22 December 2025

Clinicaltrials.gov Results Posting

Re: SRK-015-003 Results | Protocol

Sponsor:	Scholar Rock, Inc. 301 Binney Street, 3rd Floor Cambridge, MA 02142 USA
Protocol Number:	SRK-015-003 (SAPPHIRE)
Protocol Title:	Phase 3, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Apitegromab (SRK-015) in Patients with Later-Onset Spinal Muscular Atrophy Receiving Background Nusinersen or Risdiplam Therapy
NCT Number:	05156320
Protocol Document Date:	11 June 2024
Statistical Analysis Plan Document Date:	30 August 2024

Thank you,
Regulatory Affairs Record Administrator
Scholar Rock, Inc.
clinicaltrials@scholarrock.com

Scholar Rock
301 Binney Street, 3rd Floor
Cambridge, MA 02142

(857) 259-3860
scholarrock.com

CLINICAL TRIAL PROTOCOL

SRK-015-003

Phase 3, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Apitegromab (SRK-015) in Patients with Later-Onset Spinal Muscular Atrophy Receiving Background Nusinersen or Risdiplam Therapy

Protocol Number:	SRK-015-003
Brief Title:	Phase 3 Active Treatment Trial to Evaluate the Efficacy and Safety of Apitegromab in Patients with Later-Onset Spinal Muscular Atrophy Who Are Being Treated with Nusinersen or Risdiplam
Trial Name:	SAPPHIRE
Indication Studied:	Spinal Muscular Atrophy
Trial Phase:	3
Investigational Product	Apitegromab (SRK-015)
IND Number:	136872
EudraCT Number:	2021-005314-34
Sponsor:	Scholar Rock, Inc. 301 Binney Street, 3rd Floor Cambridge, MA 02142, USA Tel: +1.857.259.3860
Sponsor Contact:	[redacted]
Protocol Date and Version:	29 September 2021, Version 1.0 18 March 2022, Version 1.1 UK (country-specific) 04 April 2022, Version 1.2 FR (country-specific) 14 April 2022, Version 1.3 ES (country-specific) 23 May 2022, Version 1.4 DE (country-specific) 10 June 2022, Version 1.5 IT (country-specific) 03 August 2022, Version 2.0 11 June 2024, Version 3.0

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 trial 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. In addition, I will inform the Principal Investigator and all other [redacted] that becomes available during the conduct of this trial.

[redacted]

Date

[redacted]

Scholar Rock, Inc.

Medical Monitor Contact Information:
Medical Monitor contact information will be provided separately in a study contact list.

INVESTIGATOR'S AGREEMENT

I have read and approve this clinical protocol amendment for Study SRK-015-003 dated DD JUNE 2024. My signature, in conjunction with the signature of the Sponsor, confirms the agreement of both parties that the clinical trial 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.

_____

Institution, State, Country

_____

Printed Name of Principal Investigator

_____

Signature of Investigator

_____

Date

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

Phase 3, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Apitegromab (SRK-015) in Patients with Later-Onset Spinal Muscular Atrophy Receiving Background Nusinersen or Risdiplam Therapy

Brief Title:

Phase 3 Active Treatment Trial to Evaluate the Efficacy and Safety of Apitegromab in Patients with Later-Onset Spinal Muscular Atrophy Who Are Being Treated with Nusinersen or Risdiplam

Trial Rationale:

This Phase 3 trial (Study SRK-015-003) is being conducted in patients ≥2 years old at Screening, who were previously diagnosed with later-onset spinal muscular atrophy (SMA; ie, Type 2 and Type 3 SMA) and are receiving an approved survival motor neuron (SMN) upregulator therapy (ie, either nusinersen or risdiplam), to confirm the efficacy and safety of apitegromab [redacted] therapy to nusinersen and evaluate the efficacy and safety of apitegromab [redacted] therapy to risdiplam.

Spinal muscular atrophy is a whole-body disease (Wirth 2020). Although the SMN-targeted therapies, which include gene therapy (onasemnogene abeparvovec-xioi [ZOLGENSMA®]) and the SMN upregulator (also referred to as SMN corrector) therapies nusinersen and risdiplam, (Section 2.2.2) approved for the treatment of SMA have been shown to significantly improve clinical outcomes by preventing or reducing the decline in motor function, patients may continue to suffer from substantial motor functional impairment because SMN-targeted therapies focus on SMN-dependent pathways and do not directly impact skeletal muscle to reverse the atrophy that has already taken place (Mercuri 2018, Mercuri 2020). Consequently, there remains an unmet medical need for a complementary therapeutic strategy, namely muscle-directed therapy, that may address muscle atrophy and thereby improve motor function in patients with SMA. Through its novel mechanism of action as a selective inhibitor of myostatin activation, apitegromab (SRK-015) has the potential to produce a clinically meaningful effect on motor function in a broad population of patients with SMA who are being treated with background SMN upregulator therapies (eg, nusinersen [SPINRAZA®] or risdiplam [EVRYSDI®]) (SPINRAZA Food and Drug Administration [FDA] Prescribing Information [PI] 2020, SPINRAZA Summary of Product Characteristics [SmPC] 2022, EVRYSDI FDA PI 2022, EVRYSDI SmPC 2022).

Safety data (as of 24 April 2022) and efficacy data (12-month primary analysis) from the Phase 2 trial (Study SRK-015-002) to evaluate the safety and efficacy of apitegromab support the continued development of apitegromab in patients with later-onset SMA receiving treatment with the SMN upregulator nusinersen. Treatment with apitegromab led to improvements in Hammersmith Functional Motor Scale Expanded (HFMSE) scores in patients with Type 2 and nonambulatory Type 3 SMA with no safety risks to date.

Since both nusinersen and the SMN upregulator risdiplam treat the SMN protein deficiency in SMA by increasing the production of functional SMN protein, the positive results with nusinersen support investigating apitegromab [redacted] therapy to risdiplam as well.

Although pediatric patients ≥2 years old will be included in Study SRK-015-003, results for the 12-month primary analysis in Study SRK-015-002 indicate that younger patients (Cohort 3, age range of 2 through 6) had a greater improvement in HFMSE (59% achieved a ≥3-point increase) compared to older patients (Cohort 2, age range of 8 through 19; 29% achieved a ≥3-point increase). In addition, an exploratory post hoc analysis that pooled all patients 2 through 12 years old treated with 20 mg/kg apitegromab from Cohort 2 and Cohort 3 observed a mean HFMSE improvement of 4.4 points from Baseline. As these efficacy data point to the potential benefit of treating patients at an early age, the primary analysis in Study SRK-015-003 will be performed using data from the Main Efficacy Population, which is focused on patients who are 2 through 12 years old at Screening. This same age range was used in the Phase 3 CHERISH trial with nusinersen, in which children ages 2 through 12 with symptomatic SMA were randomized 2:1 (stratified based on Screening age <6 vs. ≥6 years) to receive 4 doses of intrathecal nusinersen (12 mg) vs. the control group during the 15-month trial (Mercuri 2018). Results from CHERISH showed that at the end of the trial, the treatment difference in change from Baseline to Month 15 in mean HFMSE score was a highly clinically and statistically significant 3.9-point improvement for nusinersen vs. a -1.0-point decline for the control group. These effects of nusinersen on HFMSE scores over the 15-month period in CHERISH were more pronounced in younger children (<6 years). In addition, the therapeutic benefit (particularly on the HFMSE outcome measure) of SMN upregulator therapies has not been as well established or characterized in patients ≥12 years old. As a result, it is difficult to reliably estimate a priori the background treatment effect from SMN upregulator therapy alone in patients ≥12 years old in order to determine the appropriate sample size. Focusing on the 2- through 12-year age range as the Main Efficacy Population facilitates a reliably powered trial, while investigation of apitegromab's effect on a broader age range can be achieved through the Exploratory Subpopulation analysis in the 13- through 21-year age range.

Two dose levels (10 mg/kg and 20 mg/kg) will be evaluated for the Main Efficacy Population in Study SRK-015-003. A dose of 20 mg/kg every 4 weeks has been safely administered in patients ranging from 2 through 21 years old over at least 1 year in Study SRK-015-002. Weight-based dosing will be used in Study SRK-015-003 because weight is a strong covariate on clearance of apitegromab (data on file). The randomized, double-blind, dose-exploration cohort (Cohort 3) of Study SRK-015-002 evaluated high-dose (20 mg/kg) vs. low-dose (2 mg/kg) apitegromab. The results of the prespecified 6-month safety and efficacy interim analyses for Cohort 3, including greater improvements in HFMSE scores for the high-dose arm and no identification of safety concerns, supported a change in dose for Cohort 3 patients from low-dose (2 mg/kg) to high-dose (20 mg/kg) apitegromab during the extension periods. The inclusion of the 10 mg/kg dose in Study SRK-015-003 will allow interrogation of a middle dose level (between already assessed 2 and 20 mg/kg dose levels) in the SMA patient population and further assessment of lowest efficacious dose level. The 10 mg/kg dose is expected to increase drug exposure to a greater extent than the 2 mg/kg dose, but lower than the 20 mg/kg dose, as well as further increase target engagement (serum latent myostatin) compared with the 2 mg/kg dose, however to a lesser degree than the 20 mg/kg dose.

Objectives and Endpoints:

Objectives	Endpoints
Main Efficacy Population – Efficacy and Additional Objectives/Endpoints	
Primary Efficacy	
Assess the efficacy of apitegromab compared with placebo using the HFMSE in patients 2 through 12 years old	Change from Baseline in HFMSE total score at 12 months
Key Secondary Efficacy	
Assess the efficacy of apitegromab compared with placebo by measuring changes in upper limb function using the Revised Upper Limb Module (RULM) in patients 2 through 12 years old	Change from Baseline in RULM total score at 12 months
Assess the efficacy of apitegromab compared with placebo based on the number of patients with clinical improvement in patients 2 through 12 years old	Proportion of patients with ≥3-point change from Baseline in the HFMSE total score at 12 months
Assess the efficacy of apitegromab compared with placebo by measuring changes in number of World Health Organization (WHO) motor development milestones in patients 2 through 12 years old	Change from Baseline in number of WHO motor development milestones attained at 12 months
Other Secondary Efficacy	
Further assess the efficacy of apitegromab compared with placebo by evaluating changes in additional motor function outcome measures and changes in HFMSE at other prespecified time points in patients 2 through 12 years old	• Proportion of patients achieving various magnitudes of change in HFMSE score from Baseline at 12 months • Proportion of patients achieving various magnitudes of change in RULM score from Baseline at 12 months • Proportion of patients who attain a new WHO motor development milestone relative to Baseline at 12 months • Change from Baseline in HFMSE total score at other prespecified time points • Change from Baseline in RULM total score at other prespecified time points • Change from Baseline in number of WHO motor development milestones attained at other prespecified time points

Objectives	Endpoints
Additional Efficacy	
Assess the efficacy of apitegromab compared with placebo by measuring changes from Baseline in motor function across the Treatment Period using the HFMSE in patients 2 through 12 years old	Change from Baseline in HFMSE total score across time during the 12-month Treatment Period
Assess the time to therapeutic effect of apitegromab compared with placebo using the HFMSE in patients 2 through 12 years old	Time to therapeutic effect (≥3-point change from Baseline in HFMSE total score) compared between apitegromab and placebo
Additional Other	
Evaluate the effects of apitegromab on patient/caregiver-reported disability, fatigability, and suicidal ideation and behavior in patients 2 through 12 years old	• 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 • Change from Baseline in Assessment of Caregiver Experience with Neuromuscular Disease (ACEND) • Change from Baseline in Columbia-Suicide Severity Rating Scale (C-SSRS)
Main Efficacy Population/Exploratory Subpopulation Combined Secondary Objectives/Endpoints	
Assess safety and tolerability of apitegromab in all randomized patients with later-onset SMA who receive at least 1 dose of apitegromab	Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) by severity
Characterize the pharmacokinetics (PK) of apitegromab in all randomized patients with later-onset SMA who receive at least 1 dose of apitegromab	Apitegromab concentrations in serum from blood samples
Evaluate the pharmacodynamic (PD) effects of apitegromab in all randomized patients with later-onset SMA who receive at least 1 dose of apitegromab	Circulating latent myostatin concentrations in blood samples
Evaluate the immunogenicity of apitegromab in all randomized patients with later-onset SMA who receive at least 1 dose of apitegromab	Presence or absence of antidrug antibody (ADA) against apitegromab in serum from blood samples

Objectives	Endpoints
Exploratory Subpopulation and Main Efficacy Population/Exploratory Subpopulation Combined Additional Objectives/Endpoints	
Assess the efficacy of apitegromab compared with placebo using the HFMSE in patients 13 through 21 years old and in patients 2 through 21 years old	Change from Baseline in HFMSE total score at 12 months
Assess the efficacy of apitegromab compared with placebo based on the number of patients with clinical improvement or stabilization in patients 13 through 21 years old	Proportion of patients with ≥0-point change from Baseline in the HFMSE total score at 12 months
Assess the efficacy of apitegromab compared with placebo based on the number of patients with clinical improvement in patients 2 through 21 years old	Proportion of patients with ≥3-point change from Baseline in the HFMSE total score at 12 months
Assess the efficacy of apitegromab compared with placebo by measuring changes in upper limb function between Baseline and the end of the Treatment Period using the RULM in patients 13 through 21 years old and in patients 2 through 21 years old	Change from Baseline in RULM total score at 12 months
Assess the efficacy of apitegromab compared with placebo by measuring changes in number of WHO motor development milestones in patients 13 through 21 years old and in patients 2 through 21 years old	Change from Baseline in number of WHO motor development milestones attained at 12 months
Further assess the efficacy of apitegromab compared with placebo by evaluating changes in additional motor function outcome measures and changes in HFMSE at other prespecified time points in patients 13 through 21 years old and in patients 2 through 21 years old	• Proportion of patients achieving various magnitudes of change in HFMSE score from Baseline at 12 months • Proportion of patients achieving various magnitudes of change in RULM score from Baseline at 12 months • Proportion of patients who attain a new WHO motor development milestone relative to Baseline at 12 months • Change from Baseline in HFMSE total score at other prespecified time points • Change from Baseline in RULM total score at other prespecified time points • Change from Baseline in number of WHO motor development milestones attained at other prespecified time points

Objectives	Endpoints
Assess the efficacy of apitegromab compared with placebo by measuring changes from Baseline in motor function across the Treatment Period using the HFMSE in patients 13 through 21 years old and in patients 2 through 21 years old	Change from Baseline in HFMSE total score across time during the 12-month Treatment Period
Assess the time to stabilization of effect of apitegromab compared with placebo using the HFMSE in patients 13 through 21 years old	Time to decline (at least a -3-point change from Baseline in HFMSE total score) compared between apitegromab and placebo
Assess the time to therapeutic effect of apitegromab compared with placebo using the HFMSE in patients 2 through 21 years old	Time to therapeutic effect (≥1-point change from Baseline in HFMSE total score) compared between apitegromab and placebo
Evaluate the effects of apitegromab on fatigability, caregiver-reported disability, and suicidal ideation and behavior in patients 13 through 21 years old and in patients 2 through 21 years old	• Change from Baseline in PEDI-CAT • Change from Baseline in PROMIS Fatigue Questionnaire • Change from Baseline in ACEND • Change from Baseline in C-SSRS

Overall Trial Design:

This Phase 3 trial will be conducted at approximately 55 to 60 trial sites globally to evaluate the safety and efficacy of apitegromab compared with placebo [redacted] nusinersen or risdiplam in nonambulatory (as defined in inclusion criterion #6) patients with later-onset SMA. In the Main Efficacy Population, 2 dose levels of apitegromab will be evaluated to further assess the lowest efficacious dose level. Patients will be randomized to receive apitegromab (10 mg/kg or 20 mg/kg) or matching placebo by intravenous (IV) infusion. As outlined in Figure 1, the trial will include Screening, Treatment, and Safety Follow-up Periods.

Approximately 204 male and female patients with later-onset SMA will be randomized into either the Main Efficacy Population (2 through 12 years old at Screening) or the Exploratory Subpopulation (13 through 21 years old at Screening). Patients in the Main Efficacy Population will be randomized separately from the patients in the Exploratory Subpopulation:

- For the Main Efficacy Population, approximately 156 patients who are 2 through 12 years old at Screening will be randomized 1:1:1 double-blind to receive apitegromab 10 mg/kg, apitegromab 20 mg/kg, or placebo every 4 weeks during the 52-week Treatment Period. Randomization for the Main Efficacy Population will be stratified by type of background therapy (ie, nusinersen or risdiplam) and age at initiation of SMN upregulator therapy (≥5 and <5).
- For the Exploratory Subpopulation, a maximum of 48 patients who are 13 through 21 years old at Screening will be randomized 2:1 double-blind to receive apitegromab 20 mg/kg or placebo every 4 weeks during the 52-week Treatment Period. Randomization for the Exploratory Subpopulation will be stratified by type of background therapy (ie, nusinersen or risdiplam).

During the Screening Period (Table 1), 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 before the first dose. Screening motor function outcome measures will be conducted a minimum of 7 days before the first dose. All subsequent motor function outcome measures will be conducted within 96 hours before dosing.

