform data monitoring/quality check will be documented. As PK/PD data can be inherently unblinding, the persons who perform the PK/PD interim analyses and review the individual data will be unblinded and documented.

In the event of a drug-related, serious, unexpected adverse event (AE), Medpace (the clinical research organization for the study) may provide a Cohort 3 patient's dose level to the Sponsor for the purpose of regulatory authority agency reporting.

2.2.3 Sample Size Determination

Sample sizes for each cohort were based on practical considerations. The following calculations are to illustrate some scenarios of the power yield by the chosen sample size with certain effect size assumptions.

Sample sizes of 15-20 patients for each cohort will provide 80% power to reject the null hypothesis involving mean changes from Baseline within each treatment group relative to prespecified alternative hypothesis using a paired t-test with 2 sided 5% Type 1 error. Table 1 presents the effect sizes within dose groups that can be detected with 80% power and two-sided 5% Type I error as well as the effect sizes that will reject the null hypothesis of no difference according to two-sided p=0.05. As an illustration, assuming a 2.5 unit standard deviation for the change from Baseline for Hammersmith Functional Motor Scale Expanded (HFMSE), a mean 1.7-unit improvement for HFMSE (n=20) and a mean 2-unit improvement for HFMSE (n=15) can be detected with 80% power while a mean 1.2 unit improvement in HFMSE (n=20) and a mean 1.3-unit improvement in HFMSE reaches two-sided p=0.05 (rules out a 0 as the two-sided 95% confidence interval [CI] for the change from Baseline).

Table 1: Paired T-test: Reject Null Hypothesis No Mean Change from Baseline

	80% Power		Two-sided p=0.05	
Test significance level, α	0.05	0.05	0.05	0.05
Effect size, e = $\lvert\Delta_1 - \Delta_2\rvert$ / s	0.66	0.778	0.462	0.543
n (after losses)	20	15	20	15

In addition, the total sample size for Cohort 3 (n= 20) provides 80% power to reject the null hypothesis of no mean change from Baseline against the prespecified difference between doses for a clinically meaningful improvement at a two-sided 5% Type I error for a 1:1 randomization (high dose vs. low dose).

Table 2 presents the effect size which could be detected with 80% power and a two-sided 5% Type 1 error as well as the effect sizes required to reject the null hypothesis of no change from Baseline for comparing Cohort 3 low vs. high dose. If the standard deviation of the change from Baseline is 2.5 units for HFMSE, then a mean 2.4-unit difference between low and high dose will reach two-sided p=0.05 (rules out 0 as the lower two-sided 95% CI as the mean difference between dose groups).

Table 2: Unpaired T-Test: Reject Null Hypothesis: No Mean Difference from Baseline

	80% Power	Two-sided p=0.05
Two-sided significance level, α	0.05	0.05
Effect size, e = $\lvert\Delta_A - \Delta_0\rvert$ / s	1.325	0.926
n per group (after losses)	10	10

2.2.4 Visits and Assessments

Assessments and visit windows at each scheduled visit are specified in the Study Schedule of Assessments (Tables 3-5). For patients who prematurely discontinue from the study during the Treatment Period, all assessments scheduled for V17 (Day 448) will be completed at the Early Termination (ET) visit, if possible; for patients who discontinue from the study during Extension Period A, all assessments scheduled for E15 (Day 784) would be completed at the ET visit for Extension Period A; for patients who discontinue from the study during Extension Period B, all assessments scheduled for EB15 (Day 1176) would be completed at the ET visit for Extension Period B.

Due to the pandemic of Coronavirus disease 2019 (COVID-19), study visits for some patients were delayed or cancelled. The sites were given the following instructions:

- If a visit window exceeds 56 days from the latest patient visit, that visit should be skipped.
- If a visit window exceeds 84 days from the latest patient visit, two consecutive visits should be skipped.

These guidelines hold true except if the patient is at Visit 15 (Day 364); regardless of the duration from the latest patient visit, Visit 15 (Day 364) should not be skipped.

If the skipped visit is one where motor function outcome measures should be conducted (i.e., Visit 4 [Day 56], Visit 6 [Day 112], Visit 8 [Day 168], etc.), motor function outcome measures are to be conducted at the next scheduled visit either as part of the visit or as unscheduled assessments.

If it is believed that a patient may miss 3 consecutive visits, the Medical Monitor should be contacted to provide guidance on a case-by-case basis.

Examples:

If a patient is seen on 01Apr2020 for Visit 7 (Day 140) but cannot return to the site until 28May2020 (57 days from latest visit), then Visit 8 (Day 168) will be considered as skipped. When the patient is seen on 28May2020, Visit 9 (Day 196) will be conducted and the PT assessments will be performed as unscheduled assessments.

If a patient is seen on 01Apr2020 for Visit 7 (Day 140) but cannot return to the site until 25Jun2020 (85 days from the latest visit), then Visit 8 (Day 168) and Visit 9 (Day 196) will be considered as skipped. When the patient is seen on 25Jun2020, Visit 10 (Day 224) will be conducted and motor function outcome measures will be performed per protocol.

Table 3: Study Schedule of Assessments: Treatment Period

Activity/Assessment	Screening	Treatment Period																Follow-up	
Visit Time Point (Study Day[a])	-28 to -1	V1 0	V2 14	V3 28	V4 56	V5 84	V6 112	V7 140	V8 168	V9 196	V10 224	V11 252	V12 280	V13 308	V14 336	V15 364	UNS	V16 392	V17 448/EOS/ ET
Informed Consent	X																		
Demographics & Medical History[c]	X																		
Inclusion/Exclusion	X																		
Pregnancy Test[d]	X	X			X				X				X						X
Weight[e]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height[f]	X	X			X		X		X		X		X			X	X	X	X
Physical Examination[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Safety Labs[i]	X	X	X	X	X		X		X		X		X		X		X	X	X
12-lead ECG[j]	X	X		X			X				X				X		X	X	X
PK and PD Sampling[k]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Antidrug Antibody Sampling[l]		X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Randomization[m]		X																	
Study Drug Administration		X		X	X	X	X	X	X	X	X	X	X	X	X				
Motor Function Outcome Measures b,f,n	X	X			X		X		X		X		X			X	X	X	X
QOL[o]		X			X		X		X		X		X			X	X	X	X
Site Check-in[p]		X		X	X	X	X	X	X	X	X	X	X	X	X				
Adverse Events	*To be collected from the date that the ICF is signed through the last study visit*																		
Concomitant Therapy	*To be collected from the date that the ICF is signed through the last study visit*																		

ECG = electrocardiogram; EOS = end-of-study; ET = early termination; ICF = informed consent form; IV = intravenous; PD = pharmacodynamic; PEDI-CAT: Pediatric Evaluation of Disability Inventory Computer Adaptive Test ; PK = pharmacokinetic; PROMIS = Patient-reported Outcomes Measurement Information System; QOL = quality of life; UNS = unscheduled.

[a] Study visits after Day 0 have a ±7-day window, excluding Day 14, which has a ±1-day window. Visit assessments may be conducted over multiple days within the visit window, as needed and in compliance with protocol requirements for the timing of each assessment.

[b] Screening motor function outcome measures must be completed at least 7 days prior to the first infusion on Day 0. All subsequent motor function outcome measures will be conducted within 96 hours prior to dosing.
[c] Includes history of present illness.
[d] Females of childbearing potential only. Urine or serum test is acceptable; however, positive urine tests must be confirmed with serum testing. Testing may be performed more frequently as per local requirements. The urine pregnancy test used is the Alere hCG cassette (25mIU/mL) and according to the product manufacturer, has >99% sensitivity.
[e] Weight is collected within 48 hours of each dose to calculate weight-based dosing.
[f] Height is collected at visits where the motor function outcome measures are conducted. Ulna length may be used to estimate height for patients who are nonambulatory or needs standing support.
[g] Changes in pubertal development must be assessed if not deemed physically mature at Screening. If menarche occurs during the study, the child will be deemed of childbearing potential and immediate pregnancy status will be checked. Further study drug can only be given if pregnancy status is negative. Contraception and pregnancy monitoring will be performed as outlined in the protocol.
[h] Heart rate, blood pressure, and respiratory rate are collected preinfusion, every 15 minutes (±5 minutes) during the infusion, at the end of the infusion, and 1 and 2 hours (±15 minutes) postinfusion. Body temperature will be collected preinfusion on dosing days.
[i] Clinical safety labs include serum chemistry, hematology, urinalysis, and coagulation. Labs are collected preinfusion at dosing visits.
[j] 12-lead ECGs are collected after 5 minutes of rest, in triplicate and at least 1-2 minutes apart. ECGs are collected within 2 hours prior to the start of the infusion. Unscheduled ECGs may be performed as clinically necessary.
[k] Blood samples for PK and PD are collected within 2 hours prior to the start of the infusion at dosing visits. An additional sample is collected via peripheral IV 2 hours (±1 hour) after completion of the infusion on Day 0, Day 140 (PK only), and Day 336 (PK only).
[l] Blood sample for anti-SRK-015 antibody testing is collected within 2 hours prior to the start of the infusion at dosing visits.
[m] Patients in Cohort 3 will be randomized to low or high-dose SRK-015 within 24 hours prior to the first infusion on Day 0.
[n] See Table 5 for motor function outcome measures conducted for each cohort. Unscheduled motor function outcome measures may be performed as needed.
[o] QOL collected using the PROMIS Fatigue Questionnaire and PEDI-CAT. If the PEDI-CAT and/or PROMIS are not available in the native language, they should not be completed. Unscheduled QOL questionnaires may be performed as needed.
[p] Sites contact patients within 7 days following each infusion to collect information on adverse events and concomitant medications.

