Clinical trial results:
Phase 2 Active Treatment Study to Evaluate the Efficacy and Safety of SRK-015 in Patients with Later-Onset Spinal Muscular Atrophy

Summary

EudraCT number	2018-004383-65
Trial protocol	NL ES DE IT
Global end of trial date	28 February 2024

Results information

Result version number	v1 (current)
This version publication date	02 January 2025
First version publication date	02 January 2025

Trial information

Trial identification

Sponsor protocol code	SRK-015-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Scholar Rock, Inc.
Sponsor organisation address	31 Binney Street, 3rd Floor, Cambridge, United States, MA 02142
Public contact	Bert Yao, Scholar Rock, Inc., +1 9195939950, byao@scholarrock.com
Scientific contact	Bert Yao, Scholar Rock, Inc., +1 9195939950, byao@scholarrock.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 October 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 February 2024
Global end of trial reached?	Yes
Global end of trial date	28 February 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the trial were:
- Assess the safety and tolerability of apitegromab in subjects with Type 2 and Type 3 SMA over 12 months
- Assess the efficacy of apitegromab based on changes in motor-function outcome measures over 12 months

Protection of trial subjects:

This study was designed and monitored in accordance with Sponsor procedures, which comply with the ethical principles of the International Council for Harmonisation (ICH) on GCP guidance and in accordance with the Declaration of Helsinki (Version 2013). The study was also conducted in accordance with national and local legal requirements and in accordance with United States (US) Investigational New Drug regulations (21 Code of Federal Regulations [CFR] 56) and the European Union (EU)'s Commission Directive 2005/28/EC of 8 April 2005.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 April 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 41
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Italy: 9
Worldwide total number of subjects	58
EEA total number of subjects	17

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	39
Adolescents (12-17 years)	13
Adults (18-64 years)	6
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Sixty-five subjects at 16 study sites in the US and EU (Italy, Netherlands, and Spain) were screened. There were 7 screen failures and 58 subjects enrolled who received treatment.

Pre-assignment

Screening details:

- Age 5 through 21 years old for Cohorts 1 and 2; Age ≥2 years old for Cohort 3
- Documented diagnosis of 5q SMA
- Diagnosed as later-onset SMA prior to receiving any therapy approved for SMA
- For Cohort 1, RHS score no greater than 63 at Screening
- For Cohort 2 and 3, HFMSE score no less than 10 at Screening

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Cohorts 1 and 2 are open-label cohorts which are directly assigned to the 20 mg/kg dose of SRK-015 while Cohort 3 patients will be randomized (1:1) in a double-blind manner to receive either 2 mg/kg or 20 mg/kg SRK-015 via an Interactive Web-based Randomization System (IWRS). The Sponsor, patients, caregivers, Investigators, and site personnel, with the exception of the Pharmacist, will be blinded to Cohort 3 SRK-015 dose level assignments.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 SRK-015 20 mg/kg

Arm description:

Ambulatory Type 3 subjects, ages 5 to 21 years, who were not receiving nusinersen (SRK-015 alone). ITT population - All enrolled/randomized subjects (enrolled for Cohorts 1 and 2 and randomized for Cohort 3) who received at least 1 dose of SRK-015.

Arm type	Experimental
Investigational medicinal product name	SRK-015
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

SRK-015 will be administered to patients at 20 mg/kg, according to the cohort assignments. Doses will be diluted in normal saline and administered by IV over 2 hours (+10-minute window).
All doses will be administered via peripheral IV (or via long-term IV access device such as a peripherally inserted central catheter or port, if the patient has such a device for their background medical care).

Arm title	Cohort 1 SRK-015 20mg/kg + SMN therapy

Arm description:

Ambulatory Type 3 subjects, ages 5 to 21 years, who were already receiving an SMN therapy (ie, nusinersen) that they would receive in the current study that was initiated when the subject was ≥5 years old (SRK-015 + nusinersen).
ITT population - All enrolled/randomized subjects (enrolled for Cohorts 1 and 2 and randomized for Cohort 3) who received at least 1 dose of SRK-015.