Patient site visits will occur every 4 weeks through the end of the Treatment Period. Dosing every 4 weeks should be targeted. However, a ±7- day window around each dosing visit (with a minimum of 21 days and a maximum of 35 days between doses) is allowed without consultation with the Sponsor. After dosing, patients will be monitored for hypersensitivity reactions at the trial site for less than or equal to 2 hours, but no less than 1 hour after completion of the infusion. After each Treatment Period dose, patients will be contacted by the site by telephone within 7 days for a safety check-in. Patients who complete the Treatment Period (12-month assessments at Visit 14) will be offered the option to enter an extension trial at that time. Patients who choose not to enroll in the extension trial will be followed for a 20-week Safety Follow-up Period after Visit 14.

No interim analysis of efficacy will be conducted for this study.

Patients, as well as the Investigator and site personnel, will remain blinded to the treatment assignment until the completion of the extension trial to minimize the bias in measures assessed in the extension trial (Section 6.3).

Patients will be monitored throughout the trial for safety. Data will be reviewed on an ongoing basis by the Medical Monitor, an Independent Data Monitoring Committee (IDMC), and the Sponsor.

Brief Summary:

The purpose of this trial is to assess the safety and efficacy of apitegromab compared with placebo for improving motor function in patients with later-onset SMA who are receiving background therapy with nusinersen or risdiplam. Trial details include:

Trial Duration: 76 weeks

Treatment Duration: 52 weeks

Visit Frequency: every 4 weeks

Number of Patients:

For the Main Efficacy Population, approximately 156 patients will be randomized to receive apitegromab 10 mg/kg, apitegromab 20 mg/kg, or placebo at a ratio of 1:1:1, such that approximately 150 evaluable patients complete the Visit 14 assessments (Section 9.2).

For the Exploratory Subpopulation, a maximum of 48 patients will be randomized to receive apitegromab 20 mg/kg or placebo at a ratio of 2:1.

Intervention Groups and Duration:

Total trial participation for an individual patient will consist of approximately 4 weeks for Screening, 52 weeks of trial visits, and 20 weeks of safety follow-up for a total duration of approximately 76 weeks (approximately 18 months).

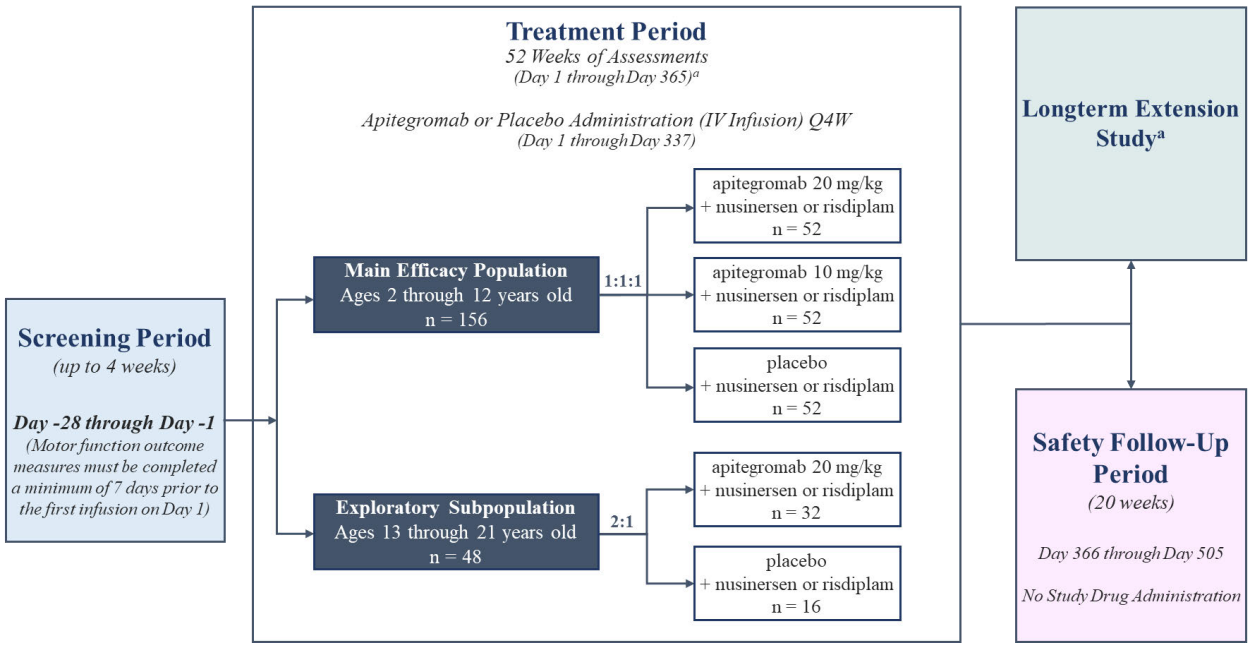
The study drug regimen in the Main Efficacy Population will be apitegromab (10 mg/kg or 20 mg/kg) or placebo every 4 weeks. The study drug regimen in the Exploratory Subpopulation will be apitegromab 20 mg/kg or placebo every 4 weeks.

Data Monitoring/Other Committee: Yes

Data will be reviewed on an ongoing basis by the Medical Monitor, an IDMC, and the Sponsor (Section 10.1.5.1).

1.2. Schema

Figure 1: Overall Trial Design



a Patients, as well as the Investigator and site personnel, will remain blinded to the treatment assignment until the completion of the extension trial to minimize the bias in measures assessed in the extension trial (Section 6.3).

1.3. Schedule of Activities/Assessments (SoA)

Table 1: Schedule of Activities/Assessments for Trial SRK-015-003

Activity/Assessment	SCR	Treatment Period															Follow-up		
Visit Time Point (Study Day)	SCR -28 to -1	V1[a] 1	V2 29	V3 57	V4 85	V5 113	V6 141	V7 169	V8 197	V9 225	V10 253	V11 281	V12 309	V13 337	V14 365/ EOS[b]/ EOT	Unsch	V15 393	V16 421	V17 505/ EOS[b]/ ET
Visit window (±days)[c]			±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7		±7	±7	±7
Informed Consent	X[d]																		
Demographics and Disease/Medical History[e]	X																		
Inclusion/Exclusion	X																		
Pregnancy Test (if applicable)[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height[h]	X	X		X		X		X		X		X			X	X	X	X	X
Physical Examination[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Safety Laboratory Assessments[k]	X	X	X	X		X		X		X		X		X	X	X	X	X	X
12-lead ECG[l]	X	X	X			X		X		X		X		X	X	X			X
PK and PD Sampling[m, n]		X	X			X		X		X		X		X	X	X			X
ADA Sampling[n, o]		X	X			X		X		X		X		X	X	X			X
Randomization		X																	
Study Drug Administration[p, q]		X	X	X	X	X	X	X	X	X	X	X	X	X					
Motor Function Outcome Measures[h, r, s, t]	X	X		X		X		X		X		X			X	X	X	X	X
PEDI-CAT and PROMIS[u]		X		X		X		X		X		X			X	X	X	X	X
ACEND Questionnaire		X						X							X	X		X	X
C-SSRS[v]		X						X							X	X		X	X

Activity/Assessment	SCR	Treatment Period															Follow-up		
Visit Time Point (Study Day)	SCR -28 to -1	V1[a] 1	V2 29	V3 57	V4 85	V5 113	V6 141	V7 169	V8 197	V9 225	V10 253	V11 281	V12 309	V13 337	V14 365/ EOS[b]/ EOT	Unsch	V15 393	V16 421	V17 505/ EOS[b]/ ET
Visit window (±days)[c]			±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7		±7	±7	±7
Site Check-in[w]		X	X	X	X	X	X	X	X	X	X	X	X	X					
Adverse Event Recording	*To be collected from the date the ICF is signed through the last trial visit*																		
SAE Reporting[x]	*To be reported from the date the ICF is signed through the last trial visit*																		
Concomitant Treatment Recording	*To be collected from the date the ICF is signed through the last trial visit*																		

ACEND: Assessment of Caregiver Experience with Neuromuscular Disease; ADA: antidrug antibody; COVID-19: coronavirus disease 2019; C-SSRS: Columbia-Suicide Severity Rating Scale; ECG: electrocardiogram; EOS: end of study; EOT: end of treatment; ET: early termination; hCG: human chorionic gonadotropin; HFMSE: Hammersmith Functional Motor Scale Expanded; 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; RULM: Revised Upper Limb Module; SAE: serious adverse event; SCR: Screening; SMA: spinal muscular atrophy; SMN: survival motor neuron; Unsch: unscheduled; V: visit; WHO: World Health Organization.

[a] Baseline is Visit 1.

[b] The EOS Visit will be V14 for patients who enter the extension trial and V17 for patients who do not enter the extension trial (these patients will complete V15 through V17).

[c] Visit windows (±7 days) are based on the previous dose during the Treatment Period and on the previous visit during the Safety Follow-up Period. Visit assessments may be conducted over multiple days within the visit window, as needed and in compliance with protocol requirements and country/site precautions/restrictions due to COVID-19 for the timing of each assessment.

[d] The ICF must be signed before any trial-specific procedures are performed.

[e] Disease history will capture the patient's SMA history (including age at symptom onset, age at diagnosis, age and WHO milestone status when SMN upregulator therapy was started, and number of copies of the *SMN2* gene).

[f] Females of childbearing potential only. Urine or serum test is acceptable and must be performed before dosing; 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 (25 mIU/mL) and, according to the product manufacturer, has >99% sensitivity.

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

[h] 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 need standing support.

[i] Changes in pubertal development must be assessed using Investigator judgment if the patient is not deemed physically mature at Screening. If menarche occurs during the trial, the child will be deemed of childbearing potential and immediate pregnancy status will be checked.

[j] Vital signs (heart rate, blood pressure, and respiratory rate) will be collected preinfusion, every 15 minutes (±5 minutes) during the infusion, at the end of the infusion, and 1 hour (±15 minutes) after completion of the infusion. For patients being monitored for hypersensitivity reactions for 2 hours postinfusion, vital signs will also be collected 2 hours (±15 minutes) after completion of the infusion. Body temperature will be collected preinfusion on dosing days.

[k] Clinical safety laboratory assessments include serum chemistry, hematology, urinalysis, and coagulation. On dosing days, laboratory samples will be collected preinfusion.

[l] 12-lead ECGs will be collected after 5 minutes of rest, in triplicate (3 individual tracings no more than 2 minutes apart). ECGs collected on dosing days will be collected within 1 hour before the start of the infusion. The timing for collection of PK-matched ECGs is provided in Table 2. If ECGs, PK/PD samples, and/or vital signs are collected at the same visit, the assessments should be performed in the following order: 1) ECG collection, 2) measurement of vital signs, and 3) PK/PD sample collection.

[m] The timing for PK/PD blood samples for PK-matched ECGs is provided in Table 2.
[n] Once emerging PK/PD data have been collected and analyzed, the PK/PD sample schedule may be adjusted to reflect a decrease in the number of samples to be collected. PK/PD/ADA samples will continue to be collected for all patients.
[o] Blood sample for anti-apitegromab antibody testing (ie, ADA testing) is collected within 1 hour before the start of the infusion on dosing days.
[p] Dosing every 4 weeks should be targeted. There is a ±7-day window around each dosing visit, with a minimum of 21 days and a maximum of 35 days between doses. If dosing cannot be performed within the ±7-day window, this divergence from the targeted dosing (ie, every 4 weeks) will be considered a protocol deviation and the Sponsor should be consulted.
[q] After dosing, patients will be monitored for hypersensitivity reactions at the trial site for less than or equal to 2 hours but no less than 1 hour after the completion of the infusion.
[r] Vaccinations within 14 days of any trial visit where motor function outcome measures are conducted are not permitted.
[s] Screening motor function outcome measures must be completed a minimum of 7 days before the first infusion on Day 1. All subsequent motor function outcome measures will be conducted within 96 hours before dosing.
[t] The following motor function outcome measures will be assessed: HFMSE, WHO Motor Development Milestones, and RULM. See Table 3.
[u] The PROMIS will be completed by/for patients who are or will turn 5 years old or older at the time of the Baseline assessment; the same questionnaire used at Baseline should be used throughout the duration of the trial (regardless of age). The self-reported PROMIS measures are suitable for children 8 to 17 years old, and the parent proxy reported PROMIS measures are suited for children 5 to 17 years old. If a caregiver completes this form, the same caregiver must complete the form throughout the trial duration. Patients who are 18 through 21 years old at Screening will complete an adult form of PROMIS.
[v] Baseline assessment of suicidal ideation and behavior and treatment-emergent suicidal ideation and behavior (Section 8.4.8) will be performed/monitored for patients who are or will turn 4 years old or older at the time of the Baseline assessment. The C-SSRS "baseline/screening" and "since last visit" will be used for patients ≥6 years old. The Children's Version of the C-SSRS "baseline/screening" and "since last visit" will be used for patients who are 4 to 5 years old at Screening until they turn 6 years old.
[w] Sites contact patients by telephone within 7 days after each infusion to collect information on adverse events and concomitant medications.
[x] Any SAE observed after the trial that the Investigator considers related to study drug must be reported to the Sponsor.

Table 2: Collection of PK-Matched ECGs

Assessment	Time Point	Dosing Study Day			Non-dosing Study Day		
		Day 1	Days 29, 113, 169, 225, 281	Day 337	Day 365	Day 505	Unscheduled Visit
Dosing Days							
	Before the start of the infusion						
12-lead ECGs[a, b]	within 1 hour before infusion starts	X	X	X			
PK/PD Samples[c]	within 10 minutes after the third/last ECG is completed	X	X	X			
	After completion of the infusion						
12-lead ECGs[a, d]	within 1 hour after infusion is completed	X		X			
PK/PD Samples	within 10 minutes after the third/last ECG is completed	X		X			
Non-dosing days							
12-lead ECGs[a]	at any time during the visit				X	X	X
PK/PD Samples[c]	within 10 minutes after the third/last ECG is completed				X	X	X

ECG: electrocardiogram; PD: pharmacodynamic; PK: pharmacokinetic.
Note: Assessments should be performed in the following order: 1) ECG collection, 2) measurement of vital signs, and 3) PK/PD sample collection (see Table 1).
[a] 12-lead ECGs will be collected after 5 minutes of rest, in triplicate (3 individual tracings no more than 2 minutes apart).
[b] ECGs collected on dosing days will be collected within 1 hour before the start of the infusion. PK-matched ECGs will be collected before the start of the infusion on dosing days.
[c] Blood samples for anti-apitegromab antibody testing (ie, ADA testing) will be collected in the same blood draw for the preinfusion PK/PD samples on Days 1, 29, 113, 169, 225, 281, and 337. On Day 365, blood samples for ADA testing will be collected in the same blood draw for the PK/PD samples.
[d] PK-matched ECGs will also be collected after completion of the infusion on Day 1 and Day 337.

Table 3: Motor Function Outcome Measures

Motor Function Outcome Measures	Performed By
HFMSE	All patients
RULM	Patients who are ≥30 months old at the time of the Baseline assessment
WHO Motor Development Milestones	All patients

Abbreviations: HFMSE: Hammersmith Functional Motor Scale Expanded; RULM: Revised Upper Limb Module; WHO: World Health Organization.

2. INTRODUCTION

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. Apitegromab is being developed for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

2.1. Trial Rationale

This Phase 3 trial (Study SRK-015-003) is being conducted in patients ≥2 years old at Screening, who were previously diagnosed with later-onset SMA (ie, Type 2 and Type 3 SMA) and are receiving an approved survival motor neuron (SMN) upregulator therapy (ie, either nusinersen or risdiplam), to confirm the efficacy and safety of apitegromab [redacted] therapy to nusinersen and evaluate the efficacy and safety of apitegromab [redacted] therapy to risdiplam.

SMA is a whole-body disease (Wirth 2020). Although the SMN-targeted therapies, which include gene therapy (onasemnogene abeparvovec-xioi [ZOLGENSMA®]) and the SMN upregulator (also referred to as SMN corrector) therapies nusinersen and risdiplam, (Section 2.2.2) approved for the treatment of SMA have been shown to significantly improve clinical outcomes by preventing or reducing the decline in motor function, patients may continue to suffer from substantial motor functional impairment because SMN-targeted therapies focus on SMN-dependent pathways and do not directly impact skeletal muscle to reverse the atrophy that has already taken place (Mercuri 2018, Mercuri 2020).

Consequently, there remains an unmet medical need for a complementary therapeutic strategy, namely muscle-directed therapy, that may address muscle atrophy and thereby improve motor function in patients with SMA. Through its novel mechanism of action as a selective inhibitor of myostatin activation, apitegromab has the potential to produce a clinically meaningful effect on motor function in a broad population of patients with SMA who are being treated with background SMN upregulator therapies (eg, nusinersen [SPINRAZA®] or risdiplam [EVRYSDI®]) (SPINRAZA Food and Drug Administration [FDA] Prescribing Information [PI] 2020, SPINRAZA Summary of Product Characteristics [SmPC] 2022, EVRYSDI FDA PI 2022, EVRYSDI SmPC 2022).

Safety data (as of 24 April 2022) and efficacy data (12-month primary analysis) from the Phase 2 trial (Study SRK-015-002) to evaluate the safety and efficacy of apitegromab (Section 2.2.3.3) support the continued development of apitegromab in patients with later-onset SMA receiving treatment with the SMN upregulator nusinersen. Treatment with apitegromab led to improvements in Hammersmith Functional Motor Scale Expanded (HFMSE) scores in patients with Type 2 and nonambulatory Type 3 SMA with no safety risks to date.

Since both nusinersen and the SMN upregulator risdiplam treat the SMN protein deficiency in SMA by increasing the production of functional SMN protein, the positive results with nusinersen support investigating apitegromab [redacted] therapy to risdiplam as well.

In the randomized, double-blind, dose-exploration cohort of Study SRK-015-002, which evaluated low-dose (2 mg/kg) vs. high-dose (20 mg/kg) apitegromab, the high-dose group

numerically outperformed the low-dose group in terms of mean change from Baseline and the proportion of patients with ≥3-point increase in Hammersmith scale scores at all assessed time points through the 12-month time point. To determine the optimal biological dose of apitegromab, 2 dose levels (10 mg/kg and 20 mg/kg) will be evaluated in this trial (Section 4.3).

2.2. Background

2.2.1. Spinal Muscular Atrophy

SMA is a neuromuscular disease characterized by atrophy of the voluntary muscles of the limbs and trunk. In almost every case, SMA is caused by a deletion or mutation in the *SMN 1* gene located on chromosome 5q that results in a deficiency of SMN protein and degeneration of the motor neurons in the anterior horn of the spinal cord (Lefebvre 1995, Arnold 2015). As SMN protein is critical to the function and survival of motor neurons that control muscle function, the deficiency caused by the deletion or mutation of the *SMN1* gene in SMA leads to significant but incomplete loss of the motor neurons in the anterior horn of the spinal cord, ensuring at least some intact innervation. This partial denervation causes substantial atrophy of fast-twitch muscle fibers that in turn leads to motor function impairment and subsequent debilitating muscular atrophy and weakness (Dubowitz 2013). Patients' muscles can become so weak that moving, breathing, and eating become difficult.

Despite being a rare disease, SMA is the most common monogenetic cause of death in infants (Kochanek 2019, Sugarman 2012). Most patients with SMA are asymptomatic following birth. The duration of the asymptomatic phase is variable but is usually correlated with disease severity, with more severe disease associated with earlier symptom onset and less SMN protein production. Once patients develop symptoms of SMA, they progressively lose motor function over time.

2.2.2. Currently Available Therapies for Spinal Muscular Atrophy

SMN-targeted therapies, which act primarily on motor neurons to prevent further loss of these cells and stabilize the disease course, are the current standard-of-care for patients with SMA.

Three therapies are currently approved by the United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of SMA. Two of these therapies (nusinersen and risdiplam) treat the SMN protein deficiency in SMA by increasing the production of functional SMN protein (SPINRAZA FDA PI 2020, SPINRAZA SmPC 2022, EVRYSDI FDA PI 2022, EVRYSDI SmPC 2022). The third approved therapy (onasemnogene abeparvovec-xioi [ZOLGENSMA®]) is a gene therapy that delivers a fully functional *SMN1* gene into patients' motor neurons to supplement their own production of the protein (ZOLGENSMA FDA PI 2021, ZOLGENSMA SmPC 2021).

These disease-stabilizing therapies have been shown to significantly improve clinical outcomes in patients with SMA by preventing or reducing the decline in motor function. Patients who start such therapy early in childhood may also have improvement in motor function. However, even with early intervention, patients may continue to suffer from substantial motor functional impairment because SMN-targeted therapies do not directly impact skeletal muscle to reverse the atrophy that has already taken place. For example, after 15 months of treatment with nusinersen, the majority of patients with Type 2 or nonambulatory Type 3 SMA who started nusinersen at

age ≥5 did not have improvements in HFMSE and <15% had a ≥3-point increase (Mercuri 2018). Irrespective of when SMN upregulator therapy is started, patients who receive these disease-stabilizing therapies after symptom onset continue to have significant unmet medical needs.

Consequently, there remains an unmet medical need for a muscle-directed therapy that can reverse muscle atrophy and thereby improve motor function in patients with SMA.

2.2.3. Apitegromab

Apitegromab (SRK-015) has the potential to be the first muscle-directed therapy to address the motor function impairment affecting patients with later-onset SMA.

By targeting the myostatin pathway (through the inhibition of myostatin activation) (Han 2013), it is hypothesized that apitegromab may address muscle atrophy and improve motor function in patients with later-onset SMA. By specifically inhibiting release of mature myostatin from the inactive precursor, apitegromab has the potential to minimize off-target effects that have been implicated as the cause of adverse effects of other less selective myostatin-directed agents (Campbell 2017, Garito 2018).

A summary of the relevant background information for apitegromab, including the mechanism of action (Section 2.2.3.1), nonclinical (Section 2.2.3.2) and clinical (Section 2.2.3.3) studies, and potential risks (Section 2.3.1) is presented below. Please refer to the apitegromab Investigator's Brochure (IB) for more detailed information.

2.2.3.1. Mechanism of Action

Data from the nonclinical program demonstrate that apitegromab specifically binds the precursor forms of myostatin and prevents activation and release of the mature growth factor. Apitegromab does not bind the mature myostatin growth factor and, unlike the majority of other myostatin inhibitors, does not bind any form of growth differentiation factor 11 (GDF11), or Activin A, or the mature forms of bone morphogenetic protein (BMP) 9/10 or transforming growth factor-β1. Please refer to Section 2.3.1 of the apitegromab IB for more detailed information on the mechanism of action.

2.2.3.2. Nonclinical Pharmacology

The ability of apitegromab to increase muscle mass and strength was demonstrated in nonclinical pharmacology studies in healthy animals as well as in multiple rodent models of muscle atrophy, including 2 models of SMA. Apitegromab also significantly increased muscle mass in nonhuman primates. Notably, in nonhuman primates, apitegromab administration led to increases in the mass of muscles rich with fast-twitch fibers. Together, these results demonstrate the potential of apitegromab in treating diseases of muscle atrophy, especially those associated with reduced fast-twitch fiber size such as SMA. Please refer to Section 4.0 of the apitegromab IB for more detailed information on the nonclinical studies.

2.2.3.3. Clinical Trials with Apitegromab

Apitegromab has been evaluated in a single Phase 1 trial in 66 healthy adult subjects (Study SRK-015-001) and a Phase 2 trial in 58 patients with later-onset SMA

(Study SRK-015-002). The long-term safety and efficacy extension period in Study SRK-015-002 is ongoing.

2.2.3.3.1. Summary of Safety

Safety results of Study SRK-015-001 in 66 healthy subjects (age range of 18 through 55 years) showed that there were no dose-limiting toxicities (DLTs) (up to the highest dose tested of 30 mg/kg), deaths, subject discontinuations due to any study drug-related adverse events (AEs), serious adverse events (SAEs) related to study drug, severe or life-threatening AEs related to study drug, or hypersensitivity reactions. The most common AEs were headache in the single ascending dose (SAD) portion (reported in 3 [3/6, 50%] subjects in the 1 mg/kg cohort) and postural dizziness in the multiple ascending dose (MAD) portion (reported in 1 [1/6, 16.7%] subject in the apitegromab 20 mg/kg cohort and in 2 [2/6, 33.3%] subjects in the placebo cohort). Immunogenicity was assessed by antidrug antibody (ADA) testing, and all apitegromab-treated subjects tested negative. One SAE (ie, obstructive pancreatitis) that was not related to study drug was reported. Please refer to Section 5.4.1 of the apitegromab IB for more detailed information on safety for Study SRK-015-001.

In Study SRK-015-002, 58 patients with later-onset SMA received apitegromab alone or in combination with the SMN upregulator nusinersen. No safety risks for apitegromab were detected during the 12-month period for the primary analysis or during the 24-month period of analysis (mean exposure duration of 105.4 weeks). The incidence and severity of AEs were consistent with the underlying patient population and background therapy. As of 24 April 2022, 22 treatment-emergent SAEs were reported; all of these SAEs were assessed by the Investigator as not related to study drug. Treatment-emergent adverse events (TEAEs) reported at a rate ≥20% were: headache (20/58, 34.5%); pyrexia (18/58, 31.0%); upper respiratory tract infection, cough, and nasopharyngitis (15/58, 25.9% each); coronavirus disease 2019 (COVID-19), nausea, and vomiting (14/58, 24.1% each); and scoliosis and fall (12/58, 20.7% each). No safety risks have been identified as of 24 April 2022.

Please refer to the apitegromab IB for more detailed information on safety.

2.2.3.3.2. Summary of Efficacy

Efficacy data from the 12-month primary analysis in Study SRK-015-002 support the clinical effect of apitegromab on motor function in patients with later-onset SMA.

The majority of patients in the cohorts with nonambulatory patients with SMA (Cohorts 2 and 3) had improvement in the HFMSE score from Baseline (based on individuals achieving a ≥1-point increase), and a subset of patients in both cohorts achieved a ≥3-point increase from Baseline. These patients on average had received ~2 years of treatment with nusinersen at Baseline (mean number of nusinersen maintenance doses at Baseline was 5.1 for Cohort 2 and 5.4 [high dose] and 5.5 [low dose] for Cohort 3) and ~3 years by the 12-month analysis time point.

Treatment with apitegromab led to improvements in HFMSE score and dose response was observed:

- Cohort 2 (age range of 8 through 19): 14 patients with Type 2 or nonambulatory Type 3 SMA who started receiving background nusinersen at ≥5 years of age treated with 20 mg/kg apitegromab:
  - The majority (64%) of patients achieved a ≥1-point increase in HFMSE and a subset (29%) achieved a ≥3-point increase.
- Cohort 3 (age range of 2 through 6): 17 patients with Type 2 SMA who started receiving background nusinersen at <5 years of age randomized to treatment with either high-dose (20 mg/kg) apitegromab (8 patients) or low-dose (2 mg/kg) apitegromab (9 patients) in a double-blind manner:
  - The majority (59%) of patients achieved a ≥5-point increase in HFMSE and a subset (35%) achieved a >10-point increase in HFMSE.
  - Dose response was observed with numerically greater mean improvement from Baseline in HFMSE score observed in the high-dose group (7.1 points) compared with the low-dose group (5.3 points) at the 12-month time point.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

A summary of the risk assessment for participating in Study SRK-015-003 is provided in Table 4.

Table 4: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Drug (Apitegromab)		
No adverse toxicology findings have been observed to date for apitegromab in the nonclinical program, including: • 4-week studies (at doses up to 100 mg/kg) in adult rodents and adult nonhuman primates • 7-week study in juvenile rodents (at doses up to 300 mg/kg) • 12-week and 26-week studies in adult rodents (at doses up to 300 mg/kg) • [redacted] • 2 embryo-fetal development studies (1 each in rabbits [gestation day 7 through 19] and adult rodents [gestation day 6 through 17]) (at doses up to 300 mg/kg)	Refer to Section 4.4 of the apitegromab IB for more detailed information on nonclinical toxicology.	The high dose (20 mg/kg) in Study SRK-015-003 is the same as the high dose in Study SRK-015-002, for which the drug exposure was 1.8- to 13.9-fold lower than the exposure measured in the nonclinical toxicity studies.
No apparent adverse effects resulting from genetic deficiency in myostatin have been observed across multiple mammalian species, including in at least 1 documented human case.	Refer to the following references: Lee 2010, Mosher 2007, McPherron 1997a, McPherron 1997b, Schuelke 2004	Not applicable.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy

No safety risks for apitegromab have been observed to date (as of 24 April 2022) in the clinical development program and no adverse drug reactions have been identified for apitegromab.	• No safety risks for apitegromab were detected in Study SRK-015-001 in healthy subjects (Section 2.2.3.3.1).
	• In Study SRK-015-002 in patients with later-onset SMA (Section 2.2.3.3.1):
	  ○ No safety risks for apitegromab were detected during the 12-month period for the primary analysis).
	  ○ The incidence and severity of AEs reported to date (as of 24 April 2022) are consistent with the underlying patient population (ie, patients with later-onset SMA) and background therapy (ie, nusinersen or risdiplam).
		• Data will be reviewed on an ongoing basis by the Medical Monitor, an IDMC, and the Sponsor.
		• Sites will contact patients by telephone within 7 days after each infusion to collect information on AEs and concomitant medications.
		• Patients will remain in the clinic for less than or equal to 2 hours but no less than 1 hour after completion of the infusion to allow monitoring by trial-site personnel for hypersensitivity reactions.
		• The first 2 doses for each patient will be infused over 2 hours. If there are no acute reactions after 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 decreased to less than 2 hours but no shorter than 1 hour.

Trial Design/Procedures		
Approximately 33% of patients will be randomized to receive placebo. Symptoms of SMA might worsen or remain unchanged for these patients.	Placebo is used to objectively assess the effects of apitegromab.	• Patients randomized to receive placebo will continue to receive the same standard-of-care, approved motor neuron-directed SMN upregulator therapy (ie, nusinersen or risdiplam) that they are currently receiving for the treatment of SMA. • Patients, including those randomized to receive placebo, who complete the Treatment Period (or are still participating in the trial if it is stopped for early efficacy or at the time the Main Efficacy

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Population completes the trial) will be offered the option to enter an extension trial in which they will receive apitegromab (Section 6.6).
Approximately 25% of patients will be randomized to receive the low dose (10 mg/kg) of apitegromab.	Two dose levels of apitegromab are being evaluated in the Main Efficacy Population to determine the optimal biological dose. Although complete target saturation may not be necessary to achieve therapeutic effect, patients in the low-dose group may have less improvement in HFMSE scores than the high-dose group based on the results for Cohort 3 of Study SRK-015-002 (Section 2.2.3.3.2).	An interim analysis may be conducted when at least 50% of the patients in the Main Efficacy Population complete the Visit 14 assessments (Section 9.5).
Other		
Identified risks of nusinersen and risdiplam	All patients will continue to receive the same standard-of-care, approved motor neuron-directed SMN upregulator therapy (ie, nusinersen or risdiplam) that they are currently receiving for the treatment of SMA.	For guidance on management of these AEs refer to the prescribing information for nusinersen (SPINRAZA FDA PI 2020, SPINRAZA SmPC 2022) and risdiplam (EVRYSDI FDA PI 2022, EVRYSDI SmPC 2022).
Potentially overlapping toxicities	To date, no identified risks or potential risks have been identified for apitegromab. Therefore, potentially overlapping toxicities with nusinersen or risdiplam cannot be determined with the available data.	Potentially overlapping toxicities will be closely monitored during the trial, through routine pharmacovigilance activities.

2.3.2. Benefit Assessment

All patients in this trial, including those randomized to receive placebo, will continue to receive the same standard-of-care, approved motor neuron-directed SMN upregulator therapy (ie, nusinersen or risdiplam) that they are currently receiving for the treatment of SMA.

Most patients (75%) will also receive the investigational muscle-directed therapy apitegromab, at either 20 mg/kg (high dose in Study SRK-015-002) or 10 mg/kg (5 times the low dose in Study SRK-015-002). Apitegromab, [redacted] offers a mechanism of action (Section 2.2.3.1) and biological effect that are distinct from those of SMN upregulator therapies. Based on the clinical activity observed for patients with SMA treated with apitegromab in Study SRK-015-002 (Section 2.2.3.3.2), patients may derive benefit due to potential improvements in their ability to perform various activities, as measured by changes in HFMSE score (Section 8.3.1). In vivo nonclinical data also support that addition of apitegromab may increase muscle mass and strength (Section 2.2.3.2).

All patients will receive medical evaluations and assessments (eg, physical examinations, electrocardiograms [ECGs], and blood tests) and their motor function will be assessed using outcome measures that have been validated in SMA (ie, HFMSE [Section 8.3.1] and Revised Upper Limb Module [RULM] [Section 8.3.3]) or in pediatric patients (ie, World Health Organization [WHO] Motor Development Milestones [Section 8.3.2]).

2.3.3. Overall Benefit: Risk Conclusion

Although nusinersen and risdiplam are approved for the treatment of patients with SMA, patients primarily stabilize or have modest and gradual improvement beyond the initial 15 months of therapy (Mercuri 2018). Based on the results from Study SRK-015-002 in which a majority of patients with Type 2 SMA or nonambulatory Type 3 SMA who had been on background nusinersen treatment for approximately 2 years at Baseline achieved a ≥1-point, ≥3-point, or ≥5-point increase in HFMSE (depending on the age that they started nusinersen), patients could potentially derive benefit from treatment with apitegromab [redacted] therapy to background SMN upregulators due to potential improvements in their ability to perform various activities, as measured by changes in HFMSE score. As no safety risks for apitegromab have been observed to date (as of 24 April 2022) in the clinical development program and no adverse toxicology findings have been observed to date in the nonclinical program, the potential risks identified in association with apitegromab are justified by the potential benefits that may be afforded to patients with SMA.