Table 4: Study Schedule of Assessments: Extension Period A (Extension A Visits 1-15)

Activity/Assessment	Extension Period A														Follow-Up/Other	
Visit Time Point (Study Day[a])	E1 364[c]	E2 392	E3 420	E4 448	E5 476	E6 504	E7 532	E8 560	E9 588	E10 616	E11 644	E12 672	E13 700	E14 728	E-UNS	E15 812/EOS/ET
Informed Consent[o]	X															
Pregnancy Test[d]	For patients who enroll into Extension Period A, assessments will merge between Treatment Period Day 364 (V15) and Extension Period A Day 364 (E1). Study drug administration and PK/PD/ADA Sampling will only be performed for patients who enroll into Extension Period A.		X				X				X					X
Weight[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height[f]					X				X					X	X	X
Physical Examination[g]		X		X		X		X		X		X		X	X	X
Vital Signs[h]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Safety Labs[i]		X			X			X			X		X		X	X
12-lead ECG[j]		X			X			X			X		X		X	X
PK and PD Sampling[k]	X	X			X			X			X		X	X	X	X
Antidrug Antibody Sampling[l]	X	X			X			X			X		X	X	X	X
Study Drug Administration	X	X	X	X	X	X	X	X	X	X	X	X	X			
Motor Function Outcome Measures[b,f,m]					X				X					X	X	X
QOL[n]					X				X					X	X	X
Adverse Events	*To be collected from the date that the ICF is signed through the last study visit*															
Concomitant Therapy	*To be collected from the date that the ICF is signed through the last study visit*															

ECG = electrocardiogram; EOS = end-of-study; ET = early termination; ICF = informed consent form; IV = intravenous; PD = pharmacodynamic; PEDI-CAT: Pediatric Evaluation of Disability Inventory Computer Adaptive Test; PK = pharmacokinetic; PROMIS = Patient-reported Outcomes Measurement Information System; QOL = quality of life; UNS = unscheduled.

[a] Study visits have a ±7-day window. Visit assessments may be conducted over multiple days within the visit window, as needed and in compliance with protocol requirements for the timing of each assessment.
[b] All motor function outcome measures will be conducted within 96 hours prior to dosing.
[c] Treatment Period Day 364 (Visit 15) and Extension Period A Day 364 (E1) occur on the same day. Treatment Period V15 will serve as the last Treatment Period visit and Extension Period A E1 will serve as the first visit for Extension Period A. There will not be any duplicate assessments performed.
[d] Females of childbearing potential only. Urine or serum test is acceptable; however, positive urine tests must be confirmed with serum testing. Testing may be performed more frequently as per local requirements. The urine pregnancy test used is the Alere hCG cassette (25mIU/mL) and according to the product manufacturer, has >99% sensitivity.
[e] Weight is collected within 48 hours of each dose to calculate weight-based dosing.
[f] Height is collected at visits where the motor function outcome measures are conducted. Ulna length may be used to estimate height for patients who are nonambulatory or not able to stand independently.
[g] Changes in pubertal development must be assessed if not deemed physically mature during Treatment Period. If menarche occurs during the study, the child will be deemed of childbearing potential and immediate pregnancy status will be checked. Further study drug can only be given if pregnancy status is negative. Contraception and pregnancy monitoring will be performed as outlined in the protocol.
[h] Heart rate, blood pressure, and respiratory rate are collected preinfusion, every 15 minutes (±5 minutes) during the infusion, at the end of the infusion, and 1 hour (±15 minutes) postinfusion. Body temperature will be collected preinfusion on dosing days.
[i] Clinical safety labs include serum chemistry, hematology, urinalysis, and coagulation. Labs are collected preinfusion at dosing visits.
[j] 12-lead ECGs are collected after 5 minutes of rest, in triplicate and at least 1-2 minutes apart. ECGs are collected within 2 hours prior to the start of the infusion. Unscheduled ECGs may be performed as clinically necessary.
[k] Blood samples for PK and PD are collected within 2 hours prior to the start of the infusion at dosing visits. An additional sample is collected via peripheral IV 1 hour (+ 30-minute window) after completion of the infusion on Day 700 (PK only).
[l] Blood sample for anti-SRK-015 antibody testing is collected within 2 hours prior to the start of the infusion at dosing visits.
[m] See Table 5 for motor function outcome measures conducted for each cohort. Unscheduled motor function outcome measures may be performed as needed.
[n] QOL collected using the PROMIS Fatigue Questionnaire and PEDI-CAT. If the PEDI-CAT and/or PROMIS are not available in the native language, they should not be completed. Unscheduled QOL questionnaires may be performed as needed.
[o] Patients may consent to participate in Extension Period A at any time prior to V15/E1 or at V15/E1.

Table 5: Study Schedule of Assessments: Extension Period B (Extension B Visits 1-15)

Activity/Assessment	Extension Period B														Follow-Up/ Other	
Visit Time Point (Study Day[d])	EB1[c] 728	EB2 756	EB3 784	EB4 812	EB5 840	EB6 868	EB7 896	EB8 924	EB9 952	EB10 980	EB11 1008	EB12 1036	EB13 1064	EB14 1092	EB-UNS	EB15 1176 /EOS/ET
Informed Consent[a]	X															
Pregnancy Test[c]	X		X				X				X					X
Weight[d]	For patients who enroll into Extension Period B, assessments will merge between Extension Period A Day 728 (E14) and Extension Period B Day 728 (EB1). Study drug administration will only be performed for patients who enroll into Extension Period B.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height[e]					X				X					X	X	X
Physical Examination[f]		X		X		X		X		X		X		X	X	X
Vital Signs[g]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Safety Labs[h]		X			X			X			X		X		X	X
12-lead ECG[i]		X			X			X			X				X	X
PK and PD Sampling[j]	X	X			X			X			X		X		X	X
Antidrug Antibody Sampling[k]	X	X			X			X			X		X		X	X
Study Drug Administration	X	X	X	X	X	X	X	X	X	X	X	X	X			
Motor Function Outcome Measures[b,e,l]					X				X					X	X	X
QOL[m]					X				X					X	X	X
Adverse Events	*To be collected from the date that the ICF is signed through the last study visit*															
Concomitant Therapy	*To be collected from the date that the ICF is signed through the last study visit*															

ECG = electrocardiogram; EOS = end-of-study; ET = early termination; ICF = informed consent form; IV = intravenous; PD = pharmacodynamic; PROMIS = Patient-reported Outcomes Measurement Information System; PK = pharmacokinetic; PROMIS = Patient-reported Outcomes Measurement Information System; QOL = quality of life; UNS = unscheduled.

[a] Study visits have a ±7-day window. Visit assessments may be conducted over multiple days within the visit window, as needed and in compliance with protocol requirements for the timing of each assessment.

[b] All motor function outcome measures will be conducted within 96 hours prior to dosing.

[c] Females of childbearing potential only. Urine or serum test is acceptable; however, positive urine tests must be confirmed with serum testing. Testing may be performed more frequently as per local requirements. The urine pregnancy test used is the Alere hCG cassette (25mIU/mL) and according to the product manufacturer, has >99% sensitivity.

[d] Weight is collected within 48 hours of each dose to calculate weight-based dosing.

[e] Height is collected at visits where the motor function outcome measures are conducted. Ulna length may be used to estimate height for patients who are nonambulatory or not able to stand independently.

[f] Changes in pubertal development must be assessed if not deemed physically mature during Extension Period A. If menarche occurs during the study, the child will be deemed of childbearing potential and immediate pregnancy status will be checked. Further study drug can only be given if pregnancy status is negative. Contraception and pregnancy monitoring will be performed as outlined in the protocol.

[g] Heart rate, blood pressure, and respiratory rate are collected preinfusion, every 15 minutes (±5 minutes) during the infusion, at the end of the infusion, and 1 hour (±15 minutes) postinfusion. Body temperature will be collected preinfusion on dosing days.

[h] Clinical safety labs include serum chemistry, hematology, urinalysis, and coagulation. Labs are collected preinfusion- at dosing visits.

[i] 12-lead ECGs are collected after 5 minutes of rest, in triplicate and at least 1-2 minutes apart. ECGs are collected within 2 hours prior to the start of the infusion. Unscheduled ECGs may be performed as clinically necessary.

[j] Blood samples for PK and PD are collected within 2 hours prior to the start of the infusion at dosing visits. An additional sample is collected via peripheral IV 1 hour (+ 30-minute window) after completion of the infusion i on Day 1008 (PK only).

[k] Blood sample for anti-SRK-015 antibody testing is collected within 2 hours prior to the start of the infusion at dosing visits.

[l] See Table 5 for motor function outcome measures conducted for each cohort. Unscheduled motor function outcome measures may be performed as needed.

[m] QOL collected using the PROMIS Fatigue Questionnaire and PEDI-CAT. If the PEDI-CAT and/or PROMIS are not available in the native language, they should not be completed. Unscheduled QOL questionnaires may be performed as needed.

[n] Patients may consent to participate in Extension Period B at any time prior to E14/EB1 or at E14/EB1.