Arm type	Experimental

Investigational medicinal product name	SRK-015
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

SRK-015 will be administered to patients at 20 mg/kg, according to the cohort assignments. Doses will be diluted in normal saline and administered by IV over 2 hours (+10-minute window).
All doses will be administered via peripheral IV (or via long-term IV access device such as a peripherally inserted central catheter or port, if the patient has such a device for their background medical care).

Arm title	Cohort 2 SRK-015 20mg/kg + SMN therapy

Arm description:

Type 2 or non-ambulatory Type 3 subjects ages 5 to 21 years who were already receiving nusinersen that was initiated after the subject turned 5 years of age.
ITT population - All enrolled/randomized subjects (enrolled for Cohorts 1 and 2 and randomized for Cohort 3) who received at least 1 dose of SRK-015.

Arm type	Experimental
Investigational medicinal product name	SRK-015
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

SRK-015 will be administered to patients at 20 mg/kg, according to the cohort assignments. Doses will be diluted in normal saline and administered by IV over 2 hours (+10-minute window).
All doses will be administered via peripheral IV (or via long-term IV access device such as a peripherally inserted central catheter or port, if the patient has such a device for their background medical care).

Arm title	Cohort 3 SRK-015 2mg/kg + SMN therapy

Arm description:

Type 2 non-ambulatory subjects ages ≥2 years already receiving nusinersen that was initiated when the subject was <5 years old.
ITT population - All enrolled/randomized subjects (enrolled for Cohorts 1 and 2 and randomized for Cohort 3) who received at least 1 dose of SRK-015.

Arm type	Experimental
Investigational medicinal product name	SRK-015
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

SRK-015 will be administered to patients at 2 mg/kg, according to the cohort assignments. Doses will be diluted in normal saline and administered by IV over 2 hours (+10-minute window).
All doses will be administered via peripheral IV (or via long-term IV access device such as a peripherally inserted central catheter or port, if the patient has such a device for their background medical care).

Arm title	Cohort 3 SRK-015 20 mg/kg + SMN therapy

Arm description:

Type 2 non-ambulatory subjects ages ≥2 years already receiving nusinersen that was initiated when the subject was <5 years old.
ITT population - All enrolled/randomized subjects (enrolled for Cohorts 1 and 2 and randomized for Cohort 3) who received at least 1 dose of SRK-015.

Arm type	Experimental
Investigational medicinal product name	SRK-015
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

SRK-015 will be administered to patients at 20 mg/kg, according to the cohort assignments. Doses will be diluted in normal saline and administered by IV over 2 hours (+10-minute window).
All doses will be administered via peripheral IV (or via long-term IV access device such as a peripherally inserted central catheter or port, if the patient has such a device for their background medical care).

Number of subjects in period 1	Cohort 1 SRK-015 20 mg/kg	Cohort 1 SRK-015 20mg/kg + SMN therapy	Cohort 2 SRK-015 20mg/kg + SMN therapy
Started	11	12	15
Completed	11	11	15
Not completed	0	1	0
Consent withdrawn by subject	-	1	-