3. OBJECTIVES AND ENDPOINTS

Table 5: Main Efficacy Population: Efficacy and Additional Objectives/Endpoints

Objectives	Endpoints
Primary Efficacy	
Assess the efficacy of apitegromab compared with placebo using the HFMSE in patients 2 through 12 years old	Change from Baseline in HFMSE total score at 12 months
Key Secondary Efficacy	
Assess the efficacy of apitegromab compared with placebo by measuring changes in upper limb function using the RULM in patients 2 through 12 years old	Change from Baseline in RULM total score at 12 months
Assess the efficacy of apitegromab compared with placebo based on the number of patients with clinical improvement in patients 2 through 12 years old	Proportion of patients with ≥3-point change from Baseline in the HFMSE total score at 12 months
Assess the efficacy of apitegromab compared with placebo by measuring changes in number of WHO motor development milestones in patients 2 through 12 years old	Change from Baseline in number of WHO motor development milestones attained at 12 months
Other Secondary Efficacy	
Further assess the efficacy of apitegromab compared with placebo by evaluating changes in additional motor function outcome measures and changes in HFMSE at other prespecified time points in patients 2 through 12 years old	• Proportion of patients achieving various magnitudes of change in HFMSE score from Baseline at 12 months • Proportion of patients achieving various magnitudes of change in RULM score from Baseline at 12 months • Proportion of patients who attain a new WHO motor development milestone relative to Baseline at 12 months • Change from Baseline in HFMSE total score at other prespecified time points • Change from Baseline in RULM total score at other prespecified time points • Change from Baseline in number of WHO motor development milestones attained at other prespecified time points

Objectives	Endpoints
Additional Efficacy	
Assess the efficacy of apitegromab compared with placebo by measuring changes from Baseline in motor function across the Treatment Period using the HFMSE in patients 2 through 12 years old	Change from Baseline in HFMSE total score across time during the 12-month Treatment Period
Assess the time to therapeutic effect of apitegromab compared with placebo using the HFMSE in patients 2 through 12 years old	Time to therapeutic effect (≥3-point change from Baseline in HFMSE total score) compared between apitegromab and placebo
Additional Other	
Evaluate the effects of apitegromab on patient/caregiver-reported disability, fatigability, and suicidal ideation and behavior in patients 2 through 12 years old	• 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 • Change from Baseline in Assessment of Caregiver Experience with Neuromuscular Disease (ACEND) • Change from Baseline in Columbia-Suicide Severity Rating Scale (C-SSRS)

Table 6: Main Efficacy Population/Exploratory Subpopulation Combined: Secondary Objectives/Endpoints

Objectives	Endpoints
Secondary	
Assess safety and tolerability of apitegromab in all randomized patients with later-onset SMA who receive at least 1 dose of apitegromab	Incidence of TEAEs and SAEs by severity
Characterize the PK of apitegromab in all randomized patients with later-onset SMA who receive at least 1 dose of apitegromab	Apitegromab concentrations in serum from blood samples
Evaluate the pharmacodynamic (PD) effects of apitegromab in all randomized patients with later-onset SMA who receive at least 1 dose of apitegromab	Circulating latent myostatin concentrations in blood samples
Evaluate the immunogenicity of apitegromab in all randomized patients with later-onset SMA who receive at least 1 dose of apitegromab	Presence or absence of ADA against apitegromab in serum from blood samples

Table 7: Exploratory Subpopulation and Main Efficacy Population/Exploratory Subpopulation Combined: Additional Objectives/Endpoints

Objectives	Endpoints
Additional	
Assess the efficacy of apitegromab compared with placebo using the HFMSE in patients 13 through 21 years old and in patients 2 through 21 years old	Change from Baseline in HFMSE total score at 12 months
Assess the efficacy of apitegromab compared with placebo based on the number of patients with clinical improvement or stabilization in patients 13 through 21 years old	Proportion of patients with ≥0-point change from Baseline in the HFMSE total score at 12 months
Assess the efficacy of apitegromab compared with placebo based on the number of patients with clinical improvement in patients 2 through 21 years old	Proportion of patients with ≥3-point change from Baseline in the HFMSE total score at 12 months
Assess the efficacy of apitegromab compared with placebo by measuring changes in upper limb function between Baseline and the end of the Treatment Period using the RULM in patients 13 through 21 years old and in patients 2 through 21 years old	Change from Baseline in RULM total score at 12 months
Assess the efficacy of apitegromab compared with placebo by measuring changes in number of WHO motor development milestones in patients 13 through 21 years old and in patients 2 through 21 years old	Change from Baseline in number of WHO motor development milestones attained at 12 months
Further assess the efficacy of apitegromab compared with placebo by evaluating changes in additional motor function outcome measures and changes in HFMSE at other prespecified time points in patients 13 through 21 years old and in patients 2 through 21 years old	• Proportion of patients achieving various magnitudes of change in HFMSE score from Baseline at 12 months • Proportion of patients achieving various magnitudes of change in RULM score from Baseline at 12 months • Proportion of patients who attain a new WHO motor development milestone relative to Baseline at 12 months • Change from Baseline in HFMSE total score at other prespecified time points • Change from Baseline in RULM total score at other prespecified time points • Change from Baseline in number of WHO motor development milestones attained at other prespecified time points
Assess the efficacy of apitegromab compared with placebo by measuring changes from Baseline in	Change from Baseline in HFMSE total score across time during the 12-month Treatment Period

Objectives	Endpoints
motor function across the Treatment Period using the HFMSE in patients 13 through 21 years old and in patients 2 through 21 years old	
Assess the time to stabilization of effect of apitegromab compared with placebo using the HFMSE in patients 13 through 21 years old	Time to decline (at least a -3-point change from Baseline in HFMSE total score) compared between apitegromab and placebo
Assess the time to therapeutic effect of apitegromab compared with placebo using the HFMSE in patients 2 through 21 years old	Time to therapeutic effect (≥1-point change from Baseline in HFMSE total score) compared between apitegromab and placebo
Evaluate the effects of apitegromab on fatigability, caregiver-reported disability, and suicidal ideation and behavior in patients 13 through 21 years old and in patients 2 through 21 years old	• Change from Baseline in PEDI-CAT • Change from Baseline in PROMIS Fatigue Questionnaire • Change from Baseline in ACEND • Change from Baseline in C-SSRS

4. TRIAL DESIGN

4.1. Overall Trial Design

This Phase 3 trial will be conducted at approximately 55 to 60 trial sites globally to evaluate the safety and efficacy of apitegromab compared with placebo [redacted] nusinersen or risdiplam in nonambulatory patients (as defined in inclusion criterion #6, Section 5.1) with later-onset SMA. In the Main Efficacy Population, 2 dose levels of apitegromab will be evaluated to determine the optimal biological dose. Patients will be randomized to receive apitegromab (10 mg/kg or 20 mg/kg) or matching placebo by intravenous (IV) infusion. As outlined in Figure 1, the trial will include Screening, Treatment, and Safety Follow-up Periods.

Approximately 204 male and female patients with later-onset SMA will be randomized into either the Main Efficacy Population (2 through 12 years old at Screening) or the Exploratory Subpopulation (13 through 21 years old at Screening). Patients in the Main Efficacy Population will be randomized separately from the patients in the Exploratory Subpopulation.

- For the Main Efficacy Population, approximately 156 patients who are 2 through 12 years old at Screening will be randomized 1:1:1 double-blind to receive apitegromab 10 mg/kg, apitegromab 20 mg/kg, or placebo every 4 weeks during the 52-week (ie, 12-month) Treatment Period. Randomization for the Main Efficacy Population will be stratified by type of background therapy (ie, nusinersen or risdiplam) and age at initiation of SMN upregulator therapy (≥5 and <5).
- For the Exploratory Subpopulation, a maximum of 48 patients who are 13 through 21 years old at Screening will be randomized 2:1 double-blind to receive apitegromab 20 mg/kg or placebo every 4 weeks during the 52-week (ie, 12-month) Treatment Period. Randomization for the Exploratory Subpopulation will be stratified by type of background therapy (ie, nusinersen or risdiplam).

During the Screening Period (Table 1), 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 before the first dose. Screening motor function outcome measures will be conducted a minimum of 7 days before the first dose. All subsequent motor function outcome measures will be conducted within 96 hours before dosing.

Patient site visits will occur every 4 weeks through the end of the Treatment Period. Dosing every 4 weeks should be targeted. However, a ±7-day window around each dosing visit (with a minimum of 21 days and a maximum of 35 days between doses) is allowed without consultation with the Sponsor. If dosing cannot be performed within the ±7-day window, this divergence from the targeted dosing (ie, every 4 weeks) will be considered a protocol deviation and the Sponsor should be consulted. After dosing, patients will be monitored for hypersensitivity reactions at the trial site for less than or equal to 2 hours but no less than 1 hour after completion of the infusion. After each Treatment Period dose, patients will be contacted by the site by telephone within 7 days for a safety check-in. Patients who complete the Treatment Period (12-month assessments at Visit 14) will be offered the option to enter an extension trial at that time (Section 6.6). Patients who choose not to enroll in the extension trial will be followed for a 20-week Safety Follow-up Period after Visit 14.

Total trial participation for an individual patient will consist of approximately 4 weeks for Screening, 52 weeks (ie, 12 months) of trial visits, and 20 weeks safety follow-up for a total duration of approximately 76 weeks (approximately 18 months).

Patients, as well as the Investigator and site personnel, will remain blinded to the treatment assignment until the completion of the extension trial to minimize the bias in measures assessed in the extension trial (Section 6.3).

Patients will be monitored throughout the trial for safety. Data will be reviewed on an ongoing basis by the Medical Monitor, an Independent Data Monitoring Committee (IDMC) (Section 10.1.5.1), and the Sponsor.

4.2. Scientific Rationale for Trial Design

Apitegromab is being evaluated as [redacted] therapy to approved SMN upregulators (ie, nusinersen and risdiplam) because it is a muscle-directed therapy that works differently from the SMN-dependent motor neuron-directed therapies that are approved for SMA.

The randomized double-blind placebo-controlled trial design is the best practice to eliminate the influence of unknown or immeasurable confounding variables that may otherwise lead to biased and incorrect estimate of treatment effect of apitegromab.

All patients, including those randomized to the placebo group, will continue to receive background SMN upregulator therapy for SMA. The use of a placebo group to scientifically confirm the efficacy and safety of a study drug is common practice when patients are on active background therapy.

Patients are required to have been on background nusinersen therapy for at least 10 months before Screening or background risdiplam therapy for at least 6 months before Screening to allow sufficient time for the patients to stabilize on background therapy before starting apitegromab.

Treatment with apitegromab led to improvements in HFMSE scores in patients with SMA when apitegromab was evaluated as [redacted] therapy to nusinersen in the Phase 2 trial, Study SRK-015-002 (Section 2.2.3.3.2). Since risdiplam treats the SMN protein deficiency in SMA in a similar manner to nusinersen (ie, by increasing the production of functional SMN protein) and is now approved and being used to treat SMA, apitegromab will also be evaluated as [redacted] therapy to risdiplam.

The primary endpoint, HFMSE (Section 8.3.1) is a well-established, clinically relevant motor function scale that has been validated in SMA and is routinely used to assess the physical abilities of patients with Type 2 and Type 3 SMA. Changes in the HFMSE scale reflect the ability of patients to function better (eg, the ability to bring their hands to their head means the child can brush their hair or dress their upper body). Although a 3-point increase in HFMSE (out of a possible score of 66 based on the 33 activities evaluated) is considered clinically meaningful, the majority of caretakers would agree to their child's participation in a clinical trial if the prospect was even an improvement in just 1 activity, suggesting that any improvement is considered meaningful to caregivers and patients (Pera 2017). Furthermore, the HFMSE assesses many motor tasks involving fast-twitch fiber activity, which is more likely to be directly affected by apitegromab (Section 2.2.3.2).

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. Available clinical data (Section 2.2.3.3) and mechanistic understanding (Section 2.2.3.1) support the investigation of apitegromab in pediatric patients. Although pediatric patients ≥2 years old will be included in Study SRK-015-003, Results for the 12-month primary analysis in Study SRK-015-002 indicate that younger patients (Cohort 3, age range of 2 through 6) had a greater improvement in HFMSE (59% achieved a ≥3-point increase) compared to older patients (Cohort 2, age range of 8 through 19; 29% achieved a ≥3-point increase). In addition, an exploratory post hoc analysis that pooled all patients 2 through 12 years old treated with 20 mg/kg apitegromab from Cohort 2 and Cohort 3 observed a mean HFMSE improvement of 4.4 points from Baseline. As these efficacy data point to the potential benefit of treating patients at an early age, the primary analysis in Study SRK-015-003 will be performed using data from the Main Efficacy Population, which is focused on patients who are 2 through 12 years old at Screening. This same age range was used in the Phase 3 CHERISH trial with nusinersen, in which children ages 2 through 12 with symptomatic SMA were randomized 2:1 (stratified based on Screening age <6 vs. ≥6 years) to receive 4 doses of intrathecal nusinersen (12 mg) vs. the control group during the 15-month trial (Mercuri 2018). Results from CHERISH showed that at the end of the trial, the treatment difference in change from Baseline to Month 15 in mean HFMSE score was a highly clinically and statistically significant 3.9-point improvement for nusinersen vs. a -1.0-point decline for the control group. These effects of nusinersen on HFMSE scores over the 15-month period in CHERISH were more pronounced in younger children (<6 years). In addition, the therapeutic benefit (particularly on the HFMSE outcome measure) of SMN upregulator therapies has not been as well established or characterized in patients ≥12 years old. As a result, it is difficult to reliably estimate a priori the background treatment effect from SMN upregulator therapy alone in patients ≥12 years old in order to determine the appropriate sample size. Focusing on the 2- through 12-year age range as the Main Efficacy Population facilitates a reliably powered trial, while investigation of apitegromab's effect on a broader age range can be achieved through the Exploratory Subpopulation analysis in the 13- through 21-year age range.

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, no adverse toxicology findings were observed in the 7-week juvenile rodent study, including at the highest dose tested (300 mg/kg IV apitegromab weekly) (Table 4). Therefore, the Exploratory Subpopulation will be included in the Safety Population (Section 9.3) and the efficacy in this population will be explored.

Weight-based dosing and a treatment duration of 52 weeks are based on the 12-month primary analysis in Study SRK-015-002 in patients with SMA. The pharmacokinetics (PK) in Study SRK-015-002 were dose-proportional, drug exposure was sustained following chronic administration of apitegromab, and clinical effect on motor function (ie, improvements in HFMSE scores) was observed after 52 weeks of treatment (Section 2.2.3.3.2).

4.3. Justification for Dose

Apitegromab was tested in SAD and MAD, adult healthy volunteer trial (Study SRK-015-001), as well as year-long SMA patient trial (Study SRK-015-002; age range 2 through 21) (Section 2.2.3.3).

In Study SRK-015-001, the first in- human trial in healthy volunteers, single and multiple doses of up to 30 mg/kg of apitegromab were administered and were generally safe and well tolerated. PK results from the Phase 1 SAD trial suggest that apitegromab has a profile generally consistent with mAbs where dose-proportional increase in exposure, as well as low variability, was observed. The serum half-life ranged from 23 to 33 days across the apitegromab dose groups. These PK characteristics of apitegromab supported the investigation of a once every 4-week dosing regimen in Study SRK-015-002.

Pharmacodynamic (PD) results suggest that apitegromab treatment leads to robust increases in latent myostatin concentrations in serum, which demonstrates successful target engagement in humans. Moreover, the levels of target engagement attain a plateau, suggesting that the target is saturated even with a single treatment of apitegromab at doses ≥3 mg/kg. The total latent myostatin was sustained for approximately 84 days following a single 20 mg/kg dose, suggesting that the target engagement is durable.

In Study SRK-015-002, the high-dose arm (20 mg/kg administered every 4 weeks) was intended to rapidly attain and sustain target saturation with chronic administration over at least 1 year. In addition, dose exploration was conducted by including a low-dose arm of 2 mg/kg. The 2 mg/kg dose level was expected to attain lower target saturation. By characterizing the time course of clinical effect from this low-dose arm and comparing it with that observed for the 20 mg/kg level, the relationship between drug exposure and therapeutic effect over time was interrogated. Insights into the level of drug exposure necessary to initiate improvements in motor function was also attained. Together, results from this analysis informed the dosing regimen for Study SRK-015-003.

The results of the prespecified 6-month safety and efficacy interim analyses in Study SRK-015-002, including greater improvements in HFMSE scores across all time points and relatively higher levels of target engagement (as reflected by the observed increases in serum latent myostatin concentrations) for the high-dose arm and no identification of safety concerns, supported a change in dose for Cohort 3 patients from low-dose (2 mg/kg) to high-dose (20 mg/kg) apitegromab during the extension periods.

The ages for the Main Efficacy Population in Study SRK-015-003 will range from 2 through 12 years old, and the ages for the Exploratory Subpopulation will range from 13 through 21 years old. A dose of 20 mg/kg every 4 weeks has been safely administered in patients ranging from 2 through 21 years old over at least 1 year in Study SRK-015-002. Weight-based dosing will be used in Study SRK-015-003 because weight is a strong covariate on clearance of apitegromab (data on file).

In addition, based on the 12-month topline results in Study SRK-015-002 and earlier data with apitegromab in a Phase 1 clinical trial in healthy volunteers (Study SRK-015-001), evaluation of the 10 mg/kg dose was prioritized for inclusion in Study SRK-015-003 in addition to the 20 mg/kg dose. The 10 mg/kg dose is expected to increase drug exposure to a greater extent than the 2 mg/kg dose, but lower than the 20 mg/kg dose, as well as further increase target

engagement (serum latent myostatin) compared with the 2 mg/kg dose, however to a lesser degree than the 20 mg/kg dose. The inclusion of the 10 mg/kg dose in Study SRK-015-003 will allow interrogation of a middle dose level (between already assessed 2 and 20 mg/kg dose levels) in the SMA patient population and further assessment of lowest efficacious dose level.

4.4. End of Trial Definition

The end of the trial is defined as the date of the last visit of the last patient in the trial.

A patient is considered to have completed the trial if he/she has completed the Screening, Treatment, and Follow-up Periods of the trial including the last visit.

5. TRIAL POPULATION

This trial will include nonambulatory male and female patients ≥2 years old but ≤21 years old at Screening, who were previously diagnosed with later-onset SMA (ie, Type 2 and Type 3 SMA), are receiving an approved SMN upregulator therapy (ie, either nusinersen or risdiplam), and meet all the inclusion criteria and none of the exclusion criteria during Screening.

Prospective approval of protocol deviations to recruitment and eligibility criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Patients must meet all the following inclusion criteria to be eligible for this trial:

1. 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. The informed consent process is described in Appendix 1, Section 10.1.3.
2. Males and females 2 through 21 years old at Screening
3. Estimated life expectancy >2 years from Screening
4. Documented diagnosis of 5q SMA
5. Diagnosed with later-onset SMA (ie, Type 2 and Type 3 SMA) before receiving an approved SMN upregulator therapy (ie, either nusinersen or risdiplam). 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.
6. Must be nonambulatory at Screening. 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 WHO motor milestones definition (Wijnhoven 2004) at Screening. Nonambulatory patients are further defined as not having the ability to independently ambulate without aids or orthotics over 10 steps at time of walk test during Screening.
7. Receiving one background therapy for SMA (ie, either nusinersen or risdiplam) for the time period specified below and anticipated to remain on that same treatment throughout the trial
    a. If receiving the SMN upregulator therapy nusinersen, must have completed at least 10 months of dosing (ie, completed the loading regimen and at least 2 maintenance doses) before Screening
    b. If receiving the SMN upregulator therapy risdiplam, must have completed at least 6 months of dosing before Screening
8. Motor Function Score (HFMSE) ≥10 and ≤45 at the Screening Visit
9. No physical limitations that would prevent the patient from undergoing motor function outcome measures throughout the trial

10. 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 trial (ie, for background medical care and not for the purpose of receiving apitegromab in the trial), throughout the trial
11. Able to adhere to the requirements of the protocol, including travel to the trial site and completing all trial procedures and trial visits
12. Females of childbearing potential (as defined in Section 10.4.1) must have a negative pregnancy test at Screening and agree to use at least 1 acceptable method of contraception (as defined in Section 10.4.3) throughout the trial and for 20 weeks after the last dose of study drug. Female patients who are expected to have reached reproductive maturity by the end of the trial must agree to adhere to trial-specific contraception requirements.

5.2. Exclusion Criteria

Patients meeting any of the following exclusion criteria are not eligible for this trial:

1. Received ZOLGENSMA® (onasemnogene abeparvovec-xioi) at any time
2. Previous treatment with apitegromab
3. Prior history of severe hypersensitivity reaction or intolerance to SMN upregulator therapies
4. Prior history of a hypersensitivity reaction to a mAb or recombinant protein bearing an Fc domain (eg, a soluble receptor-Fc fusion protein), apitegromab, or excipients of apitegromab
5. Require invasive ventilation or tracheostomy
6. Nutritional status that was not stable over the past 6 months and is not anticipated to be stable throughout the trial or medical necessity for a gastric/nasogastric feeding tube, where the majority of feeds are given by this route, as assessed by the Investigator
7. 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 motor function outcome measures, within 6 months before Screening or anticipated during the trial
8. Treatment with other investigational drugs in a clinical trial within 3 months or 5 half-lives, whichever is longer, before Screening
9. Use of valproic acid or hydroxyurea within 90 days before Screening
10. Use of therapies with potentially significant muscle effects (eg, androgens, insulin-like growth factor, growth hormone, systemic beta-agonist, botulinum toxin, or muscle relaxants or muscle-enhancing supplements) or potentially significant neuromuscular effects (eg, acetylcholinesterase inhibitors) other than approved SMN upregulator therapy within 60 days before Screening
11. Use of systemic corticosteroids within 60 days before Screening. Inhaled or topical steroids are allowed.

12. Any acute or comorbid condition interfering with the well-being of the patient within 7 days before Screening, including active systemic infection, the need for acute treatment, or inpatient observation due to any reason
13. Severe contractures (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE]) or scoliosis (general guideline for Grade 3) at Screening. Based on clinical judgment, any contractures or scoliosis present must be stable over the past 6 months, anticipated to be stable throughout the trial, and not prevent the patient from being evaluated on any motor function outcome measures throughout the trial.
14. Use of chronic daytime noninvasive ventilatory support for >16 hours daily in the 2 weeks before dosing, or anticipated to regularly receive such daytime ventilator support chronically throughout the trial
15. Pregnant or breastfeeding
16. Any other condition or clinically significant laboratory result or ECG value that, in the opinion of the Investigator, may compromise safety or compliance, would preclude the patient from successful completion of the trial, or interfere with the interpretation of the results

5.3. Lifestyle Considerations

No restrictions are required.

5.4. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical trial but are not subsequently randomized to receive either apitegromab 10 mg/kg or 20 mg/kg or placebo. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Patients who do not meet the criteria for participation in this trial (screen failure) may be rescreened after a suitable period of time (the exact length is dependent upon the reason for the screen failure) per the documented agreement of the Sponsor and the Investigator.

If a patient is rescreened, the patient must reconsent (Section 10.1.3) and repeat all of the safety assessments performed at the original Screening Visit.

- Patients who rescreen within 14 days after the date of the screen failure must also repeat any other assessments performed at the original Screening Visit that are related to the reason for the screen failure.
- Patients who rescreen ≥15 days after the date of the screen failure must repeat all of the assessments performed at the original Screening Visit.

Patients who rescreen will be assigned a new patient identification number. A patient may only fail Screening once.

5.5. Criteria for Temporarily Delaying Randomization/Administration of Study Drug

If a patient who is determined to be eligible based on Screening assessments has an acute or comorbid condition that causes a delay in their Baseline Visit (Visit 1) and first infusion (Day 1), the patient 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. Screened patients who have an acute clinical event that results in a delay of more than 14 days outside of the Screening Period must rescreen to determine eligibility.

6. STUDY DRUG(S) AND CONCOMITANT THERAPY

Study drug is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to a trial patient according to the trial protocol.

6.1. Study Drug(s) Administered

Table 8: Treatment Groups

Treatment Description	**Apitegromab plus Background Therapy**[a]		**Placebo plus Background Therapy**[a]
Treatment Group Name	Main Efficacy Population High-dose Group Exploratory Subpopulation High-dose Group	Main Efficacy Population Low-dose Group	Main Efficacy Population Placebo Group Exploratory Subpopulation Placebo Group
Study Drug Name	Apitegromab		Placebo for Apitegromab
Type	Biologic		Biologic
Dose Formulation	IV infusion		IV infusion
Unit Dose Strength(s)	[redacted] fully human mAb that specifically binds to proforms of myostatin		Not applicable
Excipients	[redacted]		[redacted]
Dosage Level(s)[b]	20 mg/kg every 4 weeks	10 mg/kg every 4 weeks	Every 4 weeks
Route of Administration	IV infusion		IV infusion
Infusion Time[c]	[redacted]		[redacted]
Use	Experimental		Placebo
IMP and NIMP	IMP plus NIMP		IMP plus NIMP
Sourcing	Provided centrally by the Sponsor		Provided centrally by the Sponsor
Packaging and Labeling	Study drug will be provided in vials Each vial will be labeled as required per country requirement		Study drug will be provided in vials Each vial will be labeled as required per country requirement
Current/Alias	Apitegromab/SRK-015		Not applicable

IMP: Investigational Medicinal Product; IV: intravenous; mAb: monoclonal antibody; NIMP: Non-Investigational Medicinal Product.

[a] Background therapy will be administered per the prescribing information for nusinersen or risdiplam. Study drug should be administered at least 24 hours before a maintenance dose of nusinersen or at least 14 days after a maintenance dose of nusinersen. The daily dose of risdiplam should not be taken during the study drug infusion.

[b] The dosing schedule for study drug, including maintaining acceptable visit windows, must be adhered to throughout the trial. Dosing every 4 weeks should be targeted. There is a ±7-day window around each dosing visit, with a minimum of 21 days and a maximum of 35 days between doses. If dosing cannot be performed within the ±7-day window, this divergence from the targeted dosing (ie, every 4 weeks) will be considered a protocol deviation and the Sponsor should be consulted.

[c] If there are no acute infusion reactions after 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 decreased to less than 2 hours but no shorter than 1 hour.

6.2. Preparation/Handling/Storage/Accountability

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.

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.
2. Only patients randomized in the trial may receive study drug and only authorized site staff may supply or administer study drug
3. All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions (2ºC to 8ºC/36ºF to 46ºF) in the carton and protected from light, with access limited to the Investigator and authorized site staff.
4. The Investigator (or designee) is responsible for maintaining accurate accountability records of the investigational product throughout the clinical trial. 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 trial, Study Monitors or designees will conduct a final accountability of all study drugs.
5. 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.
6. Unused vials should be returned to Scholar Rock, or its designated storage location, for final disposition.

6.3. Measures to Minimize Bias: Randomization and Blinding

Patients will be randomized after the Investigator has verified that they are eligible per criteria in Section 5.1 and Section 5.2. Patients in the Main Efficacy Population and the Exploratory Subpopulation will be randomized separately using a centralized Interactive Web-based Randomization System (IWRS):

- For the Main Efficacy Population, patients will be randomized 1:1:1 double-blind to receive apitegromab (10 mg/kg or 20 mg/kg) or placebo every 4 weeks IV during a 52-week Treatment Period. Randomization will be stratified by type of background therapy (ie, nusinersen or risdiplam) and age at initiation of SMN upregulator therapy (≥5 and <5).
- For the Exploratory Subpopulation, patients will be randomized 2:1 double-blind to receive apitegromab (20 mg/kg) or placebo every 4 weeks IV during the 52-week Treatment Period. Randomization will be stratified by type of background therapy (ie, nusinersen or risdiplam).

Refer to the Study Operations Manual and the IWRS Quick Reference Guide for instructions on using the IWRS.

The Sponsor, patients, caregivers, Investigators, and site personnel, with the exception of the Pharmacist, will be blinded to treatment assignments. The site Pharmacist will remain unblinded throughout the duration of the trial. If for any reason Sponsor personnel need to be unblinded, the list of personnel and the reason for unblinding will be documented.

In the event of a drug-related, serious, unexpected AE, designated unblinded Sponsor personnel may provide a patient's treatment assignment for the purpose of regulatory authority agency reporting. In the event of a drug-related SAE, the Investigator may, if deemed medically necessary to provide patient care, obtain the patient's treatment assignment from the IWRS system.

In case of an emergency, the Investigator will determine if unblinding of a patient's treatment assignment is warranted. If a patient's treatment assignment is to be unblinded, the Sponsor must be notified as soon as possible but no later than 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

6.4. Study Drug Compliance

Study drug will be administered under the supervision of the Investigator or qualified site personnel. The date and start/end time of each infusion administered in the clinic will be recorded in the source documents. The dose of study drug and trial patient identification will be confirmed at the time of dosing by a member of the trial-site staff other than the person administering the study drug. The trial site is required to adhere to all applicable laws, regulations, and guidelines including, but not limited to, the 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.

6.5. Dose Modification

If an acute infusion 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 have 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.

6.6. Continued Access to Study Drug After the End of the Trial

Patients will be offered the option to enter an extension trial when they complete the Treatment Period or if they are still participating in the trial if it is stopped for early efficacy or at the time the Main Efficacy Population completes the trial. Patients must meet the extension trial eligibility criteria before enrolling in the extension trial.

6.7. Treatment of Overdose

An overdose is defined as a significant variation from the recommended/scheduled dosage for a product. Administration of study drug for this trial will be performed in a controlled clinical setting and an overdose is not anticipated. However, in the event of an accident, any dose of study drug that is at least 2-fold higher than 20 mg/kg will be considered an overdose. Two doses within 1 week will also be considered an overdose.

In the event of an overdose, the Investigator or designee:

- Must contact the Medical Monitor within 24 hours.
- Should evaluate the patient to determine, in consultation with the Medical Monitor, whether study drug should be interrupted or whether the dose should be reduced. The evaluation process should be complete prior to the next infusion.
- Should closely monitor the patient for any AE/SAE and laboratory abnormalities for the remainder of the trial.
- In case of an AE or SAE, the Investigator, in conjunction with the Medical Monitor, may choose to stop the drug until the AE reduces in severity to Grade 1 (mild) or resolves completely. The decision to restart the study drug in this case should also be made in consultation with the Sponsor.
- Should document the quantity of the excess dose as well as the duration of the overdose.

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 on an overdose form. If an overdose results in an SAE, both the SAE and overdose forms must be completed.

For an overdose of background therapy, refer to the prescribing information for nusinersen or risdiplam or contact the manufacturer.

6.8. SMA Background Therapy

All patients, including those randomized to the placebo group, will continue to receive an approved SMA treatment (ie, nusinersen or risdiplam). Patients are expected to remain on the same background SMA therapy from at least 10 months before Screening for nusinersen or at least 6 months before Screening for risdiplam and throughout the duration of the trial. 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 who receive the SMN upregulator therapy nusinersen must receive their maintenance doses at least 24 hours after receiving study drug, or at least 14 days prior to any scheduled 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 administration of study drug should be discussed with the Medical Monitor in advance.

The daily dose of risdiplam should not be taken during the study drug infusion.

6.9. Concomitant Therapy

Concomitant therapies or interventional procedures that are medically indicated for any AEs the patient has during the trial or that are provided as part of standard supportive care for the patient, are permitted at the discretion of the Investigator and supersede any of the restrictions outlined in this protocol.

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

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

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

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the patient is receiving at the time of completion of the informed consent process or receives during the trial must be recorded in the eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

7. DISCONTINUATION OF STUDY DRUG AND PATIENT WITHDRAWAL

7.1. Discontinuation of Study Drug

7.1.1. Suspension of Dosing for All Patients

Dosing for all patients in the trial may be suspended at any time for an emergent safety concern by the Medical Monitor, and/or Sponsor in consultation with the other core IDMC (Appendix 1, Section 10.1.5.1), members until the IDMC can completely evaluate the event(s) and recommend an appropriate course of action.

The IDMC may make recommendations to restart dosing and continue the trial with no changes, continue the trial with changes to the protocol, terminate the trial (Section 10.1.9), or require more data, input, and deliberation prior to making a decision. Appropriate regulatory authority approval(s) must also be obtained before dosing is restarted.

7.1.2. Permanent Discontinuation of Study Drug for Individual Patients

Dosing for any individual patient may be permanently discontinued if:

- the patient has an SAE related to study drug or a clinically significant nonserious AE related to study drug that, in the assessment of the Investigator, warrants permanent discontinuation from further dosing for that patient's well-being
- there are safety concerns other than those described above based on review by the IDMC 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 IDMC 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.

The Investigator should promptly (eg, within 24 hours) notify the Medical Monitor if study drug dosing is permanently discontinued for an individual patient.

Patients who permanently discontinue study drug are encouraged to remain in the trial until they complete their monthly Treatment Period visits and the Safety Follow-up visits. At the time of discontinuation of study drug, the reason for discontinuation of treatment will be documented and the patient will resume their monthly visit schedule (Table 1).

If study drug dosing is permanently discontinued due to an AE or other safety concerns and the patient does not want to continue with their monthly visit schedule, the patient will complete the assessments for the End of Treatment Visit (Table 1) and continue to be followed for 20 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 10.3.3).

Patients who develop either an SAE or other toxicity meeting the individual permanent discontinuation criteria listed above will be carefully monitored and may be required to have additional assessments, including those listed below, at the discretion of the Investigator:

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

7.1.3. Temporary Discontinuation

Dosing for any individual patient may be temporarily discontinued if:

- the patient has an SAE related to study drug or a clinically significant nonserious AE related to study drug that, in the assessment of the Investigator, warrants an interruption from dosing for that patient's well-being
- there are safety concerns other than those described above based on review by the IDMC 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 IDMC 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.

The Investigator should promptly (eg, within 24 hours) notify the Medical Monitor if study drug dosing is interrupted for an individual patient.

If study drug dosing is interrupted, the patient may resume dosing only after the 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).

Patients who develop either an SAE or other toxicity meeting the individual temporary discontinuation criteria listed above will be carefully monitored and may be required to have additional assessments, including those listed below, at the discretion of the Investigator:

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

7.2. Patient Withdrawal/Discontinuation from the Trial

- A patient and/or parent or guardian may withdraw consent to participate in the trial at any time at his/her own request.
- A patient must be permanently discontinued from the trial if she becomes pregnant. The pregnancy will be followed as described in Section 8.5.5.

- A patient may be permanently discontinued from the trial at any time at the discretion of the Investigator. The Investigator may discontinue a patient from the trial for any of the following reasons:

– Protocol violation

– Serious or intolerable AE (see Section 7.1.2)

– Clinically significant change in a laboratory parameter (Section 7.1.2)

– Sponsor or Investigator decision

– Patient and/or parent or guardian request

- At the time of withdrawing/discontinuing from the trial, if possible, an Early Termination Visit should be conducted (Table 1). Any SAE will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (Section 8.5.3).
- The patient will be permanently discontinued from the study drug and withdrawn/discontinued from the trial at that time.
- If the patient and/or parent or guardian withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a patient withdraws from the trial, the patient and/or parent or guardian may request destruction of any samples taken and not tested, and the Investigator must document this in the site trial records.

7.3. Lost to Follow-up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the trial site.

The following actions must be taken if a patient fails to return to the clinic for a required trial visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the trial.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the trial.

- Site personnel, or an independent third party, will attempt to collect the vital status of the patient within legal and ethical boundaries for all patients randomized, including those who did not get study drug. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the patient will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Guidance related to discontinuation of specific sites and early termination or suspension of the trial is provided in Section 10.1.9.

8. TRIAL ASSESSMENTS AND PROCEDURES

- Trial procedures and their timing are summarized in the SoA (Table 1). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study drug.
- Adherence to the trial design requirements, including those specified in the SoA (Table 1), is essential and required for trial conduct.
- All Screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a Screening Log to record details of all patients screened and to confirm eligibility or record reasons for Screening failure, as applicable.
- Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the informed consent form (ICF) may be used for Screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 1).
- The total blood sample volume collected will be consistent with the volumes recommended in the Ethical considerations for clinical trials on medicinal products conducted with minors (Revision 1, 18 September 2017) (European Commission 2017).
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Informed Consent

Assessments in Study SRK-015-003 may not be performed until the patient (if the patient is legally an adult) or the patient's parent or legal guardian (if the patient is legally a minor) provides written informed consent and the patient provides oral or written assent (if applicable and in accordance with the regulatory and legal requirements of the participating location) (see Section 10.1.3).

8.2. Demographics and Medical History

Patient demographics and disease/medical history will be recorded on the source document and eCRF. Demographic characteristics include age, sex, race, and ethnicity. Disease history will capture the patient's SMA history (including age at symptom onset, age at diagnosis, and age and WHO milestone status when SMN upregulator therapy was started, and number of copies of the *SMN2* gene) and medical history will capture current and past relevant medical status (surgeries, allergies, and concomitant medications). Investigators should make every effort to obtain the number of *SMN2* gene copies, if possible.

8.3. Efficacy Assessments

Efficacy evaluations will be performed as described below. Planned time points for all efficacy assessments are provided in the SoA (Table 1).

The motor function outcome measures (Table 3) (eg, HFMSE, WHO Motor Development Milestones, and RULM) 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.

8.3.1. Hammersmith Functional Motor Scale Expanded

The HFMSE, which is validated in SMA, assesses the physical abilities of patients with Type 2 and Type 3 SMA (O'Hagen 2007, Glanzman 2011). 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. The item scores are summed to give a total score with a maximum of 66. The higher the total score, the greater the patient's motor function.

8.3.2. WHO Motor Development Milestones

The WHO motor development milestones are a set of 6 distinct gross motor milestones (ie, sitting without support, standing with assistance, hands-and-knees crawling, walking with assistance, standing alone, and walking alone) that are considered to be universal and fundamental to acquiring the ability to walk independently (Wijnhoven 2004). The motor development milestones of patients are assessed based on the age windows for achieving these milestones, which were validated in an international study (WHO Multicentre Growth Reference Study Group 2006).

8.3.3. Revised Upper Limb Module

The RULM, which is validated in SMA, is a 19-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. With the exception of 1 activity with a binary score, 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. The RULM will be completed by patients who are ≥30 months old at the time of the Baseline assessment.

8.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1) and details for conducting the safety assessments are provided in the Study Operations Manual.

8.4.1. Vital Signs

Vital signs will be performed by the Investigator or his/her qualified designee. Routine vital sign assessments will include heart rate, blood pressure, and respiratory rate. On dosing days these assessments will be collected at preinfusion, every 15 minutes (±5 minutes) during the infusion (measured from the start of the infusion), at the end of the infusion, and 1 hour (±15 minutes) after completion of the infusion. Vital sign assessments will also be collected at 2 hours

(±15 minutes) after completion of the infusion if the patient is being monitored for hypersensitivity reactions for 2 hours postinfusion. Body temperature will be collected preinfusion on dosing days.

8.4.2. Weight and Height

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 (as defined in inclusion criterion #6, Section 5.1) or needs standing support.

8.4.3. Physical Examinations

A complete physical examination will be performed by the Investigator or a qualified designee. 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.

8.4.4. Electrocardiograms

Triplicate 12-lead electrocardiograms (ECGs) are to be performed with the patient having rested for at least 5 minutes before the first reading and remain resting during the subsequent readings. The 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. If ECGs, PK/PD samples, and/or vital signs are collected at the same visit, the assessments should be performed in the following order: 1) ECG collection, 2) measurement of vital signs, and 3) PK/PD sample collection. ECGs collected on dosing days will be collected within 1 hour before the start of the infusion. The timing for collection of PK-matched ECGs is provided in Table 2. ECGs will be sent to a central reading vendor for assessment.

8.4.5. Concomitant Medications

All concomitant medications will be collected from the time the patient signs the ICF through 20 weeks after the final dose.

Concomitant medications will be documented for each patient. A detailed history of medications will be documented. At each trial visit, patients will be asked whether they have taken any medication other than the study drug. All concomitant medications including dietary supplements, over-the-counter medications, and oral herbal preparations, as well as changes in medication, will be recorded in the eCRFs.

8.4.6. Clinical Safety Laboratory Assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed.
- Laboratory testing (eligibility Screening, serum chemistry, hematology, urinalysis, and coagulation, PK and PD sample draw, and ADA testing) will be conducted in

accordance with the Laboratory Manual and the SoA (Table 1) and performed using established methods.

- 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 backup for retesting if necessary [redacted].

- The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the trial as an AE. The laboratory reports must be filed with the source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the Investigator to be more severe than expected for the patient's condition.
- All laboratory tests with values considered clinically significantly abnormal during the Treatment Period or within 20 weeks after the last dose of study drug should be repeated until the values return to normal or Baseline or are no longer considered clinically significant by the Investigator, in consultation with the Medical Monitor if needed.
  - If clinically significant values do not return to normal/Baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
  - If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded.

8.4.7. Pregnancy Testing

Pregnancy testing will be conducted for females of childbearing potential.

A female is considered of childbearing potential, after 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.

A urine or serum test is acceptable however, positive urine tests must be confirmed with serum testing.

Changes in pubertal development must be assessed using Investigator judgment if the patient is not deemed physically mature at Screening. If menarche occurs during the trial, the child will be deemed of childbearing potential and immediate pregnancy status will be checked.

Patients who become pregnant during the trial should not receive further study drug and should be followed according to the procedures outlined in Section 8.5.5.

8.4.8. Suicidal Ideation and Behavior Risk Monitoring

Baseline assessment of suicidal ideation and behavior and treatment-emergent suicidal ideation and behavior will be performed/monitored for patients who are or will turn 4 years old or older at the time of the Baseline assessment. The Columbia -Suicide Severity Rating Scale (C-SSRS) "baseline/screening" and "since last visit" will be used for patients ≥6 years old. The Children's Version of the C-SSRS "baseline/screening" and "since last visit" will be used for patients who are 4 to 5 years old at Screening until they turn 6 years old.

The C-SSRS involves a series of probing questions to inquire about possible suicidal thinking and behavior, but the full interview is needed only if the initial Screening questions about suicidal ideation and behavior are positive. Severity of ideation is rated on a 5-point ordinal scale ranging from 1 "Wish to be dead" to 5 "Suicidal intent with plan." Intensity of ideation includes 5 items related to most severe ideation (eg, frequency, duration, controllability, deterrents, and reasons for ideation). The suicidal behavior and actual attempt section consists of yes/no answers related to actual attempts, self-injurious behavior, interrupted and aborted attempts, preparatory acts or behaviors, and lethality (Posner 2011). Strengths of the C-SSRS include that it has been used and validated with adults and adolescents (Gipson 2015, Posner 2011), and been found to predict short-term suicidal behavior among high-risk adolescents (Conway 2016). Instruments such as the C-SSRS have been used successfully in children and adolescent patients with various psychiatric disorders that do not involve cognitive impairment. Nevertheless, assessing young children also can be challenging because many may not have reached sufficient cognitive maturity to understand the concept of death.

C-SSRS is being performed because the background therapy risdiplam is considered to be a CNS-active intervention.

Patients should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of study drug, or at the time of dose changes, either increases or decreases. Patients who have signs of suicidal ideation or behavior, should undergo a risk assessment. All factors contributing to suicidal ideation and behavior should be evaluated and consideration should be given to discontinuation of the study drug.

When informed consent or assent has been given, families and caregivers of patients should be alerted about the need to monitor patients for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior and to report such symptoms immediately to the trial Investigator.

In the event that a patient's responses on the C-SSRS or other information provided by a patient evidence suicidal ideation or behavior, this information will be shared with the patient's legal guardians or others, including mental health professionals, as appropriate or as required by local laws. These details about information sharing will be included in the ICF and assent form for the trial.

8.5. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Appendix 3 (Section 10.3).

AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up all AEs (see Section 8.5.3).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.5.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs, including SAEs, will be collected from the signing of the ICF until the final follow-up visit at the time points specified in the SoA (Table 1).

During Screening, patients may undergo more examinations and tests than they have in the past, and therefore new findings may be detected. Medical occurrences that begin before the start of study drug but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions, not as AEs. In other words, if it is reasonable that the finding started/developed before obtaining informed consent, it should be classified as Medical History/Current Medical Condition. Otherwise, or if there is no way to determine, it is an AE.

All SAEs will be recorded and reported to Safety immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to Safety within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the trial participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the trial, and he/she considers the event to be reasonably related to the study drug or trial participation, the Investigator must promptly notify the Sponsor.

8.5.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.5.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3.3).

8.5.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of patients and the safety of a study drug under clinical investigation are met.

- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

8.5.5. Pregnancy

- Details of all pregnancies in female patients will be collected after the start of study drug and until 20 weeks after the last dose of study drug.
- If a minor female patient becomes pregnant during the trial, the Investigator will share this information with the patient's legal guardian if doing so is appropriate and permitted by local laws. This information will not be shared with the patient's legal guardian without the patient's consent if the minor female is treated as an adult for purposes of medical decision making under local laws due to the pregnancy. These details about information sharing will be included in the ICF and assent form for the trial.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to Safety within 24 hours of learning of the female patient pregnancy.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the patient and the neonate, and the information will be forwarded to Safety.
- Any post-trial pregnancy-related SAE considered reasonably related to the study drug by the Investigator will be reported to Safety as described in Section 8.5.4. Although the Investigator is not obligated to actively seek this information in former trial patients, he or she may learn of an SAE through spontaneous reporting.
- Any female patient who becomes pregnant while participating in the trial will discontinue study drug and be discontinued from the trial.

8.5.6. Procedure-Related Adverse Events

Procedure-related AEs are those events considered by the Investigator to be related to the conduct of the clinical trial, independent of the study drug. That is, the event may be related to the fact that a patient is participating in the trial. Examples of procedure-related AEs include:

- Reactions at the injection site (eg, rashes, nodules, pain, bleeding)
- Pain, bruising, dizziness, syncope due to blood collection
- Shortness of breath, nausea, fall, bruises during exertion examinations
- Vomiting or dizziness due to fasting for an examination or injection
- Skin irritation, redness, or itching during an ECG

If the Investigator determines that the AE is associated with the trial procedures, the Investigator must record this causal relationship in the source documents and eCRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements.

8.6. Pharmacokinetics

PK samples will be collected during the trial.

- Whole blood samples will be collected to evaluate the PK of apitegromab (including measurement of serum concentration) as specified in the SoA (Table 1).
- Once emerging PK data have been collected and analyzed, the PK sample schedule may be adjusted to reflect a decrease in the number of samples to be collected. PK samples will continue to be collected for all patients.
- As whole blood will be collected for PD and immunogenicity assessments at the same visits that whole blood will be collected for PK samples, each collected sample will be split into approximately equal volume sample sets to allow for retesting, if required.
- Instructions for the collection and handling of biological samples will be provided in a separate Laboratory Manual. The actual date and time (24-hour clock time) of each sample will be recorded.
- Genetic analyses will not be performed on these PK samples.
- Patient confidentiality will be maintained.
- Apitegromab concentration information that would unblind the treatment assignment will not be reported to investigative sites or blinded personnel until the treatment assignment has been unblinded.

8.7. Pharmacodynamics

PD samples will be collected during the trial.

- Whole blood samples will be collected to evaluate the PD of apitegromab (ie, measurement of serum circulating latent myostatin concentration) as specified in the SoA (Table 1).

- Once emerging PD data have been collected and analyzed, the PD sample schedule may be adjusted to reflect a decrease in the number of samples to be collected. PD samples will continue to be collected for all patients.
- As whole blood will be collected for PK and immunogenicity assessments at the same visits that whole blood will be collected for PD samples, each collected sample will be split into approximately equal volume sample sets to allow for retesting, if required.
- Instructions for the collection and handling of biological samples will be provided in a separate Laboratory Manual. The actual date and time (24-hour clock time) of each sample will be recorded.
- Genetic analyses will not be performed on these PD samples.
- Patient confidentiality will be maintained.
- Circulating latent myostatin concentration information that would unblind the treatment assignment will not be reported to investigative sites or blinded personnel until the treatment assignment has been unblinded.

8.8. Genetics and/or Pharmacogenomics

Genetics are not evaluated in this trial.

[redacted]

8.10. Immunogenicity Assessments

Samples to evaluate the immunogenicity of apitegromab will be collected during the trial.

Whole blood samples will be collected to evaluate the presence or absence of antibodies to apitegromab in serum as specified in the SoA (Table 1).

As whole blood will be collected for PK and PD at the same visits that whole blood will be collected for serum immunogenicity assessments, each collected sample will be split into approximately equal volume sample sets to allow for retesting, if required.

Serum samples will be screened for antibodies binding to apitegromab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to apitegromab and/or further characterize the immunogenicity of apitegromab.

The detection and characterization of antibodies to apitegromab will be performed using a validated assay method by or under the supervision of the Sponsor. All samples collected for

detection of antibodies to apitegromab will also be evaluated for apitegromab serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of apitegromab. Samples may be stored for a maximum of 15 years (or according to local regulations) following the last patient's last visit for the trial at a facility selected by the Sponsor to enable further analysis of immune responses to apitegromab.

8.11. Assessment of Patient/Caregiver-Reported Outcomes

8.11.1. 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 trial duration. The answers are scored on a 4-point scale (unable to easy). The test is suitable to assess function in newborns through 21-year-olds; this questionnaire should be completed throughout the duration of the trial (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 may be required for accurate assessment per local regulations.

8.11.2. Patient-Reported Outcomes Measurement Information System

The 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 PROMIS will be completed by/for patients who are or will turn 5 years old or older at the time of the Baseline assessment; the same questionnaire used at Baseline should be used throughout the duration of the trial (regardless of age). The self-reported PROMIS measures are suitable for children 8 to 17 years old, and the parent proxy reported PROMIS measures are suited for children 5 to 17 years old. If a caregiver completes this form, the same caregiver must complete the form throughout the trial duration. Patients who are 18 through 21 years old at Screening will complete an adult form of PROMIS.

8.11.3. Assessment of Caregiver Experience with Neuromuscular Disease

The Assessment of Caregiver Experience with Neuromuscular Disease (ACEND) is a validated self-administered instrument for assessing caregiver impact on parents raising children severely affected by neuromuscular disease (Matsumoto 2011). The ACEND is completed by the caregiver. The same caregiver must complete the assessment throughout the trial duration.

The ACEND instrument includes 2 domains, 7 subdomains, and 41 items. Domain 1, examining physical impact, includes 4 subdomains: feeding/grooming/dressing (6 items), sitting/play (5 items), transfers (5 items), and mobility (7 items). Domain 2, which examines general

caregiver impact, includes 3 subdomains: time (4 items), emotion (9 items), and finance (5 items).

8.12. Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this trial.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The alternative hypotheses of the primary objective are as follows:

- Apitegromab 20 mg/kg is superior to placebo for change from Baseline in HFMSE total score at 12 months.
- Apitegromab combined dose (10 mg/kg and 20 mg/kg combined) is superior to placebo for change from Baseline in HFMSE total score at 12 months.

Both hypotheses will be tested simultaneously using the Hochberg procedure (Hochberg 1988).

9.2. Sample Size Determination

A sample size of 50 patients each in the apitegromab 20 mg/kg group and placebo group for the primary analysis (Main Efficacy Population) would yield at least 80% power to detect a mean (± standard deviation) difference of 3 ± 5 points between the 20 mg/kg dose group and the placebo group in change from Baseline in the HFMSE score, at a 2-sided alpha (α) level of 0.05 and assuming a drop off rate of 5% after randomization.

With 50 patients in the apitegromab 10 mg/kg group, a sample size of 100 patients in the apitegromab combined dose group and 50 patients in the placebo group would yield at least 90% power to detect a mean (± standard deviation) difference of 3 ± 5 points between the apitegromab combined dose group and the placebo group.

With the Hochberg procedure to control for multiplicity of the 2 hypotheses, the power to reject at least 1 of the hypotheses is approximately 90%.

For the Main Efficacy Population, approximately 156 patients will be randomized to receive apitegromab 10 mg/kg, apitegromab 20 mg/kg, or placebo at a ratio of 1:1:1, such that approximately 150 evaluable patients complete the Visit 14 assessments.

For the Exploratory Subpopulation, a maximum of 48 patients will be randomized to receive apitegromab 20 mg/kg or placebo at a ratio of 2:1. This sample size is based on practical considerations and is not powered to detect statistical significance for efficacy.

9.3. Analysis Sets

The Intention-to-Treat (ITT) Set is defined as all randomized patients in the Main Efficacy Population, even if the patient does not receive the correct treatment or otherwise did not follow the protocol. The primary efficacy analyses will be conducted on the Modified Intention-to-Treat (MITT) Set, defined as all ITT Set patients who received at least 1 dose of study drug and had at least 1 postbaseline evaluable HFMSE assessment. Patients will be analyzed according to the treatment to which they were assigned. The Protocol Set is defined as all MITT Set patients who have no major protocol violations affecting the efficacy. Efficacy outcome analyses will be conducted on the Exploratory Subpopulation and the Pooled population (Main Efficacy Population + Exploratory Subpopulation) as an exploratory analysis, following the same principle.

Safety analyses will be done on the Safety Set, which includes all randomized patients who receive at least 1 dose of study drug.

Further details of other analysis sets will be described in the statistical analysis plan (SAP).

9.4. Statistical Analyses

The SAP will be finalized prior to the unblinding of treatment assignment and will include a more technical and detailed description of the statistical analyses described in this section. A summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints is included in this section. Changes in the analysis methods before the database lock that are not part of a protocol amendment will be delineated in the SAP, and any deviations from the SAP will be documented in the clinical study report.

9.4.1. General Considerations

A statistical analysis of this trial will be the responsibility of Scholar Rock or its designee. A detailed SAP describing the statistical methodologies will be developed by Scholar Rock or its designee.

All analyses will be conducted using Statistical Analysis System (Version 9.4 or later, Cary, North Carolina). A 2-sided 0.05 critical level will be deemed as statistically significant unless otherwise noted, and when confidence interval (CI) is used, the 2-sided 95% CI will be reported.

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

The primary efficacy analysis will analyze efficacy data up to Visit 14, and efficacy measurements collected during the Safety Follow-up Period will be provided where applicable.

9.4.2. Primary Efficacy Endpoint Analysis

The primary efficacy endpoint, change from Baseline in HFMSE total score at12 months (ie, 52 weeks), will be assessed in patients from 2 through 12 years old by the comparison between apitegromab 20 mg/kg and placebo as well as the comparison between apitegromab combined dose and placebo simultaneously. The primary outcomes are the least squares mean differences in change from Baseline at 12 months comparing apitegromab 20 mg/kg versus placebo and apitegromab combined dose versus placebo, using the HFMSE total score in MITT patients.

A restricted maximum likelihood model-based mixed effects model with repeated measurement (MMRM) is planned as the primary analysis. Change from Baseline in HFMSE will be analyzed using an MMRM analysis with unstructured covariance modeling of time, the treatment-by-time interaction, and within-patient errors. The model will have fixed effects of treatment, categorical time, the treatment-by-time interaction, Baseline HFMSE total score, the interaction between Baseline HFMSE total score and time, and the stratification factors at randomization as covariates. The Kenward–Roger method will be used to estimate the degrees of freedom. If the model with the unstructured covariance structure fails to converge, the Heterogeneous First-Order Autoregression covariance structure will be used to model the within-patient variability. Type III sums of squares for the least squares means will be used for the statistical comparison; 95% CI will also be reported (Kenward and Roger 1997). Contrasts will be set up within the

model to test treatment groups at specific time points of interest. Further details on the use of MMRM will be described in the SAP.

A hybrid strategy will be used to handle intercurrent events. Following Meyer (Meyer 2020) and Qu (Qu 2021), a hybrid strategy for handing intercurrent events that depends on the nature and the cause of the intercurrent events will be used. The detailed list of the nature of the intercurrent events and their handling will be prespecified in the SAP. Missing data will be imputed by different imputation approaches based on the reasons for the missing data and/or different assumption of missing mechanisms.

Sensitivity analyses will be performed to evaluate the impact of missing data on the primary efficacy analysis. The sensitivity analyses may include different assumptions of missing mechanism from the primary analysis and a tipping point analysis.

9.4.3. Secondary Efficacy Endpoints Analyses

The key secondary endpoints, change from Baseline in RULM at 12 months and change from Baseline in WHO motor milestones attained at 12 months, will be analyzed using the same model as the primary endpoint. The key secondary endpoint, proportion of patients with ≥3-point change from Baseline in the HFMSE total score at 12 months, will be compared between the apitegromab 20 mg/kg (or 10 mg/kg) group versus placebo using a logistic model, adjusting for Baseline HFMSE total score and the stratification factors at randomization. The same strategy applied to the primary endpoint will be used to handle intercurrent events for the key secondary endpoints.

The testing sequence of the key secondary endpoints and details for other secondary endpoints will be specified in the SAP.

9.4.4. Multiplicity

To account for multiple confirmatory tests for the primary endpoint and key secondary endpoints, the hierarchical testing procedure will be applied:

1. The 2 hypotheses of the primary endpoint for apitegromab 20 mg/kg against placebo and the apitegromab combined dose against placebo will be tested simultaneously using the Hochberg procedure.
2. The key secondary endpoints for the apitegromab 20 mg/kg group will only be tested against the placebo group if both tests of the primary endpoint are statistically significant using the Hochberg procedure.
3. The apitegromab 10 mg/kg group will only be tested against the placebo group if all the tests of the key secondary endpoints are statistically significant for the apitegromab 20 mg/kg group vs. the placebo group.

Within each dose group, key secondary endpoints will be tested in the following order:

1. Change from Baseline in RULM total score at 12 months
2. Proportion of patients with ≥3-point change from Baseline in the HFMSE total score at 12 months

3. Change from Baseline in number of WHO development motor milestones attained at 12 months.

9.4.5. Safety Endpoints Analyses

Safety data will be descriptively summarized by treatment group and analyzed using the Safety Set (Section 9.3).

Treatment-emergent adverse events are defined as AEs that started or worsened in severity after the first dose of study drug. The number of TEAEs as well as the number and percentage of patients who have at least 1 TEAE will be summarized using the Medical Dictionary for Regulatory Activities for each system organ class (or a body system) and each preferred term by group. SAEs and AEs that lead to discontinuation of study drug will also be summarized by treatment group.

All clinical laboratory results and change from Baseline will be descriptively summarized by treatment group. Individual results that are outside of normal reference ranges will be flagged in data listings.

Categorical variables, including the incidence of abnormal values and incidence of AEs, will be summarized by frequency and percentage of patients in corresponding categories. Shift tables will be presented for selected measures.

Observed values and changes from Baseline for vital signs and physical characteristics will be descriptively summarized by treatment group and time point.

9.4.6. Secondary Pharmacokinetic and Pharmacodynamic Endpoints Analyses

All patients who receive at least 1 dose of study drug and have at least 1 quantifiable PK result will be included in the PK analysis. Apitegromab concentrations will be listed and summarized in tabular formats using descriptive statistics and will plotted against time points by cohort. The latent myostatin concentrations will be listed for each patient and summarized by treatment arm. The apitegromab and latent myostatin concentrations from this trial will be combined with other trial data to support the population PK analysis, PK/PD, and exposure response analysis, if data permit.

9.4.7. Secondary Immunogenicity Analyses

All patients who receive at least 1 dose of study drug and have at least 1 evaluable result will be included in the Immunogenicity Analysis Set for immunogenicity evaluation. The number and percentage of patients who become positive for antibodies will be listed and summarized in tabular format using descriptive statistics by cohort, visit.

9.4.8. Additional Endpoints Analyses

Analyses for the additional endpoints will be described in the SAP.

9.4.9. Subgroup Analysis

To assess whether the treatment effect is similar across subgroups for the primary efficacy outcome, an MMRM model will be used and will include the subgroup variable and the subgroup by treatment interaction (if the subgroup is a stratification factor, only the subgroup by

treatment interaction will be added to the model). If the interaction is statistically significant at $\alpha = 0.10$, the nature of the interaction will be explored, that is, within each subgroup the treatment effect will be estimated. The subgroups to be explored (eg, region, age at initiation of SMN therapy, type of SMN therapy at randomization) will be specified in the SAP. As this trial is not powered for subgroup analyses, all subgroup analyses will be treated as exploratory.

9.5. Interim Analysis

No interim analysis of efficacy will be conducted for this study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This trial will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the trial is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial patients.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to trial patients.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the trial to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the trial at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical trials (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and for 1 year after completion of the trial.

10.1.3. Informed Consent Process

- The Investigator or his/her representative will explain the nature of the trial to the patient or their legally authorized representative and answer all questions regarding the trial.
- Patients must be informed that their participation is voluntary. Patients or their legally authorized representative (defined as the patient's parent or legal guardian) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or trial center.
- Patients who have not reached the age of legal consent will also sign an assent form as required per age and legal requirements. If the patient reaches the age of legal consent during the clinical trial, notification may be required, and a new consent form may need to be signed by patient.
- The medical record must include a statement that written informed consent was obtained before the patient began any trial-specific procedures and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the trial.
- A copy of the ICF(s) must be provided to the patient or their legally authorized representative.

A patient who is rescreened is not required to sign another ICF if the rescreening occurs within 14 days from the previous ICF signature date.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

10.1.4. Data Protection

- Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that his/her personal trial-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the ICF and assent form.
- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the

Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Committees Structure

10.1.5.1. Independent Data Monitoring Committee

An IDMC will be set up to review data for this trial. The IDMC is made up of a group of individuals with pertinent expertise that reviews, on a predetermined schedule, safety data from this clinical trial. It is the IDMC's responsibility to weigh risks and benefits throughout the trial's duration. The IDMC will provide oversight and safety monitoring of the trial in compliance with applicable regulations, legislation, and associated guidance materials for the nature of the trial. The IDMC will provide recommendations to the Sponsor regarding continuation, modification, or discontinuation of the trial based on its assessment of the reviewed safety data. The IDMC membership, functioning, and procedures are described in a separate IDMC charter.

10.1.6. Dissemination of Clinical Trial Data

The Sponsor will comply with current regulatory requirements for disclosure and submission of trial results. The Sponsor's policy on publication of trial results is described in Section 10.1.10.

10.1.7. Data Quality Assurance

- All patient data relating to the trial will be recorded in the eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the case report form (CRF).
- Guidance on completion of CRFs will be provided in the Completion Guidelines provided by Data Management.
- The Investigator must permit trial-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be predefined in the Integrated Quality Risk Management: Risk Assessment Categorization Tool to identify systematic issues that can impact patient safety and/or reliability of trial results. These predefined parameters will be monitored during the trial and important deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan and/or the Risk Management Plan.
- The Sponsor or designee is responsible for the data management of this trial, including quality checking of the data.

- The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the Investigator for 2 years after trial completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8. Source Documents

- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the trial. Current medical records must be available.
- Definition of what constitutes source data can be found in ICH guidance for industry E6 GCP: Consolidated Guidance.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9. Trial Closure

Trial/Site Termination

The Sponsor or designee reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of the Sponsor.

Criteria for trial termination include the assessment of safety concerns that may arise during the conduct of the trial or from data from the apitegromab nonclinical and clinical program. The trial may be terminated if the IDMC (Section 10.1.5.1) determines that further drug exposure would pose an undue risk to patients.

Trial sites will be closed upon trial completion. A trial site is considered closed when all required documents and trial supplies have been collected and a trial-site closure visit has been performed.

The Investigator may initiate trial-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a trial site by the Sponsor or Investigator may include but are not limited to:

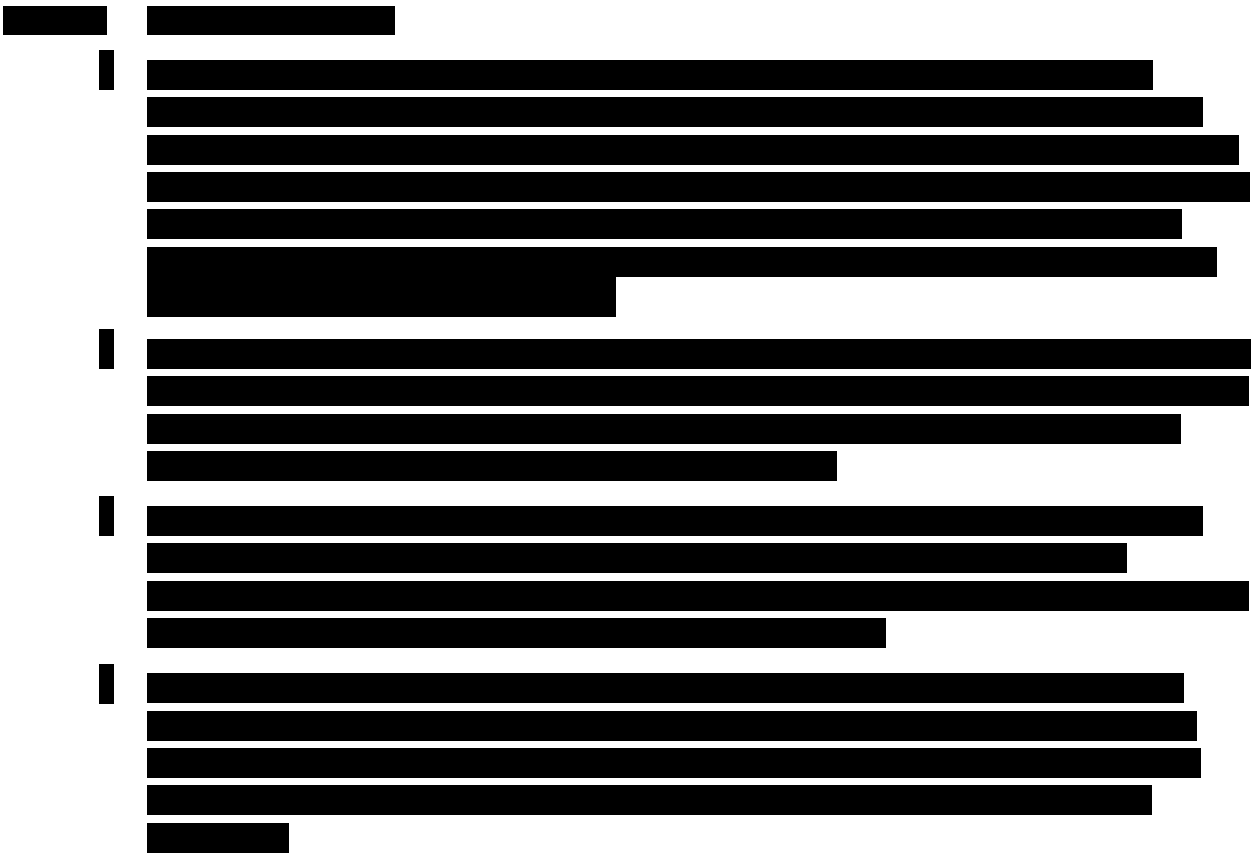
For trial termination:

- Discontinuation of further study drug development
- Safety data suggesting that further drug exposure would pose an undue risk to patients

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of patients by the Investigator

If the trial is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up. Patients will continue to be followed for 20 weeks after their final dose.



[redacted]

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 9 will be performed by the 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. Investigators must document their review of each laboratory safety report.
- Additional tests may be performed at any time during the trial as determined necessary by the Investigator or required by local regulations.

Table 9: Protocol-Required Safety Laboratory Tests

Laboratory Tests	**Parameters**			
Hematology	Absolute platelet count RBC count Hemoglobin Hematocrit	Red blood cell (RBC) Indices: Mean corpuscular volume Mean corpuscular hemoglobin (MCH) MCH concentration %Reticulocytes	White blood cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Serum Chemistry	Blood urea nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)	Total and direct bilirubin
	Creatinine	Sodium	Alanine aminotransferase (ALT)	Total Protein
	Glucose (nonfasting)	Calcium	Alkaline phosphatase	Albumin
	Carbon dioxide	Chloride	Creatine phosphokinase	Gamma-glutamyl transferase
	Lactate dehydrogenase	Magnesium	Phosphate	Total cholesterol
	Triglycerides	Uric acid		
Coagulation	Activated partial thromboplastin time (APTT)		Prothrombin time/international normalized ratio (PT/INR)	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, nitrite, by dipstick • Blood microscopy (if urinalysis is abnormal)			
Pregnancy Testing	• Highly sensitive serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[a] • Positive urine tests must be confirmed with serum testing			

[a] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical trial patient, temporally associated with the use of study drug, whether or not considered related to the study drug.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, serum chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator.
  Specifically, abnormal laboratory test result must be reported as an AE if it meets any of the following criteria:
  - Is accompanied by clinical symptoms
  - Results in a change in study drug
  - Results in a medical intervention
  - Is clinically significant in the Investigator's judgment

    Note: if the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. If a clinically significant laboratory abnormality is a sign of a disease or syndrome, only the diagnosis should be reported. Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once as an AE.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the trial.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

SPECIAL CASES

AEs that are Secondary to Other AEs:

- These events are also called "cascade events" or "clinical sequelae."

- In general, these events should be identified by their primary cause, with the exception of severe or serious secondary events.
- If a medically significant secondary AE occurs, the event may be recorded as an independent AE after consultation with the Sponsor.
- All AEs should be recorded separately if it is not evident whether the events are associated.

Persistent and Recurrent Adverse Events:

- Persistent AE: AE that extends continuously, without resolution, between patient evaluation time points. Record only once. The initial severity of the AE will be recorded at the time the event is first reported. If it becomes more severe, the most extreme severity should be recorded. If it becomes serious, the end date of the AE will be the date the AE became serious, which will be the same as the start date of the SAE. For this SAE, all requirements for SAEs apply.
- Recurrent AE: AE that resolves between patient visits and subsequently recurs. Each recurrence must be recorded as a separate AE.

Events NOT Meeting the AE Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the trial that do not worsen.
- Findings discovered during Screening, or between Screening and the first dose, where it is reasonable to assume these findings were present before informed consent.

10.3.2. Definition of SAE

An SAE is defined as any serious adverse event that, at any dose:

1. Results in death

2. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.

An SAE is defined as any serious adverse event that, at any dose:

3. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the patient has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that **did not worsen** from Baseline is not considered an AE or SAE (eg, for work-up of persistent pretreatment lab abnormality).
- Planned/Scheduled Hospitalization: A hospitalization planned and scheduled **prior to ICF** is to be considered a therapeutic intervention and not the result of a new SAE. It is **not** enough to know that in the near future the patient will need said surgery; the surgery needs to be already scheduled before ICF for it not to be considered an AE/SAE. If the planned hospitalization or procedure is executed as planned, it will be recorded in the patient's medical history or procedures. However, if the event/condition worsens during the trial, it must be reported as an AE and/or SAE.
  - Scoliosis/spinal surgery: SMA patients may need to undergo back surgery at some point. Unless the surgery is scheduled (booked with a hospital) before ICF, the understanding is that scoliosis and/or back issues may worsen during the trial and will become an SAE once the surgery/hospitalization occurs.
- Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself a SAE. Examples include:
  - Social admission (eg, patient has no place to sleep),
  - Administrative admission (eg, for yearly physical exam),
  - Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery).
- As a reminder, "hospitalization" should not be reported as the event term, and the same is true for procedures. The cause of the hospitalization and/or procedure should be the event term.

4. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Patients with SMA who are ambulatory may become wheelchair bounded during the trial. If the extent of the disability is considered substantial (eg, patient does not get up at all anymore, or patient's life was severely disrupted by the loss of ambulation), this should be considered a SAE.

5. Is a congenital anomaly/birth defect

An SAE is defined as any serious adverse event that, at any dose:

6. Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

10.3.3. Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the patient's medical records to Safety in lieu of completion of the SAE form.
- There may be instances when copies of medical records for certain cases are requested by Safety. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to Safety.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- There may be instances when an AE becomes a SAE. In such cases, the AE will end when the SAE starts. If a SAE becomes nonserious, the same applies: the SAE will end when the nonserious AE starts.
- SAE recording: for an AE to be serious, it needs to meet one of the regulatory seriousness criteria defined in Section 10.3.2. Hence, event start and end dates should match the start and end dates of when the criterion/criteria was/were met. If a patient is hospitalized from Friday to Sunday, the start date will be Friday and the end date will be Sunday. If the Investigator feels that the event also met another seriousness criterion outside of the hospitalization dates, the event start and end dates may be different than the admission and discharge dates as the extra days are covered by the additional seriousness criterion.

AE and SAE Recording

Assessment of Intensity

The Investigator will assess intensity for each AE and SAE reported during the trial according to the NCI CTCAE Grading Scale, Version 5.0 or higher (see web page https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_60 for details). Only AEs not listed in the CTCAE should be graded as summarized in the table below.

CTCAE Grade	Equivalent To:	Definition
Grade 1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]
Grade 4	Life-threatening/ disabling	Life-threatening consequences; urgent intervention indicated
Grade 5	Death	Death related to AE

Abbreviations: ADL: activities of daily living; AE: adverse event, CTCAE: Common Terminology Criteria for Adverse Events.
A Semi-colon indicates 'or' within the description of the grade.
[a]Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b]Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

Assessment of Causality

- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Safety. However, it is very important that the Investigator always assess causality for every event before the initial transmission of the SAE data to Safety.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Safety to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a patient dies during participation in the trial or during a recognized follow-up period, the Investigator will provide Safety with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to Safety within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the trial is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a trial patient or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section).
- Contacts for SAE reporting can be found in the SAE form, in the site binder.

SAE Reporting to Safety via Paper Data Collection Tool

- The primary method for SAE reporting is via email using the email address provided in the site binder. Should technical issues not allow for email transmission of the SAE Report Form, the form may be submitted using the fax number provided in the site binder.

SAE Reporting to Safety via Paper Data Collection Tool
• In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in the SAE form, in the site binder.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

A female is considered to be of childbearing potential after 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.

10.4.2. Contraception Guidance

The effects of apitegromab on conception, pregnancy, and lactation are unknown.

No changes in reproductive organs were noted during rat and monkey repeat-dose toxicology studies and no changes in reproductive organs, sperm parameters, or fertility were observed in a juvenile rat toxicology study. An increase in mean estrous cycle length in females and a decrease in sperm concentration in males was noted during a study on rat fertility and early embryonic development; however, these changes had no effect on mating or fertility indices. Increases in mean maternal and/or fetal body weights were also observed in rabbit and rat embryo/fetal development studies that had no impact on maternal well-being or embryo-fetal development. No effects in skeletal variations or developmental malformations were observed in these studies. The long-term effects of these changes on reproductive potential are unknown.

Female patients of childbearing potential must use at least 1 acceptable method of contraception (see Section 10.4.3) throughout the trial and for 20 weeks after the last dose of study drug.

The use of contraceptive methods is not required if the male partner (of the female patient) has a documented history of a vasectomy or if the female patient has a documented history of hysterectomy, bilateral salpingectomy, or bilateral oophorectomy, or if she is postmenopausal for at least 12 months.

Male patients are not required to use contraceptive methods.

However, all patients should be reminded to use the most conservative method of contraception that is consistent with the local prescribing information (eg, SmPC, FDA PI) for their concomitant medications (eg, nusinersen or risdiplam).

See Section 8.5.5 for requirements for pregnancy reporting.

10.4.3. Acceptable Methods of Contraception

The acceptable methods of contraception allowed during the trial are listed in Table 10.

Table 10: Methods of Contraception Allowed During the Trial

Highly Effective Methods[a] That Have Low User Dependency[b]
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)[c]
Bilateral tubal occlusion
Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the female patient of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male patient can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.
Highly Effective Methods[a] That Are User Dependent
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] • oral • intravaginal • transdermal
Progestogen-only hormone contraception associated with inhibition of ovulation[c] • oral • injectable
Sexual abstinence *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 drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the patient.*
Effective Methods[d] That Are Not Considered Highly Effective
Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
Male or female condom with or without spermicide
Cervical cap, diaphragm, or sponge with spermicide
A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[e]

Note: Contraceptive use by males or females should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical trials.

[a] Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
[b] These methods of contraception, which are considered to have low user dependency, should preferably be used, in particular when contraception is introduced as a result of participation in the clinical trial.
[c] If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.
[d] Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception.
[e] Male condom and female condom should not be used together (due to risk of failure from friction).

10.5. Appendix 5: Abbreviations and Definitions

Abbreviation or Specialist Term	Explanation
ACEND	Assessment of Caregiver Experience with Neuromuscular Disease
ADA	antidrug antibody
ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APTT	activated partial thromboplastin time
BMP	bone morphogenetic protein
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
DLT	dose-limiting toxicity
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EOS	end of study
EOT	end of treatment
ET	early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDF11	growth differentiation factor 11
hCG	human chorionic gonadotropin

Abbreviation or Specialist Term	Explanation
HFMSE	Hammersmith Functional Motor Scale Expanded
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	intention-to-treat
IV	intravenous
IWRS	Interactive Web-based Randomization System
mAb	monoclonal antibody
MAD	multiple ascending dose
MCH	mean corpuscular hemoglobin
MITT	Modified Intention-to-Treat
MMRM	mixed effects model with repeated measurement
NCI	National Cancer Institute
NIMP	Non-Investigational Medicinal Product
PD	pharmacodynamic(s)
PEDI-CAT	Pediatric Evaluation of Disability Inventory Computer Adaptive Test
PI	prescribing information
PK	pharmacokinetic(s)
PT/INR	prothrombin time/international normalized ratio
PROMIS	Patient-Reported Outcomes Measurement Information System
QTL	quality tolerance limits
RBC	red blood cell

Abbreviation or Specialist Term	Explanation
RULM	Revised Upper Limb Module
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SCR	Screening
SMA	spinal muscular atrophy
SMN	survival motor neuron
SMN upregulator	SMN corrector (ie, SPINRAZA, EVRYSDI)
SmPC	Summary of Product Characteristics
SoA	schedule of activities/assessments
SOP	standard operating procedure
SRK-015	apitegromab
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
Unsch	unscheduled
US	United States
V	visit
WBC	white blood cell
WHO	World Health Organization

11. REFERENCES

Ader D (2007). Developing the Patient-Reported Outcomes Measurement Information System (PROMIS). Med Care. 5(5):S1-S2.

Arnold WD, Kassar D, and Kissel JT (2015). Spinal muscular atrophy: diagnosis and management in a new therapeutic era. Muscle Nerve. 51(2):157-167.

Campbell C, McMillan HJ, Mah JK, et al. (2017). Myostatin inhibitor ACE-031 treatment of ambulatory boys with Duchenne muscular dystrophy: Results of a randomized, placebo-controlled clinical trial. Muscle Nerve. 55(4):458-464.

Conway PM, Erlangsen A, Teasdale TW, et al. (2016). Predictive validity of the Columbia-Suicide Severity Rating Scale for short-term suicidal behavior: a Danish study of adolescents at a high risk of suicide. Archives of Suicide Research. 21(3):455-469.

DeMets DL, Lan KKG (1994). Interim analysis: the alpha spending function approach. Statistics in Medicine. 13(13-14):1341-1352.

Dubowitz V, Sewry CA, Oldfors A (2013). Neurogenic disorders. In Muscle Biopsy: A Practical Approach. Saunders Press, Philadelphia, PA:235-249.

European Commission (2017). Ethical considerations for clinical trials on medicinal products conducted with minors: Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use. Revision 1, 18 September 2017. Available from: https://ec.europa.eu/health/system/files/2018-02/2017_09_18_ethical_consid_ct_with_minors_0.pdf.

EVRYSDI® (risdiplam) for oral solution. United States Prescribing Information. South San Francisco, CA: Genentech; 2022. (revised May 2022). Available from: https://www.gene.com/download/pdf/evrysdi_prescribing.pdf.

EVRYSDI® (risdiplam) for oral solution. Summary of Product Characteristics. Grenzach-Wyhlen, Germany: Roche; 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/evrysdi-epar-product-information_en.pdf.

Garito T, Zakaria M, Papanicolaou DA, et al. (2018). Effects of bimagrumab, an activin receptor type II inhibitor, on pituitary neurohormonal axes. Clin Endocrinol (Oxf). 88(6):908-919.

Gipson PY, Agarwala P, Opperman KJ, et al. (2015). Columbia-Suicide Severity Rating Scale. Pediatric Emergency Care 31(2): 88-94.

Glanzman AM, O'Hagen JM, McDermott MP, et al. (2011). Validation of the Expanded Hammersmith Functional Motor Scale in spinal muscular atrophy type II and III. J Child Neurol. 26(12):1499-1507.

Haley SM, Raczek AE, Coster WJ, et al. (2005). Assessing mobility in children using a computer adaptive testing version of the pediatric evaluation of disability inventory. Arch Phys Med Rehabil. 86(5):932-939.

Han HQ, Zhou X, Mitch WE, et al. (2013). Myostatin/activin pathway antagonism: molecular basis and therapeutic potential. Int J Biochem Cell Biol. 45:2333-2347.

Hochberg, YA (1988). Sharper Bonferroni procedure for multiple significance testing. Biometrika. 75:800-803.

Kenward MG, Roger JH (1997). Small sample inference for fixed effects from restricted maximum likelihood. Biometrics. 53(3):983-997.

Kochanek KD, Murphy SL, Xu JQ, Arias E (2019). Deaths: Final data for 2017. Nat Vit Stat Rep. 68(9):1-77.

Lee SJ (2010). Extracellular regulation of myostatin: A molecular rheostat for muscle mass. Immunol Endocr Metab Agents Med Chem. 10:183-194.

Lefebvre S, Burglen L, Reboullet S, et al. (1995). Identification and characterization of a spinal muscular atrophy-determining gene. Cell. 80(1):155-165.

Matsumoto H, Clayton-Krasinski DA, Klinge SA, et al. (2011). Development and initial validation of the assessment of caregiver experience with neuromuscular disease. J Pediatr Orthop. 31(3):284-292.

Mazzone ES, Mayhew A, Montes J, et al. (2017). Revised upper limb module for spinal muscular atrophy: Development of a new module. Muscle Nerve. 55(6):869-874.

McPherron AC, Lawler AM, Lee SJ (1997a). Regulation of skeletal muscle mass in mice by a new TGF-beta superfamily member. Nature. 387(6628):83-90.

McPherron AC, Lee SJ (1997b). Double muscling in cattle due to mutations in the myostatin gene. Proc Natl Acad Sci USA 94(23): 12457-12461.

Mercuri E, Darras BT, Chiriboga CA, et al. (2018). Nusinersen versus sham control in later-onset spinal muscular atrophy. N Engl J Med. 378(7):625-635.

Mercuri E, Barisic N, Boespflug-Tanguy O, et al. (2020). SUNFISH Part 2: Efficacy and safety of risdiplam (RG7916) in patients with Type 2 or non-ambulant Type 3 spinal muscular atrophy (SMA). 2nd International Scientific and Clinical Congress on Spinal Muscular Atrophy. February 5-7, 2020. Evry, France.

Meyer RD, Ratitch B, Wolbers M, et al. (2020). Statistical issues and recommendations for clinical trials conducted during the COVID-19 pandemic. Stat Biopharm. 12(4):399-411.

Mosher DS, Quignon P, Bustamante CD, et al. (2007). A mutation in the myostatin gene increases muscle mass and enhances racing performance in heterozygote dogs. PLoS Genet. 3(5):e79.

O'Hagen JM, Glanzman AM, McDermott MP, et al. (2007). An expanded version of the Hammersmith Functional Motor Scale for SMA II and III patients. Neuromuscul Disord. 17(9-10):693-697.

Pasternak A, Sideridis G, Fragala-Pinkham M, et al. (2016). Rasch analysis of the Pediatric Evaluation of Disability Inventory-computer adaptive test (PEDI-CAT) item bank for children and young adults with spinal muscular atrophy. Muscle Nerve. 54(6):1097-1107.

Pera MC, Coratti G, Forcina N, et al. (2017). Content validity and clinical meaningfulness of the HFMSE in spinal muscular atrophy. BMC Neurology. 17(1):39-49.

Posner K, Brown GK, Stanley B, et al. (2011). The Columbia-Suicide Severity Rating Scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 168(12):1266-1277.

Qu Y, Shurzinske L, Sethuraman S (2021). Defining estimands using a mix of strategies to handle intercurrent events in clinical trials. Pharm Stat. 20(2):314-323.

Schuelke M, Wagner KR, Stolz LE, et al. (2004). Myostatin mutation associated with gross muscle hypertrophy in a child. N Engl J Med. 350(26):2682-2688.

SPINRAZA® (nusinersen) injection, for intrathecal use. United States Prescribing Information. Cambridge, MA: Biogen; 2020. (revised June 2020). Available from: https://www.spinraza.com/content/dam/commercial/spinraza/caregiver/en_us/pdf/spinraza-prescribing-information.pdf.

SPINRAZA® (nusinersen) injection, for intrathecal use. Summary of Product Characteristics. Badhoevedorp, The Netherlands: Biogen; 2022. Available from: https://www.ema.europa.eu/en/documents/product-information/spinraza-epar-product-information_en.pdf.

Sugarman EA, Nagan N, Zhu H, et al. (2012). Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72400 specimens. Eur J Hum Genet. 20(1):27-32.

WHO Multicentre Growth Reference Study Group (2006). WHO Motor Development Study: windows of achievement for six gross motor development milestones. Acta Paediatr Suppl. 450:86-95.

Wijnhoven TM, de Onis M, Onyango AW, et al. (2004). Assessment of gross motor development in the WHO multicenter growth reference study, Food Nutr Bull. 25(1 Suppl):S37-S45.

Wirth B, Karakaya M, Kye MJ, et al. (2020). Twenty-five years of spinal muscular atrophy research: from phenotype to genotype to therapy, and what comes next. Annu Rev Genomics Hum Genet. 21(1):231-261.

ZOLGENSMA® (onasemnogene abeparvovec-xioi) suspension, for intravenous infusion. United States Prescribing Information. Bannockburn, IL: AveXis; 2021. (revised March 2021). Available from: https://www.novartis.us/sites/www.novartis.us/files/zolgensma.pdf.

ZOLGENSMA® (onasemnogene abeparvovec-xioi) suspension, for intravenous infusion. Summary of Product Characteristics. Dublin, Ireland: Novartis; 2021. Available from: https://www.ema.europa.eu/en/documents/product-information/zolgensma-epar-product-information_en.pdf.

9. DOCUMENTATION OF STATISTICAL METHODS

1. Statistical Analysis Plan, Version 1.0, 30 August 2024