[o] Extension Period A Day 728 (E14) and Extension Period B Day 728 (EB1) occur on the same day. Extension Period A E14 will serve as the last Extension Period A visit and Extension Period B EB1 will serve as the first visit for Extension Period B. There will not be any duplicate assessments performed.

2.3 Study Endpoints

2.3.1 Efficacy Endpoints

The efficacy endpoints for each cohort are outlined in Table 6. Functional outcome measures (e.g., HFMSE/Revised Hammersmith Scale [RHS], 6-minute Walk Test [6MWT], World Health Organization [WHO] Motor Milestones, Revised Upper Limb Module [RULM], 30-Second Sit-to-Stand, Endurance Shuttle Nine Hole Peg Test [ESNHPT], or Endurance Shuttle Box and Block Test [ESBBT]) will be conducted and assessed by the Physical Therapist. Requirements for the order of assessments, duration of assessments and rest periods between assessments will be outlined in a separate Physical Therapist training manual. Similarly, total score from each assessment should there be any missing values will be determined per the instrument tool scoring algorithm for these cases.

Study procedures will not be conducted for patients who develop an AE (e.g., musculoskeletal injury) during the study, irrespective of relatedness to study drug, that the Investigator considers would make it unsafe to perform a functional outcome assessment. Upon resolution of the AE, and if the Investigator assesses it would be safe to do so, performance of that study procedure will be resumed at the next scheduled assessment as indicated in Table 3, Table 4, and Table 5.

Table 6: Efficacy Endpoints by Cohort

	Cohort 1	**Cohorts 2 and 3**
Primary:	Change from Baseline in the RHS total score at Day 364 (V15)	Change from Baseline in the HFMSE total score at Day 364 (V15)
Secondary:	• Change from Baseline in the RHS total score at other prespecified timepoints • Proportion of patients achieving various magnitudes of change in RHS score from Baseline • Change from Baseline in the 6MWT • Change from Baseline in the 30- Second Sit-to-Stand • Change from Baseline in the 10-meter Walk/Run (from the RHS) • Change from Baseline in the time to rise from floor (from the RHS)	• Change from Baseline in the HFMSE total score at other prespecified timepoints • Proportion of patients achieving various magnitudes of change in HFMSE score from Baseline • Change from Baseline in the RULM total score • Proportion of patients achieving various magnitudes of change in RULM from Baseline • Change from Baseline in the number of WHO motor development milestones attained • Proportion of patients who attain a new WHO motor development milestone relative to Baseline

Tertiary:	• Change from Baseline in the Pediatric Evaluation of Disability Inventory Computer Adaptive Test (PEDI-CAT) • Change from Baseline in the Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue Questionnaire	• Change from Baseline in time to limitation on the ESNHPT or ESBBT • Change from Baseline in the PEDI-CAT • Change from Baseline in the PROMIS Fatigue Questionnaire **Cohort 3 only:** • Time to therapeutic effect as compared between low- and high-dose SRK-015 [details see section 3.4.3.3]

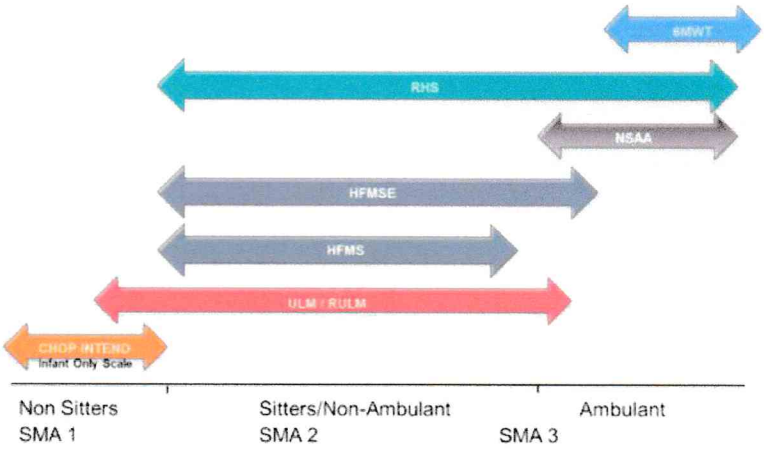
6MWT = 6-minute Walk Test; ESBBT = Endurance Shuttle Box and Block Test; ESNHPT = Endurance Shuttle Nine Hole Peg Test; HFMSE = Hammersmith Functional Motor Scale Expanded; PEDI-CAT = Pediatric Evaluation of Disability Inventory Computer Adaptive Test; PROMIS = Patient-Reported Outcomes Measurement Information System; RHS = Revised Hammersmith Scale; RULM = Revised Upper Limb Module; WHO = World Health Organization.

2.3.1.1 Revised Hammersmith Scale (RHS)

The RHS will be performed for the ambulatory patient subgroup (Cohort 1). Administration of the RHS includes the timed rise from floor and 10-meter Walk/Run tests. The RHS is a 36-item clinical assessment for physical abilities of patients with Type 2 SMA, and ambulatory and nonambulatory patients with Type 3 SMA. The RHS includes 33 items that are graded on a scale of 0, 1, 2, where 0 denotes the lowest level of ability/function and 2 denotes the highest level of ability (Ramsey 2017). The remaining 3 items are scored 0, 1, where 0 denotes an inability and 1 denotes an ability to achieve. The RHS is calculated by the sum of the 36 items and achievable score range is [0, 69].

The RHS for SMA is based on the original HFMSE. Differences are seen on page 44 of the RHS manual. RHS is used for Cohort 1, as it is appropriate for the SMA Type 3 ambulatory patients. Based on the decline in placebo patients in the HFMSE scale by Day 364 in a previous trial across similar cohort groups to this study (e.g., Darras 2019), any population mean increase above baseline would be clinically relevant for either RHS or HFMSE. Additional analyses will be performed on a patient level with success defined as any patient with a change from Baseline of 3 or more at V15 (Day 364). The figure below is an excerpt from Figure 1 in the RHS manual (SMA REACH UK, 2015):

Figure 4: How the RHS Fits in the Continuum of Outcome Measures in RHS



2.3.1.2 10-meter Walk/Run

The 10-meter Walk/Run test is an enhanced function of the RHS used for ambulant patients with Type 3 SMA. It is a measure of the time taken to walk/run 10 meters.

2.3.1.3 Timed Rise from Floor

The timed rise from floor test is an enhanced function of the RHS used for ambulant patients with Type 3 SMA. It is a measure of the time taken to rise to standing from the floor.

2.3.1.4 6-minute Walk Test (6MWT)

The 6MWT is an assessment of exercise capacity and fatigue that has been used in clinical studies of ambulatory later-onset SMA patients (Young 2016). Ambulant patients in Cohort 1 will complete the 6MWT. Patients are directed to walk along a 25-meter course as fast as possible for 6 minutes. The minute distances and total distance walked over 6 minutes are measured.

2.3.1.5 30-Second Sit-to-Stand

The 30-Second Sit-to-Stand test is used by researchers and clinicians as an assessment of functional lower limb strength (Jones 1999). The test was modified for ambulatory SMA population based on recent research of the modified 30-second Sit-to-Stand being a reliable, feasible tool for use in a general geriatric population with a lower level of function (McAllister 2019) and was related to fall risk in institutionalized veterans (Applebaum 2017, Le Berre 2016). The test measures the maximal number of times the patient can transition from sitting to standing in 30 seconds.

2.3.1.6 Hammersmith Functional Motor Scale Expanded (HFMSE)

The HFMSE assesses the physical abilities of patients with Type 2 and Type 3 SMA (O'Hagen 2007; Glanzman 2011) and will be performed for nonambulatory patient subgroups (Cohorts 2 and 3). It consists of 33 items graded on a scale of 0, 1, 2, where 0 denotes unable, 1 denotes performed with modification or adaption, and 2 denotes without modification or adaptation. The HFMSE total score is the sum of all the 33 items and the maximum score is 66.

In conducting the HFMSE test, Question 3 reported the score for both hands. The higher score will be used in calculating the total score.

2.3.1.7 Revised Upper Limb Module (RULM)

The RULM is a 20-item assessment of upper limb function in nonambulatory SMA patients (young children as well as adults) (Mazzone 2017). The 19 scored items test functions that relate to everyday life, such as bringing hands from lap to table, pressing a button, and picking up a token. The items are scored 0, 1, 2, where 0 denotes unable, 1 denotes able with modification, and 2 denotes able with no difficulty. The RULM is calculated by the sum of the 19 items. The maximum score achievable is 37 (since one item only has possible values of 0 or 1). Responses marked as 'Could Not Test' (CNT) will be considered the same as 0 when determining the total score. Non-ambulant patient subgroups (Cohorts 2 and 3) will perform the RULM. The RULM will be completed by patients who are 30 months of age or older at the time of the baseline assessment.

To calculate RULM, where scores for both hands were collected, but only one score is needed, the higher of the two scores will be used to calculate the total score.

2.3.1.8 World Health Organization (WHO) Motor Development Milestones

The WHO Multicentre Growth Reference Study (MGRS) performance criteria are being utilized to assess motor development milestones of patients with Type 2 and nonambulatory Type 3 SMA enrolled in Cohort 2 and Cohort 3. The following table depicts the 6 categories of the milestones (Wijnhoven et al, 2004).

Gross motor milestone	MGRS performance criteria
Sitting without support	Child sits up straight with the head erect for at least 10 seconds. Child does not use arms or hands to balance body or support position
Hands-and-knees crawling	Child alternately moves forward or backward on hands and knees. The stomach does not touch the supporting surface. There are continuous and consecutive movements, at least three in a row
Standing with assistance	Child stands in upright position on both feet, holding onto a stable object (e.g., furniture) with both hands without leaning on it. The body does not touch the stable object, and the legs support most of the body weight. Child thus stands with assistance for at least 10 seconds
Walking with assistance	Child is in upright position with the back straight. Child makes sideways or forward steps by holding onto a stable object (e.g., furniture) with one or both hands. One leg moves forward while the other supports part of the body weight. Child takes at least five steps in this manner

Standing alone	Child stands in upright position on both feet (not on the toes) with the back straight. The legs support 100% of the child's weight. There is no contact with a person or object. Child stands alone for at least 10 seconds
Walking alone	Child takes at least five steps independently in upright position with the back straight. One leg moves forward while the other supports most of the body weight. There is no contact with a person or object

2.3.1.9 Endurance Shuttle Nine Hole Peg Test (ESNHPT)

The ESNHPT is an endurance test for severely affected patients with SMA. Patients are instructed to repeatedly perform the original 9 Hole Peg Test at 75% of their individual maximum speed. The shuttles refer to the set speed marked by auditory cues, with the test ending when the patient missed 2 consecutive beeps. Primary outcome parameter is 'time to limitation (Tlim)', the time a task can be maintained at the preset intensity. Maximum test duration is 20 minutes (Stam 2018). Non-ambulant patients who score ≤3 on Item A of the RULM at Screening will perform the ESNHPT at Screening and all subsequent assessments. If a patient maxes out of an endurance test, the PT Advisory Board will be consulted to potentially change assessment designation. The ESNHPT will be completed by patients who are or will turn 8 years of age or older during the study. Patients who turn 8 years of age in Extension Periods A or B who score ≤3 on Item A of the RULM at Screening should perform the ESNHPT as early as possible (preferred to begin at E1) and all subsequent visits until the end of the study.

2.3.1.10 Endurance Shuttle Box and Block Test (ESBBT)

ESBBT is an endurance test for moderately affected patients with SMA. Patients are instructed to repeatedly perform the original Box and Block Test at 75% of their individual maximum speed. The shuttles refer to the set speed marked by auditory cues, with the test ending when the patient missed 2 consecutive beeps. The primary outcome parameter is 'time to limitation (Tlim)' being the time a task can be maintained at the pre-set intensity. Maximal test duration is 20 minutes (Stam 2018). Non-ambulant patients who score >3 on Item A of the RULM at Screening will perform the ESBBT at Screening and all subsequent assessments. If a patient maxes out of an endurance test, the PT Advisory Board will be consulted to potentially change assessment designation. The ESBBT will be completed by patients who are or will turn 8 years of age or older during the study. Patients who turn 8 years of age in Extension Periods A or B who score >3 on Item A of the RULM at Screening should perform the ESBBT as early as possible (preferred to begin at E1) and all subsequent visits until the end of the study.

2.3.1.11 Pediatric Evaluation of Disability Inventory Computer Adaptive Test (PEDI-CAT)

A caregiver (who may or may not be a parent and/or legal guardian) must complete the PEDI-CAT Assessment. The PEDI-CAT Assessment should not be administered if a caregiver is not present. The PEDI-CAT Assessment should not be administered to the patient. The PEDI-CAT is a questionnaire completed by the caregiver that assesses the patient's ability to perform daily functions (Haley 2005). The PEDI-CAT is filled out by the caregiver in a location where they are not watching the patient perform any functional assessment tests. The same

caregiver must fill out the assessment throughout the study duration. The answers are scored on a 4-point scale (unable to easy). The test is suitable to assess function in newborns to 21-year-olds; this questionnaire should be completed throughout the duration of the study (regardless of age). Properties of the PEDI-CAT have been studied in the SMA population. A Rasch analysis with results published in 2016 revealed that the distribution of abilities for the Mobility and Daily Activities domains of the PEDI-CAT are best represented in the Type 2 and Type 3 populations (Pasternak 2016). As the PEDI-CAT is an age-dependent questionnaire, a patient's full date of birth is required for accurate assessment.

2.3.1.12 Patient-reported Outcomes Measurement Information System (PROMIS)

The PROMIS is a person-centered measure intended to be completed by the patient or parent proxy without help from anyone (Ader 2007). The PROMIS includes 8 items and achievable range is [8, 40]. The fatigue profile domain measures a range of symptoms, from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion. The self-report measures are suitable for children 8-17 years old and the parent proxy report measures are suited for children 5-17 years old. If a caregiver completes this form, the same caregiver must complete the form throughout the study duration. Patients age 18 through 21 will complete an adult form of PROMIS. The PROMIS will be completed by patients who are or will turn 5 years of age or older at the time of the baseline assessment; the same questionnaire used at Screening should be used throughout the duration of the study (regardless of age).

The PROMIS assessments will be analyzed separately for each type of assessment identified as follows: adult form assessments, pediatric form assessments, and parent proxy assessments.

2.3.2 Safety Endpoints

In this study, safety will be evaluated based on occurrence of:

- Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs); and
- Concomitant medications.

or changes from baseline in the following parameters:

- Vital signs, including blood pressure, heart rate, body temperature, and respiratory rate;
- Height and weight;
- Physical examinations;
- Laboratory assessments (hematology and coagulation, serum chemistry, urinalysis);
- 12-lead electrocardiogram (ECG); and
- Concomitant medications.

2.3.2.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical trial patient administered a pharmaceutical product that does not necessarily have to have a causal relationship with the treatment administered. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not it is related to the medicinal product.

- AEs may be new events or may be pre-existing conditions that have become aggravated or have worsened in severity, seriousness or frequency from Baseline at any time during the study.
- AEs may be clinically significant changes from Baseline in physical examination, laboratory tests, or other diagnostic investigation (e.g., laboratory results, x-ray findings).

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or later.

The severity of AEs will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. The causal relationship between the study drug and the AE will be assessed using one of the following categories:

- Not Related: Factors consistent with an assessment of Not Related include:
  - Temporal relationship is lacking (e.g., the event did not occur within a reasonable time frame following administration of the study drug); or
  - Other causative factors more likely explain the event (e.g., a pre-existing condition, other concomitant medications).
- Related: Factors consistent with an assessment of Related include:
  - There is a positive temporal relationship (e.g., the event occurred within a reasonable time frame following administration of study drug); or
  - The AE is more likely explained by the investigational product than by another cause (e.g., the AE shows a pattern consistent with previous knowledge of the investigational product or the class of the investigational product).

2.3.2.2 Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as those AEs satisfying one of the following:

- Occur after the first administration of study drug; or
- Occur prior to the administration of study drug and worsen in severity/grade or relationship to investigational medication after the administration of study drug.

2.3.2.3 Serious Adverse Events

An SAE is any adverse event occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening experience; Note: "Life-threatening" refers to a situation in which the patient was at risk of death at the time of the event; it does not refer to an event that might have caused death if it were more severe.
- Inpatient hospitalization or prolongation of existing hospitalization. The following are excluded as per this criterion:
  - Emergency room visits/hospital admissions for AEs less than 24 hours in duration do not meet SAE criterion unless they meet any of the other SAE criteria in this list.
  - A scheduled or elective hospitalization for medical/surgical procedure planned prior to informed consent for a pre-existing condition that has not worsened from Baseline during participation in the study. However unexpected complications

and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- Persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly or birth defect
- Is considered to be an important medical event: Important medical events are those that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

2.3.2.4 Vital Signs

Vital signs include blood pressure, heart rate, body temperature, and respiratory rate. Vital signs will be collected according to the schedule of assessments provided in Table 3, Table 4, and Table 5.

2.3.2.5 Height, Weight and Body Mass Index (BMI)

Weight will be collected within 48 hours of each dose in order to calculate weight-based dosing, and height will be collected at visits where the motor function outcome measures are conducted.

Standing height will be collected for all individuals who are able to independently stand. Surrogate height may be estimated using ulna length if the patient is nonambulatory or needs standing support.

The Gauld's equation (Gauld 2004) that is used for calculated height (in cm) using ulna length, for males:

$$Estimated\ height\ =\ (4.605 * ulna\ length) + (1.308 \times age^{*}) + 28.003$$

and for females:

$$Estimated\ height\ =\ (4.459 * ulna\ length) + (1.315 \times age^{*}) + 31.485$$

Where age^{*} is the patient's age if under 18, and 18 if patient is 18 or older.

The BMI will be derived as,

$$BMI\ = \frac{Weight\ in\ kg}{(Height\ in\ cm\ /\ 100)^{2}}.$$

2.3.2.6 Physical Examination

A complete physical examination will be performed by the Investigator or a qualified designee according to the schedule of assessments provided in Table 3, Table 4, and Table 5. The findings of each examination will be recorded on the source documents and eCRF. The physical examination will include an assessment of the following: general appearance, skin, lymph nodes,

head-eyes-ears-nose-throat, neck, abdomen, extremities, and the respiratory, cardiovascular, musculoskeletal, and neurologic body systems.

2.3.2.7 Electrocardiogram

A 12-lead ECG will be collected at the times indicated in Table 3, Table 4, and Table 5. ECGs are to be performed with the patient having rested for at least 5 minutes before each reading. ECGs are to be performed in triplicate, each approximately 1 to 2 minutes apart. On infusion days, ECG will be collected within 2 hours prior to the start of the infusion. ECGs will be sent to a central reading vendor for assessment.

2.3.2.8 Laboratory Testing

Laboratory testing (eligibility screening, serum chemistry, hematology, urinalysis, and coagulation, PK and PD sample draw, and ADA testing) will be performed using established methods at the times indicated in Table 3, Table 4, and Table 5. All safety laboratory analyses will be performed at a central laboratory.

The following hematology and coagulation parameters will be assessed:

- Hemoglobin
- Red blood cell count
- Hematocrit
- White blood cell count with differential
- Absolute platelet count
- Mean corpuscular hemoglobin
- Mean corpuscular hemoglobin concentration
- Mean corpuscular volume
- Activated partial thromboplastin time (APTT)
- Prothrombin Time/International Normalized Ratio (PT/INR)

The following serum chemistry parameters will be assessed:

- Albumin
- Alanine aminotransferase
- Alkaline phosphatase
- Aspartate aminotransferase
- Bilirubin (total and direct)
- Blood urea nitrogen
- Calcium
- Carbon dioxide
- Chloride
- Creatinine
- Creatine phosphokinase
- Gamma-glutamyl transferase
- Glucose
- Pregnancy (females only)
- Lactate dehydrogenase
- Magnesium
- Phosphate
- Potassium
- Sodium
- Total cholesterol
- Total protein
- Triglycerides
- Uric acid

The following urinalysis parameters will be assessed:

- Bilirubin
- Blood microscopy (if urinalysis is abnormal)
- Glucose
- Ketones
- Nitrite
- pH
- Protein
- Specific gravity

2.3.3 Pharmacokinetics (PK), Pharmacodynamics (PD), and Immunogenicity Endpoints

2.3.3.1 Pharmacokinetics Blood Sample Collection

Blood samples for the measurement of SRK-015 concentrations will be obtained prior to study drug infusion as indicated in the schedule of assessments in Table 3, Table 4, and Table 5. In the Treatment Period, the 2-hour (± 1 hour) postdose (from the stop of the infusion) sample collection on Day 0, Day 140, and Day 336 must be collected via peripheral venipuncture. In Extension Periods A and B, the 1-hour (+30-minute window) postdose (from the stop of the infusion) sample collection on Day 700 and Day 1008 must be collected via peripheral venipuncture.

Each collected sample will be split into approximately equal volume sample sets to allow for retesting, if required. Aliquots from the PK blood samples may be used for additional immunogenicity or PD testing as appropriate, and Baseline and postdose samples may be used to support PK, PD and/or ADA assay validation.

2.3.3.2 Pharmacodynamics Blood Sample Collection

Blood samples will be collected for the measurement of latent myostatin levels. These blood samples will be obtained prior to infusion as indicated in the schedule of assessments in Table 3, Table 4, and Table 5. The 2-hour (+30-minute window) postdose (from stop of infusion) sample collection on Day 0 must be collected via peripheral venipuncture.

Each collected sample will be split into approximately equal volume sample sets to allow for retesting, if required. Aliquots from the PD blood samples may be used for additional PK or immunogenicity testing as appropriate, and Baseline and postdose samples may be used to support PK, PD, and/or ADA assay validation.

2.3.3.3 Immunogenicity Blood Sample Collection

Blood samples for the measurement of anti-SRK-015 antibodies will be obtained prior to infusion as indicated in the schedule of assessments in Table 3, Table 4, and Table 5.

Each collected sample will be split into approximately equal volume sample sets to allow for retesting, if required. Aliquots from the immunogenicity samples may be used for additional PK or PD testing as appropriate, and Baseline and postdose samples may be used to support PK, PD, and/or ADA assay validation.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

The primary analysis will focus on safety and efficacy data up to V15 (Day 364), which will be referred as the 12-month analysis. The interim analysis will focus on safety and efficacy data up to V8 (Day 168). Extension Period analyses where the focus will be safety and efficacy data in

the Extension Period will be carried out separately. The method used in the 12-month analysis will be applied for the Extension Periods and the analyses of the Extension periods will be considered exploratory.

3.1.1 Analysis Day

Analysis day will be calculated using the first dose date of study drug as the reference. Analysis day = date - date of first dose +1 according to Clinical Data Interchange Standards Consortium (CDISC) standards. The day the patient takes the first dose is Analysis Day 1. The day before Analysis Day 1 is Analysis Day -1.

3.1.2 Analysis Visits

Scheduled post-baseline assessments will be assigned to an analysis visit based on the visit captured in EDC. Unscheduled post-baseline and early termination assessments for motor function outcome measures will be assigned to an analysis visit based on the calculated Analysis Day and windows defined in the following table:

Visit	Analysis Visit	Analysis Day Target	Analysis Day Window
Visit 4/Day 56	Visit 4/Week 8	57	44 - 99
Visit 6/Day 112	Visit 6/Week 16	113	100 – 155
Visit 8/Day 168	Visit 8/Week 24	169	156 - 211
Visit 10/Day 224	Visit 10/Week 32	225	212 - 267
Visit 12/Day 280	Visit 12/Week 40	281	268 – 351
Visit 15/Day 364	Visit 15/Week 52	365	352 - 379
Visit 16/Day 392	Visit 16/Week 56	393	380 - 421
Visit 17/Day 448	Visit 17/Week 64	449	>421
Visit E1/Day 364 …	Visit E1/Week 52	365 …	352-379 (target date-13 days to the next target date - 14 days)

For each analysis visit, if a scheduled visit is captured in EDC, then the measurement from this scheduled visit will be used as the measurement for the analysis visit. If no scheduled visit is captured in EDC, the unscheduled measurement within the window closest to the target date will be used. Visits that occurred outside a +/- 28-day window of the target date used as analysis visits will be listed. For safety measurements, unscheduled and ET visits will not be re-assigned and will be listed, and the ET visit will be summarized separately.

3.1.3 Definition of Baseline

Baseline for all efficacy and safety variables will be defined as the last measurement prior to the first dose of study drug.

3.1.4 Summary Statistics

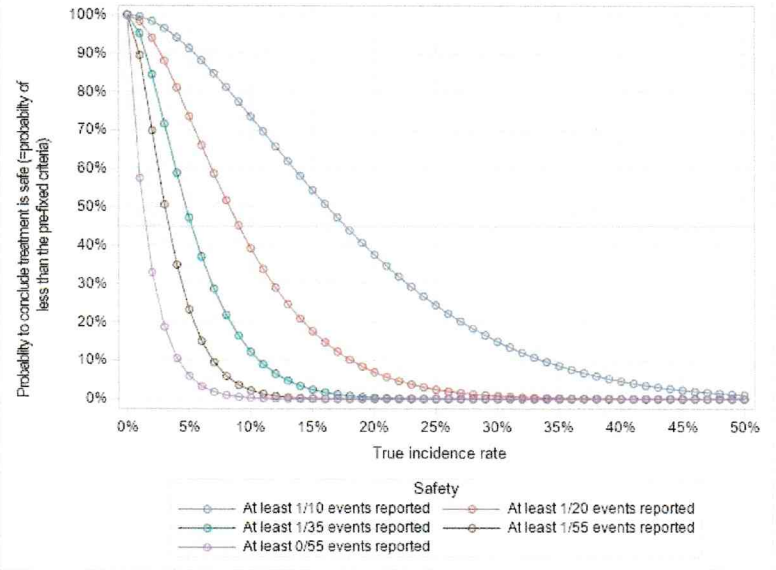
Descriptive statistics (number of patients, mean, standard deviation, median, minimum, and maximum) will be used to summarize the continuous data. Discrete measures will be summarized using counts and percentages.

3.1.5 Hypothesis Testing

No formal statistical testing will be applied for the interim or 12-month analyses.

Regarding safety, the purpose is to estimate the event rates. The figure below can serve as a guideline to inform safety. For example, for a given event type if an event rate of 1/35 or more would be of safety concern, and the true rate of this type of event is 5%, then there is about a 50% probability to report such concern in the study.

Figure 5: Probability of the True Incidence Rate as Shown Will Be Identified Under Different Scenarios as the Number of Patients in the Study Accrue



3.1.6 Evaluation of Site Effect

This is a multicenter study enrolling patients from approximately 20 study sites across the United States and Europe. Site effect will not be evaluated for any planned analysis since the number of patients at each site is expected to be too small for such evaluation.

3.1.7 Handling of Dropouts and Missing Data

3.1.7.1 Missing or Incomplete Dates

Dates will be printed in ISO 8601 date format (YYYY-MM-DD). If only year and month are available, date will be displayed as YYYY-MM. If only year, then just YYYY. Dates that are

missing because they are not applicable for the patients will be output as "NA", unless otherwise specified.

Adverse events with missing start dates will be considered as treatment-emergent unless the partial date excludes that possibility, e.g., the adverse event month is prior to the study drug administration month. Otherwise, the first day of the month will be used to impute missing start days and January will be used to impute missing start months. If the causality for an adverse event is missing, the adverse event will be assumed to be related.

3.1.7.2 Missing Primary Efficacy Endpoints

For continuous endpoints, where applicable, the last observation carried forward (LOCF) method will be used for missing data, where the patient's last non-missing value (including baseline) will be used to impute the missing value if a patient is lost to follow-up. For the interim analysis, if there are patients who missed V8 (Day 168) but have V9 (Day 196) or V10 (Day 224) efficacy data, then V9 (Day 196) or V10 (Day 224) data, whichever were obtained earlier, will be used to fill in the gap. For the 12-month analysis, the LOCF method will be used in the descriptive analyses (see Section 3.1.7.3 for intercurrent event handling due to site restriction).

In calculating HFMSE and RHS, if 20% or fewer items are missing, then these items will be imputed to be 0 (unable) when summing all 33 items. If greater than 6 items are missing, then the total score will be set to be missing.

3.1.7.3 Intercurrent Event Caused by COVID-19

The Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency Guidance for Industry states the following: "For a trial with sites closed for a period of time because of COVID-19, the missing endpoint ascertainments during this period may not necessarily be related to the treatment assignment or participant characteristics and outcomes. In this case, removing all participants from closed sites who were scheduled for an endpoint ascertainment from the analysis should not bias the findings.... if the closure of a site for a certain period of time greatly impacts trial specified treatment for participants such that it is unlikely that any treatment effect can be observed, then it may be reasonable to exclude participants who were impacted during that period of time" (FDA, June 2020).

Following this guidance, if a patient misses 3 consecutive doses or more due to site access restriction caused by the COVID-19 public health emergency, the assessments after the dose interruption will be treated as missing in the analysis. A sensitivity analysis including all data collected will be conducted (see Section 3.2.1).

3.2 Analysis Populations

3.2.1 Intention-to-Treat (ITT) Population

The ITT Population is defined as all enrolled/randomized patients (enrolled for Cohort 1 and 2 and randomized for Cohort 3) who receive at least one dose of study drug. The ITT Population will be the main population for analysis of efficacy endpoints; the analysis will include all assessments from all patients with the exception of the missing assessments due to missing 3 doses, whereas a sensitivity analysis will include all assessments from all patients. The ITT and Safety Populations (see definition in Section 3.2.3) are identical except in the case that any patient in Cohort 3 was not dosed as randomized. The ITT Population is analyzed as randomized.

3.2.2 Per-Protocol (PP) Population

The PP Population is defined as all patients in the ITT Population who completed the study with no major protocol deviations that may impact the primary efficacy assessment. The PP Population will be a secondary population for analysis of the primary efficacy endpoint. Major protocol deviations that may impact the primary efficacy assessment may include but are not limited to:

- Failed to meet eligibility criteria;
- Took the wrong study drug (i.e., did not take the randomized study drug or full dose);
- Had study drug compliance <80%;
- Took a restricted concomitant medication; or
- Failed to complete the efficacy assessment at certain time points.

A list of patients with major protocol deviations leading to exclusion from the PP Population will be finalized prior to the Sponsor's review of the efficacy data and before unblinding of the randomized treatment assignments.

3.2.3 Safety Population

The Safety Population is defined as all enrolled/randomized patients who receive at least one dose of study drug. All safety data will be analyzed using the Safety Population. In the event that a patient takes the wrong study drug (i.e., did not take the randomized study drug), the actual treatment received will be used for analysis. The ITT Population is the same as the Safety Population except in the case that any patient in Cohort 3 was not dosed as randomized. The Safety Population is analyzed as treated.

3.2.4 Pharmacokinetic Population

The PK Population will include all patients who are enrolled/randomized and receive at least 1 dose of study drug and have at least 1 quantifiable concentration of PK sample.

3.2.5 Pharmacodynamics Population

The PD Population will include all patients who are enrolled/randomized and receive at least 1 dose of study drug and have at least 1 quantifiable post-baseline PD measurement.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

The following disposition categories will be presented:

- Patients who were enrolled/randomized,
- Patients who completed the Treatment Period of interest at the analysis, and
- Patients who completed the follow-up period.

For patients who did not complete the Treatment Period of interest at the analysis, a summary will be provided for the primary reason of discontinuation.

3.3.2 Protocol Deviations

Protocol deviations will be identified based on the clinical data as defined in the Protocol Deviation Plan. The Protocol Deviation Plan will define all protocol deviations as either CSR reportable or

non-CSR reportable deviations. Counts and percentages of patients with CSR reportable protocol deviations by deviation category will be summarized within each cohort and by dose within Cohort 3 for the ITT Population for the 12-month analysis.

3.3.3 Analysis Populations

Counts and percentages of patients in each analysis population will be summarized by cohort, dose (for Cohort 3), treated with background SMA therapy (for Cohort 1), and in total based on all enrolled/randomized patients.

3.3.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age at Informed Consent (years),
- Age at Diagnosis (years)
- Sex,
- Race,
- Ethnicity,
- SMA History (including SMA type, contractures, and scoliosis),
- Number of Maintenance Doses Received,
- SMN2 Gene Copy Number,
- Height (cm),
- Weight (kg), and
- Body Mass Index (kg/m^2)

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of patients as appropriate by treatment within each cohort and in total for the ITT, Safety (if different from ITT), and PP populations.

3.3.5 Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or later. Counts and percentages of patients with medical history by system organ class and preferred term will be summarized by treatment within each cohort and in total for the Safety and PP populations.

Medical history capturing the patient's SMA history as well as current and past relevant medical status (surgeries, allergies, and concomitant medications) will be listed.

3.3.6 Prior/Concomitant Medications

Prior medications are any medications stopped prior to the administration of study drug. Concomitant medications are any non-study medications taken concurrently while on study drug, regardless of when the non-study medications are started or ended.

Prior/concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the WHO Drug Mar 2020 or later.

Counts and percentages of patients taking prior and concomitant medications by ATC class and preferred term will be summarized by treatment within each cohort and in total for Safety and PP populations.

3.3.7 Study Drug Exposure and Compliance

Weeks of exposure = (date of analysis Visit or lost to follow-up - date of first dose + 1)/7. Note that the study drug exposure calculation is intended to describe the length of time a patient was exposed to study drug and therefore does not take study drug interruptions into account.

Compliance will be summarized with descriptive statistics for the study overall based on treatment duration and number of infusions from the eCRFs and also based on treatment duration and number of infusions from the EDC.

Compliance = 100 × (number of injections) ÷ (treatment duration in weeks / 4).

For the 12-month analysis, if a patient completed the 52-week Treatment Period per protocol, they should have 13 infusions (1-infusion every 4 weeks). For patients entering Extension Period A, the dose administered at V15/E1 will not be counted as part of the Treatment Period and will considered as part of the Extension Period. Percent compliance to the study drug regimen will be summarized by treatment within each cohort for the Safety and PP populations with descriptive statistics and with counts and percentages of patients with compliance in the following categories:

- <80%
- 80-120%
- >120%

The compliance for the Extension Period will be calculated separately from the Treatment Period.

3.4 Efficacy Assessment

The study is regarded as 3 separate cohorts. In general, efficacy endpoints will be analyzed for each cohort separately. Cohort 1 will be analyzed as total, and by patients who received SRK-015 as monotherapy or in addition to a SMN up-regulator therapy. Cohort 3 will be analyzed as total, and by dose level.

The ITT Population will be the main analysis population for efficacy parameters. Section 3.1.7.3 specifies intercurrent events caused by the COVID-19 public health emergency. Accordingly, a sensitivity analysis will be performed as defined in Section 3.2.1. The efficacy parameters will be evaluated for the PP Population as further sensitivity analyses.

3.4.1 Cohort 1: High Dose

3.4.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from Baseline at V15 (Day 364) in RHS total score. Summary statistics will be generated along with the 95% CI based on the Student's t-distribution for the change from Baseline.

The cohort will be analyzed as total and by patients who received SRK-015 as monotherapy and in addition to a SMN upregulator therapy.

A waterfall plot of unit changes from baseline in functional scores will be displayed for each post-baseline visit.

3.4.1.2 Secondary Efficacy Endpoints

The following secondary endpoints will be analyzed for Cohort 1:

- Change from Baseline in RHS score at prespecified timepoints
- Proportion of patients achieving various magnitudes of change in RHS score from Baseline to scheduled visits. For example, proportion of patients achieving (at least) 5 points, 4 points, 3 points, 2 points or 1 point increase in RHS score from baseline to V15 (Day 364), V8 (Day 168) and all other scheduled visits.
- Change from Baseline in 6MWT to V15 (Day 364), V8 (Day 168) and all other scheduled visits
- Change from Baseline in 30-Second Sit-to-Stand to V15 (Day 364), V8 (Day 168) and all other scheduled visits
- Change from Baseline in 10-meter Walk/Run (from the RHS) to V15 (Day 364), V8 (Day 168) and all other scheduled visits
- Change from Baseline in timed rise from floor (from the RHS) to V15 (Day 364), V8 (Day 168) and all other scheduled visits.

For continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum, maximum) will be provided. The baseline, post-baseline values and changes from baseline will be included, and a 95% CI will be provided for change from Baseline. Mean change from Baseline over time and the corresponding standard errors will be reported graphically.

For categorical variables, frequency tables will be provided to display the number and percentage of patients in each category at each visit.

3.4.1.3 Tertiary Efficacy Endpoints

The following tertiary endpoints will be analyzed for Cohort 1,

- Change from Baseline in PEDI-CAT; and
- Change from Baseline in PROMIS Fatigue Questionnaire.

For continuous variables, descriptive statistics (n, mean, standard deviation, median, minimum, maximum) will be provided. The baseline, post-baseline values and changes from Baseline will be included.

For categorical variables, frequency tables will be provided to display the number and percentage of patients in each category and change from Baseline at each visit.

For questionnaires with different domains, the summaries for scores and change from Baseline in each domain and in total will be summarized.

3.4.2 Cohort 2: High Dose

3.4.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from Baseline to Day 364 (V15) in HFMSE total score. Summary statistics will be generated along with the 95% CI based on the Student's t-distribution for the change from Baseline.

3.4.2.2 Secondary Efficacy Endpoints

The following secondary endpoints will be analyzed for Cohort 2,

- HFMSE total score change from Baseline at prespecified timepoints
- Proportion of patients achieving various magnitudes of change in HFMSE score (e.g., at least 5 points, 4 points, 3 points, 2 points, 1 point) from Baseline to V15 (Day 364), V8 (Day 168) and all other scheduled visits
- Change from Baseline in RULM scores to V15 (Day 364), V8 (Day 168) and all other scheduled visits
- Change from Baseline in number of WHO motor development milestones attained to V15 (Day 364), V8 (Day 168) and all other scheduled visits
- Proportion of patients achieving various magnitudes of change in RULM score from Baseline to V15 (Day 364), V8 (Day 168) and all other scheduled visits
- Proportion of patients who attain a new WHO motor development milestone relative to Baseline at V15 (Day 364), V8 (Day 168) and all other scheduled visits.

The same analysis method as the primary efficacy analysis in Cohort 2 will be used for RULM. The same analysis method as the secondary efficacy analysis in Cohort 1 will be used for the rest of the variables.

3.4.2.3 Tertiary Efficacy Analyses

The following tertiary endpoints will be analyzed for Cohort 2:

- Change from Baseline in Time to limitation on ESNHPT or ESBBT;
- Change from Baseline in PEDI-CAT (total score and each domain)
- Change from Baseline in PROMIS Fatigue Questionnaire.

The same analysis method as the tertiary efficacy analysis in Cohort 1 will be used.

3.4.3 Cohort 3: Low Dose and High Dose

3.4.3.1 Primary Efficacy Analyses

The primary efficacy endpoint is the change from Baseline to Day 364 (V15) in HFMSE total score in the high-dose arm. This analysis will also be performed to evaluate the low-dose arm as well as the entire Cohort 3 in total (i.e., high-dose arm and low-dose arm pooled together).

The difference in the change from Baseline in HFMSE total score will also be explored using descriptive statistics and the corresponding 95% CI based on the Student's t-distribution will be reported.

3.4.3.2 Secondary efficacy analyses

The following secondary endpoints will be analyzed for Cohort 3:

- Change from Baseline in the HFMSE total score at prespecified timepoints
- Proportion of patients achieving various magnitudes of change in HFMSE score from Baseline to V15 (Day 364), V8 (Day 168) and all other scheduled visits
- Change from Baseline in the RULM total score to V15 (Day 364), V8 (Day 168) and all other scheduled visits
- Proportion of patients achieving various magnitudes of change in RULM from Baseline to V15 (Day 364), V8 (Day 168) and all other scheduled visits

- Change from Baseline in the number of WHO motor development milestones attained to V15 (Day 364), V8 (Day 168) and all other scheduled visits
- Proportion of patients who attain a new WHO motor development milestone relative to baseline at V15 (Day 364), V8 (Day 168) and all other scheduled visits.

The same analysis method as the primary efficacy analysis in Cohort 3 will be used for RULM. The same analysis method as the secondary efficacy analysis in Cohort 1 will be used for the rest of variables.

3.4.3.3 Tertiary Efficacy Analyses

The following tertiary endpoints will be analyzed for Cohort 3:

- Change from Baseline in Time to limitation on ESNHPT or ESBBT to V15 (Day 364), V8 (Day 168) and all other scheduled visits
- Change from Baseline in PEDI-CAT to V15 (Day 364), V8 (Day 168) and all other scheduled visits
- Change from Baseline in PROMIS Fatigue Questionnaire to V15 (Day 364), V8 (Day 168) and all other scheduled visits and
- Time to therapeutic effect as compared between low and high dose SRK-015 arms to V15 (Day 364), V8 (Day 168) and all other scheduled visits.

The same analysis method as the secondary efficacy analysis in Cohort 3 will be used for all tertiary endpoints except the time to therapeutic effect, as compared between low and high dose SRK-015 arms. The time to therapeutic effect will be assessed using Kaplan-Meier life tables. The following therapeutic effects will be examined separately: improvement of at least 3.0 points from Baseline in HFMSE total score, and improvement of at least 2.0 points from Baseline in RULM score.

3.5 Pharmacokinetic Assessment

3.5.1 Sample Collections for Pharmacokinetic Analysis

SRK-015 concentrations and circulating latent myostatin concentrations will be determined using blood samples collected before and after dosing through the final follow-up visit.

3.5.2 Handling Missing or Below the Lower Limit of Quantification Data

The following general rules will apply for the concentration summary and mean plot construction:

- Below the Limit of Quantitation (BLQ) are set to zero for the calculation of these mean values.
- Missing values are excluded from the calculation of these means.

The following rules will be used to handle BLQ for the PK parameter calculation and individual concentration data:

- If BLQ value(s) occurs in a profile before the first measurable concentration, it is assigned as zero concentration for single dose and as lower limit of quantification (LLOQ) for multiple doses.
- If BLQ values occur between measurable concentrations in a profile, the BLQ should be omitted (set to missing).
- If BLQ values occur after the last measurable concentration in a profile, the BLQ should be omitted (set to missing).
- The BLQ at trough is assigned as LLOQ.

In case of missing predose concentration, the missing component is assumed as zero. For the other missing predose cases, the missing data will not be imputed.

3.5.3 Pharmacokinetic Concentration

Individual plasma concentrations of SRK-015 will be summarized by cohort and dose level at each nominal time point for the PK Population descriptively. Individual plasma concentrations will also be listed for the PK Population. The latent myostatin concentrations will be listed for each patient and summarized by separated cohorts.

Individual plasma concentration will be plotted by cohort and dose level on a linear and semi-log scale against actual sampling time points relative to dosing time. Mean (±SD) concentration will be plotted on a linear and semi-logarithmic scale against nominal time points by cohort and dose level, when available. LLOQ will be plotted as a reference line in both instances.

Actual sampling times that are outside the sampling time windows may be excluded from concentration summary and mean concentration plotting but will still be used in the calculations of PK parameters and individual concentration plotting.

3.5.4 Pharmacokinetic Parameters

The following PK parameters will be calculated from the individual concentration, including Day 0 PK concentration data through Day 28 predose concentration data, Day 140, Day 336, and Day 700.

Parameters	Description
C_{max}	Maximum drug concentration; observed directly from the data. If not unique, then the first maximum concentration is used
T_{max}	Time to $C_{max, D1}$
C_{last}	The last measurable concentration
T_{last}	Time of C_{last}
$AUC_{0\text{-}28d}$	Area under the concentration-time curve (AUC) from time 0 to the time of the last measurable concentration (C_{last}) to Day 28 predose
RClast	Accumulation ratio based on C_{last}; calculated as C_{last} after multiple dose divided by C_{last} after the first dose (Days 140, 336, 700)
RCmax	Accumulation ratio based on Cmax; calculated as C_{last} after multiple dose divided by Cmax after the first dose (Days 140, 336, 700)

Actual collection times will be used in PK parameter calculations. The Linear-Log Trapezoidal method (equivalent to the Linear Up/Log Down option in WinNonlin) will be used in the computation of all AUC values.

No PK parameters will be calculated for subjects with 2 or fewer detectable concentrations in their PK profile.

AUC may not be calculated for the subjects that only have one measurable postdose PK concentration.

If a subject has only one non-zero concentration at the 2 hours post dose time point, C_{last} will not be calculated for this subject.

The latent myostatin concentrations will be listed for each patient and summarized by separated cohorts.

The BLQ values of latent myostatin will not be imputed and set as missing.

Anti-drug antibody data will be listed and summarized in tabular format reporting positive count and percentage. Confirmed positive samples will be further tested for the presence of neutralizing activity.

3.6 Safety Assessment

Safety data will be evaluated for vital signs, laboratory outcomes, ECGs, and AEs. Clinically significant outcomes will be noted. All safety analyses will be performed on the Safety Population in each cohort, by cohort, by dose (combining all cohorts), and by patients being treated with and without an approved SMA treatment, and the entire Safety Population.

3.6.1 Adverse Events (AEs)

A summary overview of TEAEs will be provided, which presents the number and percentage of patients in each cohort and dose level from the Safety Population satisfying each of the following categories:

- Any AEs,
- Any SAEs,
- Any TEAEs,
- Any AEs leading to death,
- Any AEs leading to study drug discontinuation,
- Any SAEs leading to death,
- Any SAEs leading to study drug discontinuation,
- Any TEAEs leading to death, and
- Any TEAEs leading to study drug discontinuation,

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or later. The number and percentage of patients with specific criteria will be summarized by their MedDRA preferred term within system organ class and by treatment within each cohort. These summaries will include patients with the following criteria: TEAEs, SAEs, TEAEs with severity of Grade 3 and above, drug related TEAEs, TEAEs present in 5% or more of patients, and various categories of TEAEs by Time (on or before Week 12 vs. Post Week 12). For patient count summaries, multiple AE events with the same MedDRA coded terms (preferred term and system organ class) from the same patient will only be counted once.

The number and percentage of patients with TEAEs will be summarized by reported maximum severity within each MedDRA preferred term within system organ class and by dose-level within each cohort.

All SAEs will be listed with an indication of whether the SAE was treatment emergent or started prior to treatment. All TEAEs that are reported as leading to study drug discontinuation will be listed. TEAEs leading to death, if applicable, will be listed.

3.6.2 Laboratory Assessments

Descriptive statistics for each parameter will be presented for baseline, each visit, and the change from Baseline. The 95% CI based on the Student's t-distribution for the change from Baseline will be presented.

Frequency tables will be provided to display the number and percentage of patients with laboratory abnormalities after administration of study drug.

3.6.3 Vital Signs

Vital signs include heart rate, blood pressure, and respiratory rate. Vital signs parameters will be summarized using descriptive statistics for each visit. The change from Baseline will also be summarized for each visit along with the 95% CI based on the Student's t-distribution.

3.6.4 Electrocardiograms (ECGs)

Summary statistics for continuous ECG parameters and the change from Baseline, along with the 95% CI based on the Student's t-distribution, will be presented by treatment group for each scheduled visit. Counts and percentages of the overall interpretation of the ECG findings will be

presented by treatment group for each scheduled visit. The 12-Lead Electrocardiogram data will be listed by patient.

3.6.5 Physical Examinations

Physical examination includes an assessment of the following: general appearance, skin, lymph nodes, head-eyes-ears-nose-throat, neck, abdomen, extremities, and the respiratory, cardiovascular, musculoskeletal, and neurologic body systems. Physical examination data will be listed by patient.

4 SAFETY SURVEILLANCE TEAM

An SST will review safety data approximately every 12 weeks, and on an ad hoc basis as needed, throughout the duration of the study (inclusive of Treatment, Extension, and Safety Follow-up Periods) to assess patient safety. Safety reviews prepared by the independent Clinical Research Organization will be provided to a core team comprised of the Scholar Rock Medical Director, the Scholar Rock Product Safety Lead, the Medical Monitor, an independent biostatistician, and a physician not participating as an Investigator in the study. To further assist in the safety assessments, the core SST may request that other individuals such as SMA experts or others within their organizations review the data and participate in the discussions. The SST reviews will not include any efficacy data.

The SST may make recommendations to continue the study with no changes, continue the study with changes to the protocol, terminate the study, or require more data, input, and deliberation prior to making a decision. Criteria for study termination are based on the assessment of safety concerns that may arise during the conduct of the study or from data from the SRK-015 preclinical and clinical program. The study may be discontinued at any time at the Sponsor's discretion, or if the SST determines that further drug exposure would pose an undue risk to patients. The responsibilities and actions of the SST will be governed by a separate SST charter.

5 ANALYSIS TIMING

5.1 Interim Analysis

5.1.1 PK and PD Interim Analysis

Prespecified interim analyses to initially evaluate drug exposure (PK) and target engagement (PD) in patients with SMA will be conducted. For Cohorts 1 and 2, this analysis will be conducted after approximately 4 patients in each cohort have received at least 2 doses of SRK-015. For Cohort 3, this analysis will be conducted after approximately 6 patients have received at least 2 doses of SRK-015. Because individual PK data can reveal treatment assignment, only designated personnel will have access to the PK data and treatment assignments for Cohort 3, and the results will be presented in an aggregated manner. No clinical efficacy endpoints will be examined in this PK and PD interim analysis. Data from multiple cohorts may be combined as necessary. Enrollment will continue while the interim analysis is ongoing. Based on these results, and taking into consideration any available safety data, the cohort-specific dose levels may be adjusted. Any adjustment in dose level will not change the frequency of dosing (i.e., every 4 weeks) and the highest dose will not exceed 30 mg/kg, as tested in the Phase 1 study.

A PK and PD analysis will also be performed at the safety and efficacy interim analysis (see 5.1.2) and the relationship of PK, PD, and efficacy response will be examined. The analysis will be

performed by designated personnel who have access to the PK data and treatment assignments for Cohort 3, and the results will be presented in an aggregated manner.

5.1.2 Safety and Efficacy Interim Analysis

Prespecified interim analyses to evaluate the initial safety and efficacy of SRK-015 in SMA patients was planned in the protocol when all enrolled patients complete V8 (Day 168) or are terminated from the study. Interim analyses were to be performed on the selected efficacy endpoints up to V8 (Day 168), in addition to available selected safety outcomes and PK and PD results (see 5.1.1). Due to COVID-19, some patients delayed or skipped V8 (Day 168). The study sites were given instructions that if the actual visit date is > 56 days but $\leq$ 84 days from the previous visit then one visit is considered skipped; if >84 days but ≤ 112 days, two visits are considered to be skipped. In addition, some sites kept patient dosing on schedule (no skipping) but did not perform outcome assessment due to PT department closure. If the outcome assessment is skipped regardless of dosing, the site was instructed to perform an outcome assessment at the next visit, which may be unscheduled. Considering these impacts, the safety and efficacy interim analyses will target all patients who have either a V8 (Day 168) measurement or a post V8 (Day 168) visit if V8 (Day 168) is skipped, but will exclude patients with numerous skipped visits.

The following strategies will be adopted to analyze the primary endpoints and to address the COVID-19 impact, where applicable. Because some cohorts may be affected more than others, the strategies may not apply to all cohorts:

1) Use the earliest of V8 (Day 168), V9 (Day 196), and V10 (Day 224) data, where available, and for those not having V8-V10 not due to COVID-19, LOCF will be applied.
2) For sites closed or patients experiencing travel restrictions/difficulties due to COVID-19 and patients not having V8 (Day 168), V9 (Day 196) and V10 (Day 224) data, those visits will be excluded from the analysis.
3) Descriptive analysis will include the earliest of V8/V9/V10.

Descriptive statistics will be used for Efficacy and Safety endpoints at this interim analysis. For continuous efficacy endpoints, the 95% CI of change from Baseline will also be reported.

5.2 Primary / 12-Month Analysis

A 12-month analysis will be performed when all enrolled patients complete V15 (Day 364) or are terminated from the study. The 12-month analysis will be performed on all available efficacy and safety data as described in the above sections of the SAP. Due to COVID-19, some patients delayed or skipped V15 (Day 364).

The database will be frozen before the 12-month analysis is generated and the process for unfreezing any data will be defined in the Data Management Plan. In addition to TFLs, SDTM data and ADaM data along with associated files will be provided. Associated files may include the following: annotated case report forms (CRFs), SDTM specifications, SDTM programs, ADaM specifications, ADaM programs, TFL programs, and CDISC Define packages for both SDTM and ADaM data.

The result of this analysis will be used for the clinical study report.

5.3 Extension Period Analyses

The analyses performed after the 12-month analysis in the Extension periods will be considered exploratory. The timing and content will be pre-approved by the study team before the analyses are performed.

6 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

The statistical analysis section was updated in protocol version 3.0, dated 21 November 2019, and protocol version 4.0, dated 13 November 2020. Subsequent changes in the statistics of the study are detailed here.

The protocol (Section 11.2.1) states, "Vital signs and laboratory outcomes will be evaluated using paired t-tests within cohorts and unpaired t-tests between the 2 dose groups for Cohort 3; corresponding two-sided 95% CIs will be computed as well for the paired and unpaired differences". In this SAP, descriptive statistics will be used to summarize safety assessments and no statistical testing will be conducted.

The protocol (Section 11.2.2) states, "...proportion and the 95% CI based on Wilson's method will be reported". In this SAP, only the proportion will be reported and the 95% CI for proportion will not be calculated.

The protocol (Section 11.2.2) states, "The primary endpoints and other efficacy continuous endpoints will be analyzed using paired t-tests within cohorts and unpaired t-tests between the 2 dose groups for Cohort 3; corresponding 2-sided 95%. CIs will be computed as well for the paired and unpaired differences." Additionally, the protocol states, "Time to outcome improvement will be assessed using Kaplan-Meier lifetables and a log rank test to compare time to efficacy for Cohort 3 low versus high dose." In this SAP, descriptive statistics will be used to summarize efficacy and no statistical testing will be conducted.

The protocol (Section 11.4.2) states, "Safety data at all visits and efficacy endpoints at Day 168 (Visit 8) will be included in this analysis." Due to data cleaning, efforts were focused on up to V10 (Day 224), the interim analysis will include safety data up to V10 (Day 224).

7 PROGRAMMING SPECIFICATIONS

Statistical analyses will be performed using SAS® (Cary, NC) version 9.4 or above. All available data will be presented in patient data listings, which will be sorted by Cohort, site number, unique patient identifier and where appropriate, visit number and visit/assessment date. For the interim safety and efficacy analysis, efficacy-related listings that may unblind treatment assignment for individual patients will not be delivered to the Sponsor unless the Sponsor requested such and documented accordingly.

The programming specifications, including the mock-up validity listings, analysis tables, figures, and data listings, as well as the derived database specifications, will be prepared in stand-alone documents.

APPENDIX A: REFERENCES

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