Number of subjects in period 1	Cohort 3 SRK-015 2mg/kg + SMN therapy	Cohort 3 SRK-015 20 mg/kg + SMN therapy
Started	10	10
Completed	10	10
Not completed	0	0
Consent withdrawn by subject	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1 SRK-015 20 mg/kg
Reporting group description:	
Ambulatory Type 3 subjects, ages 5 to 21 years, who were not receiving nusinersen (SRK-015 alone). ITT population - All enrolled/randomized subjects (enrolled for Cohorts 1 and 2 and randomized for Cohort 3) who received at least 1 dose of SRK-015.	
Reporting group title	Cohort 1 SRK-015 20mg/kg + SMN therapy
Reporting group description:	
Ambulatory Type 3 subjects, ages 5 to 21 years, who were already receiving an SMN therapy (ie, nusinersen) that they would receive in the current study that was initiated when the subject was ≥5 years old (SRK-015 + nusinersen). ITT population - All enrolled/randomized subjects (enrolled for Cohorts 1 and 2 and randomized for Cohort 3) who received at least 1 dose of SRK-015.	
Reporting group title	Cohort 2 SRK-015 20mg/kg + SMN therapy
Reporting group description:	
Type 2 or non-ambulatory Type 3 subjects ages 5 to 21 years who were already receiving nusinersen that was initiated after the subject turned 5 years of age. ITT population - All enrolled/randomized subjects (enrolled for Cohorts 1 and 2 and randomized for Cohort 3) who received at least 1 dose of SRK-015.	
Reporting group title	Cohort 3 SRK-015 2mg/kg + SMN therapy
Reporting group description:	
Type 2 non-ambulatory subjects ages ≥2 years already receiving nusinersen that was initiated when the subject was <5 years old. ITT population - All enrolled/randomized subjects (enrolled for Cohorts 1 and 2 and randomized for Cohort 3) who received at least 1 dose of SRK-015.	
Reporting group title	Cohort 3 SRK-015 20 mg/kg + SMN therapy
Reporting group description:	
Type 2 non-ambulatory subjects ages ≥2 years already receiving nusinersen that was initiated when the subject was <5 years old. ITT population - All enrolled/randomized subjects (enrolled for Cohorts 1 and 2 and randomized for Cohort 3) who received at least 1 dose of SRK-015.	

Reporting group values	Cohort 1 SRK-015 20 mg/kg	Cohort 1 SRK-015 20mg/kg + SMN therapy	Cohort 2 SRK-015 20mg/kg + SMN therapy
Number of subjects	11	12	15
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	5	5	9
Adolescents (12-17 years)	5	4	4
Adults (18-64 years)	1	3	2
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	8	7	8
Male	3	5	7

Reporting group values	Cohort 3 SRK-015 2mg/kg + SMN therapy	Cohort 3 SRK-015 20 mg/kg + SMN therapy	Total
Number of subjects	10	10	58
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	10	10	39
Adolescents (12-17 years)	0	0	13
Adults (18-64 years)	0	0	6
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	3	5	31
Male	7	5	27

End points

End points reporting groups

Reporting group title	Cohort 1 SRK-015 20 mg/kg

Reporting group description:

Ambulatory Type 3 subjects, ages 5 to 21 years, who were not receiving nusinersen (SRK-015 alone).
ITT population - All enrolled/randomized subjects (enrolled for Cohorts 1 and 2 and randomized for Cohort 3) who received at least 1 dose of SRK-015.

Reporting group title	Cohort 1 SRK-015 20mg/kg + SMN therapy

Reporting group description:

Ambulatory Type 3 subjects, ages 5 to 21 years, who were already receiving an SMN therapy (ie, nusinersen) that they would receive in the current study that was initiated when the subject was ≥5 years old (SRK-015 + nusinersen).
ITT population - All enrolled/randomized subjects (enrolled for Cohorts 1 and 2 and randomized for Cohort 3) who received at least 1 dose of SRK-015.

Reporting group title	Cohort 2 SRK-015 20mg/kg + SMN therapy

Reporting group description:

Type 2 or non-ambulatory Type 3 subjects ages 5 to 21 years who were already receiving nusinersen that was initiated after the subject turned 5 years of age.
ITT population - All enrolled/randomized subjects (enrolled for Cohorts 1 and 2 and randomized for Cohort 3) who received at least 1 dose of SRK-015.

Reporting group title	Cohort 3 SRK-015 2mg/kg + SMN therapy

Reporting group description:

Type 2 non-ambulatory subjects ages ≥2 years already receiving nusinersen that was initiated when the subject was <5 years old.
ITT population - All enrolled/randomized subjects (enrolled for Cohorts 1 and 2 and randomized for Cohort 3) who received at least 1 dose of SRK-015.

Reporting group title	Cohort 3 SRK-015 20 mg/kg + SMN therapy

Reporting group description:

Type 2 non-ambulatory subjects ages ≥2 years already receiving nusinersen that was initiated when the subject was <5 years old.
ITT population - All enrolled/randomized subjects (enrolled for Cohorts 1 and 2 and randomized for Cohort 3) who received at least 1 dose of SRK-015.

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

End point title	Change from Baseline in the RHS total score at Day 364 (Visit 15)[1][2]

End point description:

The end point was summarized using descriptive statistics for all treated subjects who did not miss 3 consecutive doses due to site access restrictions caused by COVID-19. Last observation carried forward (LOCF) was used for patients missing data for other reasons.

End point type	Primary

End point timeframe:

Primary efficacy endpoint was assessed at Month 12 (Day 364)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary endpoint results were summarized using descriptive statistics by cohort and by dose for Cohort 2 and 3. No statistical hypothesis analysis has been conducted.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This primary endpoint was only for assessment of Cohort 1.

End point values	Cohort 1 SRK-015 20 mg/kg	Cohort 1 SRK-015 20mg/kg + SMN therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	12		
Units: RHS score				
arithmetic mean (standard deviation)	-0.1 (± 5.01)	0.0 (± 2.56)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in HFMSE total score at Day 364 (Visit 15)

End point title	Change from Baseline in HFMSE total score at Day 364 (Visit 15)[3][4]

End point description:

The end point was summarized using descriptive statistics for all treated subjects who did not miss 3 consecutive doses due to site access restrictions caused by COVID-19. Last observation carried forward (LOCF) was used for patients missing data for other reasons.

End point type	Primary

End point timeframe:

Primary efficacy endpoint was assessed at Month 12 (Day 364)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The primary endpoint results were summarized using descriptive statistics by cohort and by SMN therapy for Cohort 1. No statistical hypothesis analysis has been conducted.
[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This primary endpoint was only for assessment of Cohort 2 and 3.

End point values	Cohort 2 SRK-015 20mg/kg + SMN therapy	Cohort 3 SRK-015 2mg/kg + SMN therapy	Cohort 3 SRK-015 20 mg/kg + SMN therapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	9	8	
Units: HFMSE total score				
arithmetic mean (standard deviation)	0.6 (± 3.50)	5.3 (± 8.93)	7.1 (± 6.42)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
During the 48-month study period.	
Adverse event reporting additional description:	
The adverse events (AEs) described in this section correspond to treatment-emergent adverse events (TEAEs).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups	
Reporting group title	Safety Population
Reporting group description:	
All subjects who received at least 1 dose of SRK-015.	

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 58 (48.28%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Joint dislocation			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pneumothorax traumatic			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post lumbar puncture syndrome			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Developmental hip dysplasia			

subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Scoliosis surgery			
subjects affected / exposed	7 / 58 (12.07%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Joint dislocation reduction			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Adenoidectomy			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hospitalisation			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal fusion surgery			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal implantation			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Gait inability			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Asthma			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atelectasis			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Obstructive sleep apnoea syndrome			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sleep apnoea syndrome			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tonsillar hypertrophy			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Liver injury			

subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Major depression			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Scoliosis			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Joint contracture			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory syncytial virus infection			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Influenza			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection viral			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rhinovirus infection			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	57 / 58 (98.28%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	4		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	6		
Vaccination site pain			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	26 / 58 (44.83%)		
occurrences (all)	72		
Immune system disorders			
Seasonal allergy			

subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	23 / 58 (39.66%)		
occurrences (all)	53		
Nasal congestion			
subjects affected / exposed	11 / 58 (18.97%)		
occurrences (all)	25		
Oropharyngeal pain			
subjects affected / exposed	11 / 58 (18.97%)		
occurrences (all)	24		
Rhinitis allergic			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Rhinorrhoea			
subjects affected / exposed	9 / 58 (15.52%)		
occurrences (all)	20		
Tonsillar hypertrophy			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Investigations			
Heart rate increased			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	15 / 58 (25.86%)		
occurrences (all)	71		
Ligament sprain			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	6		
Post lumbar puncture syndrome			
subjects affected / exposed	6 / 58 (10.34%)		
occurrences (all)	10		
Contusion			

subjects affected / exposed occurrences (all) Procedural pain subjects affected / exposed occurrences (all) Joint dislocation subjects affected / exposed occurrences (all) Skin laceration subjects affected / exposed occurrences (all) Tibia fracture subjects affected / exposed occurrences (all) Femur fracture subjects affected / exposed occurrences (all)	6 / 58 (10.34%) 7 3 / 58 (5.17%) 3 8 / 58 (13.79%) 8 5 / 58 (8.62%) 6 4 / 58 (6.90%) 5 3 / 58 (5.17%) 3		
Cardiac disorders Tachycardia subjects affected / exposed occurrences (all)	6 / 58 (10.34%) 8		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	24 / 58 (41.38%) 59 7 / 58 (12.07%) 13		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Abdominal pain upper	18 / 58 (31.03%) 27 9 / 58 (15.52%) 15		

subjects affected / exposed	8 / 58 (13.79%)		
occurrences (all)	11		
Constipation			
subjects affected / exposed	9 / 58 (15.52%)		
occurrences (all)	10		
Toothache			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	18 / 58 (31.03%)		
occurrences (all)	43		
Abdominal pain			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	4		
Gastritis			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	5		
Dental caries			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	14 / 58 (24.14%)		
occurrences (all)	22		
Erythema			
subjects affected / exposed	6 / 58 (10.34%)		
occurrences (all)	7		
Eczema			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	5		
Pruritus			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		

Musculoskeletal and connective tissue disorders			
Scoliosis			
subjects affected / exposed	15 / 58 (25.86%)		
occurrences (all)	19		
Arthralgia			
subjects affected / exposed	9 / 58 (15.52%)		
occurrences (all)	16		
Pain in extremity			
subjects affected / exposed	9 / 58 (15.52%)		
occurrences (all)	18		
Joint contracture			
subjects affected / exposed	8 / 58 (13.79%)		
occurrences (all)	13		
Muscle spasms			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	4		
Myalgia			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	8 / 58 (13.79%)		
occurrences (all)	9		
Muscle contracture			
subjects affected / exposed	10 / 58 (17.24%)		
occurrences (all)	13		
Osteopenia			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	4		
Infections and infestations			
COVID-19			
subjects affected / exposed	26 / 58 (44.83%)		
occurrences (all)	29		
Upper respiratory tract infection			
subjects affected / exposed	24 / 58 (41.38%)		
occurrences (all)	50		
Nasopharyngitis			

subjects affected / exposed	22 / 58 (37.93%)			
occurrences (all)	65			
Gastroenteritis				
subjects affected / exposed	7 / 58 (12.07%)			
occurrences (all)	7			
Ear infection				
subjects affected / exposed	6 / 58 (10.34%)			
occurrences (all)	13			
Gastroenteritis viral				
subjects affected / exposed	5 / 58 (8.62%)			
occurrences (all)	5			
Otitis media				
subjects affected / exposed	4 / 58 (6.90%)			
occurrences (all)	6			
Pharyngitis streptococcal				
subjects affected / exposed	5 / 58 (8.62%)			
occurrences (all)	8			
Respiratory tract infection				
subjects affected / exposed	4 / 58 (6.90%)			
occurrences (all)	6			
Urinary tract infection				
subjects affected / exposed	4 / 58 (6.90%)			
occurrences (all)	5			
Viral rash				
subjects affected / exposed	3 / 58 (5.17%)			
occurrences (all)	3			
Influenza				
subjects affected / exposed	13 / 58 (22.41%)			
occurrences (all)	16			
Viral infection				
subjects affected / exposed	4 / 58 (6.90%)			
occurrences (all)	4			
Viral upper respiratory tract infection				
subjects affected / exposed	3 / 58 (5.17%)			
occurrences (all)	4			
Respiratory syncytial virus infection				

subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Rhinovirus infection			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	5		
Metabolism and nutrition disorders			
Iron deficiency			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Vitamin D deficiency			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 July 2019	The SRK-015-002 protocol was amended under version 2.0 as follows: • Increased time between dosing and conducting motor function outcome measures in order to reduce patient burden and add scheduling flexibility. • Updated inclusion criteria to include prolonged contraception in female and male populations. • Added definition of Women of Childbearing Potential (WOCBP). • Added pregnancy test sensitivity to provide additional clarification and details on pregnancy test used in the study. • Updated exclusion criteria to ensure patients with prior hypersensitivity reaction to SRK-015 or excipients of SRK-015 are excluded and to ensure adequate washout of prior investigational drugs and potential muscle enhancing drugs. • Updated currently available treatments to include newly approved SMA treatment. • Updated endpoint language to clarify score utilization in evaluations. • Added language for several endpoints that were previously not included. • Updated Phase 1 study (SRK015-001) data to include results from the completedstudy. • Increased time between dosing and weight measurement in order to reduce patient burden and add scheduling flexibility. • Specified that height is collected at visits where the motor function outcome measures are conducted to ensure consistent collection of height throughout the study. • Updated PK and PD blood sample collection language in order to provide additional samples to further support PK, PD and/or ADA assay validation and to enhance the meaningfulness of the analyses. • Removed Crystatin A as a safety assessment. • Added data protection language to clarify procedures. • Various typographical and formatting corrections as well as corrections for consistency made throughout the document.
21 November 2019	The SRK-015-002 protocol was amended as follows: - An optional extension period, with treatment for an additional 52 weeks, to observe long-term safety and efficacy effects of SRK-015 has been added - Minor clarifications throughout the protocol have been included
13 November 2020	The primary reasons for amending the SRK-015-002 protocol are to: • Revise the dosing for patients in Cohort 3 from low-dose (2 mg/kg) to high-dose (20 mg/kg) SRK-015 after completion of the Treatment Period. This dosing change is based on the results of the prespecified 6-month safety and efficacy interim analyses. Due to the variability in timing of regulatory authority and/or Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approvals, the timepoint at which patients who received the low dose (2 mg/ kg) will begin receiving the high dose (20 mg/ kg) during Extension Period A or B will vary. • Extend the Extension Period for an additional 52 weeks (as Extension Period B; Extension Visits EB1-15) to allow for collection and analysis of longer-term safety and efficacy data (104 weeks in total). To distinguish between the separate Extension Periods, the original Extension Period (Extension Visits E1-15) is now referred to as Extension Period A. • Add optional assessments to Unscheduled Visits, as follows: − Pharmacokinetic (PK)/Pharmacodynamic (PD)/antidrug antibody (ADA) sampling to provide the maximum confidence in population analyses and dosing predictions − Motor Function Outcome Measures and Quality-of-Life (QOL) questionnaires to allow for these assessments to be completed at a subsequent visit in the event that a protocol-specific visit is missed/skipped − Electrocardiograms (ECGs), as clinically necessary for safety

03 August 2021	The primary reasons for amending the SRK-015-002 protocol are to: • Extend the Extension Period for an additional 52 weeks (as Extension Period C; Extension Visits EC1-15) to allow for collection and analysis of longer-term safety and efficacy data (224 weeks in total duration). • Revise the frequency for SST review of safety data based on the schedule recommended by the pharmacovigilance and medical teams.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported