Clinical trial results:
An Open-Label Study of Risdiplam in Infants With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy

Summary

EudraCT number	2018-002087-12
Trial protocol	BE PL IT
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	06 March 2024
First version publication date	06 March 2024

Trial information

Trial identification

Sponsor protocol code	BN40703

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03779334
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002070-PIP01-16
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?	Yes

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	20 February 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 February 2023
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the clinical study is to investigate the efficacy of risdiplam in infants aged from birth to 6 weeks who have been genetically diagnosed with spinal muscular atrophy (SMA) but are not yet presenting with symptoms.

Protection of trial subjects:

A legally authorized representative for the participant was required to read and sign an informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 August 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Russian Federation: 5
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	26
EEA total number of subjects	6

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	15
Infants and toddlers (28 days-23 months)	11

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

Subject disposition

Recruitment

Recruitment details:

Overall, 26 infants with spinal muscular atrophy (SMA) were enrolled in the study across 7 different sites in 7 countries.

Pre-assignment

Screening details:

The study enrolled infants aged from birth to 6 weeks who were genetically diagnosed with SMA but were not yet presenting with symptoms. Study arms were based on the number of copies of the SMN2 gene.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	2 SMN2 Copies, Risdiplam

Arm description:

Infants with 2 copies of SMN2 were enrolled to receive risdiplam orally once daily at a dose selected to achieve the targeted exposure range.

Arm type	Experimental
Investigational medicinal product name	risdiplam
Investigational medicinal product code	
Other name	Evrysdi
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Risdiplam was administered orally at a dose selected to achieve the targeted exposure range of close to 2000 ng*hr/mL.

Arm title	3 SMN2 Copies, Risdiplam

Arm description:

Infants with 3 copies of SMN2 were enrolled to receive risdiplam orally once daily at a dose selected to achieve the targeted exposure range.

Arm type	Experimental
Investigational medicinal product name	risdiplam
Investigational medicinal product code	
Other name	Evrysdi
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Risdiplam was administered orally at a dose selected to achieve the targeted exposure range of close to 2000 ng*hr/mL.

Arm title	>/=4 SMN2 Copies, Risdiplam

Arm description:

Infants with 4 or more copies of SMN2 were enrolled to receive risdiplam orally once daily at a dose selected to achieve the targeted exposure range.

Arm type	Experimental

Investigational medicinal product name	risdiplam
Investigational medicinal product code	
Other name	Evrysdi
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Risdiplam was administered orally at a dose selected to achieve the targeted exposure range of close to 2000 ng*hr/mL.

Number of subjects in period 1	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam
Started	8	13	5
Primary Efficacy Population	5	0	0
Completed	0	0	0
Not completed	8	13	5
Consent withdrawn by subject	3	-	-
Ongoing in Study	5	13	5

Baseline characteristics

Reporting groups	
Reporting group title	2 SMN2 Copies, Risdiplam
Reporting group description:	
Infants with 2 copies of SMN2 were enrolled to receive risdiplam orally once daily at a dose selected to achieve the targeted exposure range.	
Reporting group title	3 SMN2 Copies, Risdiplam
Reporting group description:	
Infants with 3 copies of SMN2 were enrolled to receive risdiplam orally once daily at a dose selected to achieve the targeted exposure range.	
Reporting group title	>/=4 SMN2 Copies, Risdiplam
Reporting group description:	
Infants with 4 or more copies of SMN2 were enrolled to receive risdiplam orally once daily at a dose selected to achieve the targeted exposure range.	

Reporting group values	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam
Number of subjects	8	13	5
Age categorical Units: Subjects			
Age Continuous Units: days			
arithmetic mean	22.8	28.9	31.2
standard deviation	± 5.0	± 7.5	± 6.1
Sex: Female, Male Units: participants			
Female	4	9	3
Male	4	4	2

Reporting group values	Total		
Number of subjects	26		
Age categorical Units: Subjects			
Age Continuous Units: days			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: participants			
Female	16		
Male	10		

End points

End points reporting groups

Reporting group title	2 SMN2 Copies, Risdiplam
Reporting group description:	
Infants with 2 copies of SMN2 were enrolled to receive risdiplam orally once daily at a dose selected to achieve the targeted exposure range.	
Reporting group title	3 SMN2 Copies, Risdiplam
Reporting group description:	
Infants with 3 copies of SMN2 were enrolled to receive risdiplam orally once daily at a dose selected to achieve the targeted exposure range.	
Reporting group title	>/=4 SMN2 Copies, Risdiplam
Reporting group description:	
Infants with 4 or more copies of SMN2 were enrolled to receive risdiplam orally once daily at a dose selected to achieve the targeted exposure range.	

Primary: Percentage of participants with two copies of the survival motor neuron (SMN) 2 gene (excluding the known SMN2 gene modifier mutation c.859G>C) and baseline compound muscle action potential (CMAP) >=1.5 millivolt (mV) who are sitting without support

End point title	Percentage of participants with two copies of the survival motor neuron (SMN) 2 gene (excluding the known SMN2 gene modifier mutation c.859G>C) and baseline compound muscle action potential (CMAP) >=1.5 millivolt (mV) who are sitting without support[1][2]

End point description:

The Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) Gross Motor Scale is a commonly used measure of infant and toddler development (0 to 42 months). The gross motor scale consists of 72 items scored at 0 (unable to perform the activity) or 1 (item achieved). Item 22, "sits without support for 5 seconds", is not considered achieved if the infant sits alone for less than 5 seconds before losing balance and falling over, or if the infant uses his or her arms to prop him- or herself up. Primary efficacy population included all infants in the ITT population with two SMN2 copies (excluding the known SMN2 gene modifier mutation c.859G>C) and a baseline compound muscle action potential (CMAP) amplitude >/= 1.5 mV. 90% CI for one sample binomial was computed using Clopper-Pearson (exact) method. An exact binomial test was performed. If the lower limit of the two-sided 90% CI was above the 5% threshold, the primary objective of the study was considered achieved.

End point type	Primary

End point timeframe:

At Month 12

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: Data were reported for only one arm and no statistical analysis could be 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: Only one arm in the study met the requirements for the primary efficacy analysis population of this endpoint.

End point values	2 SMN2 Copies, Risdiplam			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: percentage of participants				
number (confidence interval 90%)	80.0 (34.26 to 98.98)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants developing clinically manifested SMA

End point title	Percentage of participants developing clinically manifested SMA

End point description:

End point type	Secondary

End point timeframe:

At Month 12 and 24

End point values	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[3]	0[4]	0[5]	
Units: percentage of participants				
number (confidence interval 90%)	(to)	(to)	(to)	

Notes:

[3] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

[4] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

[5] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who are alive without permanent ventilation

End point title	Percentage of participants who are alive without permanent ventilation

End point description:

End point type	Secondary

End point timeframe:

At Month 12 and 24

End point values	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[6]	0[7]	0[8]	
Units: percentage of participants				
number (confidence interval 90%)	(to)	(to)	(to)	

Notes:

[6] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

[7] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

[8] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to permanent ventilation and/or death

End point title	Time to permanent ventilation and/or death

End point description:

End point type	Secondary

End point timeframe:

Up to 7 years

End point values	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[9]	0[10]	0[11]	
Units: months				
median (full range (min-max))	(to)	(to)	(to)	

Notes:

[9] - Data collection is still ongoing. Results to be reported at final analysis.

[10] - Data collection is still ongoing. Results to be reported at final analysis.

[11] - Data collection is still ongoing. Results to be reported at final analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants alive

End point title	Percentage of participants alive

End point description:

End point type	Secondary

End point timeframe:

At Month 12 and 24

End point values	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[12]	0[13]	0[14]	
Units: percentage of participants				
number (not applicable)				

Notes:

[12] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

[13] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

[14] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who achieve the attainment level of the motor milestones as assessed in the Hammersmith Infant Neurological Examination-2 (HINE-2)

End point title	Percentage of participants who achieve the attainment level of the motor milestones as assessed in the Hammersmith Infant Neurological Examination-2 (HINE-2)

End point description:

HINE-2 assessment includes head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking

End point type	Secondary

End point timeframe:

At Month 12 and 24

End point values	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[15]	0[16]	0[17]	
Units: percentage of participants				
number (confidence interval 90%)	(to)	(to)	(to)	

Notes:

[15] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

[16] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

[17] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with two copies of the SMN2 gene sitting without support for 5 seconds (independent of the CMAP value at baseline).

End point title	Percentage of participants with two copies of the SMN2 gene sitting without support for 5 seconds (independent of the CMAP value at baseline).[18]

End point description:

Assessed in Item 22 of the BSID-III Gross Motor Scale. The BSID-III is a commonly used measure of infant and toddler development (0 to 42 months). The normed-scores derived from the BSID-III are

used in clinical practice to detect infants with developmental delays, as well as to evaluate developmental progress and the impact of therapeutic interventions. The gross motor scale consists of 72 items scored at 0 (unable to perform the activity) or 1 (criteria for item achieved). Item 22, "sits without support for 5 seconds", is not considered achieved if the infant sits alone for less than 5 seconds before losing balance and falling over, or if the infant uses his or her arms to prop him- or herself up. Intent-to-treat (ITT) population included all enrolled participants, regardless of whether they received risdiplam or not. Only participants with two copies of the SMN2 gene were included in this endpoint. 90% CI for one sample binomial was computed used Clopper-Pearson (exact) method.

End point type	Secondary

End point timeframe:

At Month 12

Notes:

[18] - 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: Only one arm in the study met the requirements for the efficacy analysis population of this endpoint.

End point values	2 SMN2 Copies, Risdiplam			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: percentage of participants				
number (confidence interval 90%)	87.5 (52.93 to 99.36)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants sitting without support for 30 seconds

End point title	Percentage of participants sitting without support for 30 seconds

End point description:

Assessed with BSID-III Gross Motor Scale

End point type	Secondary

End point timeframe:

At Month 12 and 24

End point values	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[19]	0[20]	0[21]	
Units: percentage of participants				
number (confidence interval 90%)	(to)	(to)	(to)	

Notes:

[19] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

[20] - Data collection is still ongoing. Results to be reported at two-year interim analysis.
[21] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants standing for at least 3 seconds

End point title	Percentage of participants standing for at least 3 seconds
End point description: Assessed with BSID-III Gross Motor Scale	
End point type	Secondary
End point timeframe: At Month 24	

End point values	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[22]	0[23]	0[24]	
Units: percentage of participants				
number (confidence interval 90%)	(to)	(to)	(to)	

Notes:
[22] - Data collection is still ongoing. Results to be reported at two-year interim analysis.
[23] - Data collection is still ongoing. Results to be reported at two-year interim analysis.
[24] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants sitting without support for 5 seconds

End point title	Percentage of participants sitting without support for 5 seconds
End point description: Assessed with BSID-III Gross Motor Scale	
End point type	Secondary
End point timeframe: At Month 24	

End point values	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[25]	0[26]	0[27]	
Units: percentage of participants				
number (confidence interval 90%)	(to)	(to)	(to)	

Notes:

[25] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

[26] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

[27] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline score in the Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) motor function scale at Month 12

End point title	Change from baseline score in the Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) motor function scale at Month 12

End point description:

The CHOP-INTEND is a measure of motor function that was developed from the Test of Infant Motor Performance specifically for weak infants with neuromuscular disease. It consists of 16 items, where each item assesses a specific motor task (such as spontaneous movement of upper and lower extremity, hand grasping, rolling, head control, and others) graded on a scale of 0 to 4, where zero is no response and 4 is a complete response. A total score is calculated by summing the item scores (range 0 to 64) with lower scores indicating greater severity. A positive change from baseline indicates an improvement. ITT population included all enrolled participants, regardless of whether they received risdiplam or not. n indicates the number of participants analyzed for each time point.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	13	5	
Units: score on a scale				
median (full range (min-max))				
Baseline (n=8, 13, 5)	46.50 (35.0 to 52.0)	55.00 (44.0 to 62.0)	50.00 (44.0 to 52.0)	
Change from Baseline at Month 12 (n=8, 13, 4)	9.50 (-6.0 to 20.0)	8.00 (2.0 to 20.0)	16.00 (8.0 to 19.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants demonstrating the ability to achieve a scaled score on BSID-III Gross Motor Subtests within 1.5 standard deviations of chronological reference standard

End point title	Percentage of participants demonstrating the ability to achieve a scaled score on BSID-III Gross Motor Subtests within 1.5 standard deviations of chronological reference standard

End point description:

Assessed through BSID-III Gross Motor Scale

End point type	Secondary

End point timeframe:

At Month 24 and 42

End point values	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[28]	0[29]	0[30]	
Units: percentage of participants				
number (confidence interval 90%)	(to)	(to)	(to)	

Notes:

[28] - Data collection is still ongoing. Results to be reported at final analysis.

[29] - Data collection is still ongoing. Results to be reported at final analysis.

[30] - Data collection is still ongoing. Results to be reported at final analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants walking (takes at least 3 steps)

End point title	Percentage of participants walking (takes at least 3 steps)

End point description:

Assessed with BSID-III Gross Motor Scale

End point type	Secondary

End point timeframe:

At Month 24

End point values	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[31]	0[32]	0[33]	
Units: percentage of participants				
number (confidence interval 90%)	(to)	(to)	(to)	

Notes:

[31] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

[32] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

[33] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who meet CHOP INTEND stopping criteria at any point

End point title	Percentage of participants who meet CHOP INTEND stopping criteria at any point

End point description:

End point type	Secondary

End point timeframe:

Up to Month 24

End point values	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[34]	0[35]	0[36]	
Units: percentage of participants				
number (confidence interval 90%)	(to)	(to)	(to)	

Notes:

[34] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

[35] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

[36] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who achieve a score of 40 or higher, 50 or higher, and 60 or higher in the CHOP INTEND motor function scale at Month 12

End point title	Percentage of participants who achieve a score of 40 or higher, 50 or higher, and 60 or higher in the CHOP INTEND motor function scale at Month 12

End point description:

The CHOP-INTEND is a measure of motor function that was developed from the Test of Infant Motor Performance specifically for weak infants with neuromuscular disease. It consists of 16 items, where each item assesses a specific motor task (such as spontaneous movement of upper and lower extremity, hand grasping, rolling, head control, and others) graded on a scale of 0 to 4, where zero is no response and 4 is a complete response. A total score is calculated by summing the item scores (range 0 to 64) with lower scores indicating greater severity. ITT population included all enrolled participants, regardless of whether they received risdiplam or not. Data are presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion.

End point type	Secondary

End point timeframe:

At Month 12

End point values	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	8	13	4	
Units: percentage of participants				
number (confidence interval 90%)				
Score >=40	75.0 (40.03 to 95.36)	100 (79.42 to 100.00)	100 (47.29 to 100.00)	
Score >=50	75.0 (40.03 to 95.36)	100 (79.42 to 100.00)	100 (47.29 to 100.00)	
Score >=60	37.5 (11.11 to 71.08)	100 (79.42 to 100.00)	100 (47.29 to 100.00)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the Hammersmith Functional Motor Scale Expanded (HFMSE) score

End point title	Change from baseline in the Hammersmith Functional Motor Scale Expanded (HFMSE) score

End point description:

End point type	Secondary

End point timeframe:

At Month 60

End point values	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[37]	0[38]	0[39]	
Units: score on a scale				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[37] - Data collection is still ongoing. Results to be reported at final analysis.

[38] - Data collection is still ongoing. Results to be reported at final analysis.

[39] - Data collection is still ongoing. Results to be reported at final analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants within 3rd percentile of normal range for head circumference-for-age

End point title	Percentage of participants within 3rd percentile of normal range for head circumference-for-age

End point description:

Based on the WHO Child Growth Standards (WHO 2019)

End point type	Secondary

End point timeframe:

At Month 12 and 24

End point values	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[40]	0[41]	0[42]	
Units: percentage of participants				
number (confidence interval 90%)	(to)	(to)	(to)	

Notes:

[40] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

[41] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

[42] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants within 3rd percentile of normal range for weightforage, length/heightforage and weightforlength/height

End point title	Percentage of participants within 3rd percentile of normal range for weightforage, length/heightforage and weightforlength/height

End point description:

Based on the WHO Child Growth Standards (WHO 2019)

End point type	Secondary

End point timeframe:

At Month 12, 24, 36, 48 and 60

End point values	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[43]	0[44]	0[45]	
Units: percentage of participants				
number (confidence interval 90%)	(to)	(to)	(to)	

Notes:

[43] - Data collection is still ongoing. Results to be reported at final analysis.

[44] - Data collection is still ongoing. Results to be reported at final analysis.

[45] - Data collection is still ongoing. Results to be reported at final analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline percentiles for head circumference- for-age

End point title	Change from baseline percentiles for head circumference- for-age

End point description:

End point type	Secondary

End point timeframe:

At Month 12 and 24

End point values	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[46]	0[47]	0[48]	
Units: percentile				
number (not applicable)				

Notes:

[46] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

[47] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

[48] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in chest circumference

End point title	Change from baseline in chest circumference

End point description:

End point type	Secondary

End point timeframe:

At Month 12 and 24

End point values	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[49]	0[50]	0[51]	
Units: percentile				
number (not applicable)				

Notes:

[49] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

[50] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

[51] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline percentiles for weight-for-age, length/height-for-age, and weight-for- length/height

End point title	Change from baseline percentiles for weight-for-age, length/height-for-age, and weight-for- length/height

End point description:

End point type	Secondary

End point timeframe:

At Month 12, 24, 36, 48 and 60

End point values	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[52]	0[53]	0[54]	
Units: percentile				
number (not applicable)				

Notes:

[52] - Data collection is still ongoing. Results to be reported at final analysis.

[53] - Data collection is still ongoing. Results to be reported at final analysis.

[54] - Data collection is still ongoing. Results to be reported at final analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Ratio between chest and head circumferences

End point title	Ratio between chest and head circumferences

End point description:

End point type	Secondary

End point timeframe:

At Month 12 and 24

End point values	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[55]	0[56]	0[57]	
Units: chest/head ratio				
number (not applicable)				

Notes:

[55] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

[56] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

[57] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with the ability to swallow and to feed orally

End point title	Percentage of participants with the ability to swallow and to feed orally

End point description:

End point type	Secondary

End point timeframe:

At Month 12, 24, 36, 48 and 60

End point values	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[58]	0[59]	0[60]	
Units: percentage of participants				
number (confidence interval 90%)	(to)	(to)	(to)	

Notes:

[58] - Data collection is still ongoing. Results to be reported at final analysis.

[59] - Data collection is still ongoing. Results to be reported at final analysis.

[60] - Data collection is still ongoing. Results to be reported at final analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in compound muscle action potential (CMAP) amplitude

End point title	Change from baseline in compound muscle action potential (CMAP) amplitude

End point description:

Measured by CMAP

End point type	Secondary

End point timeframe:

At Month 12 and 24

End point values	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[61]	0[62]	0[63]	
Units: mV				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[61] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

[62] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

[63] - Data collection is still ongoing. Results to be reported at two-year interim analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with adverse events

End point title	Percentage of participants with adverse events

End point description:

Adverse event severity is determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5 (NCI CTCAE) v5

End point type	Secondary

End point timeframe:

Up to 7 years

End point values	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[64]	0[65]	0[66]	
Units: percentage of participants				
number (not applicable)				

Notes:

[64] - Data collection is still ongoing. Results to be reported at final analysis.

[65] - Data collection is still ongoing. Results to be reported at final analysis.

[66] - Data collection is still ongoing. Results to be reported at final analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with clinically meaningful changes in ophthalmological measures as appropriate for age

End point title	Percentage of participants with clinically meaningful changes in ophthalmological measures as appropriate for age

End point description:

End point type	Secondary

End point timeframe:

Up to 7 years

End point values	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[67]	0[68]	0[69]	
Units: percentage of participants				
number (not applicable)				

Notes:

[67] - Data collection is still ongoing. Results to be reported at final analysis.

[68] - Data collection is still ongoing. Results to be reported at final analysis.

[69] - Data collection is still ongoing. Results to be reported at final analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentration of risdiplam and its metabolites to characterize the PK profile

End point title	Plasma concentration of risdiplam and its metabolites to characterize the PK profile

End point description:

End point type	Secondary

End point timeframe:

Up to 7 years

End point values	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[70]	0[71]	0[72]	
Units: ng/mL				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[70] - Data collection is still ongoing. Results to be reported at final analysis.

[71] - Data collection is still ongoing. Results to be reported at final analysis.

[72] - Data collection is still ongoing. Results to be reported at final analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Measurement of pharmacodynamic marker levels in blood

End point title	Measurement of pharmacodynamic marker levels in blood

End point description:

End point type	Secondary

End point timeframe:

Day 1, 56, 196, 364, 728 and at early withdrawal

End point values	2 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[73]	0[74]	0[75]	
Units: nanograms/milliliter (ng/mL)				
arithmetic mean (standard deviation)	()	()	()	

Notes:

[73] - Data collection is still ongoing. Results to be reported at final analysis.

[74] - Data collection is still ongoing. Results to be reported at final analysis.

[75] - Data collection is still ongoing. Results to be reported at final analysis.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From baseline up to the clinical cut off date (a minimum of 12 months and a maximum of 3.5 years)	
Adverse event reporting additional description:	
The safety population included all participants who received at least one dose of risdiplam, whether prematurely withdrawn from the study or not.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups	
Reporting group title	2 SMN2 Copies, Risdiplam
Reporting group description:	
Infants with 2 copies of SMN2 were enrolled to receive risdiplam orally once daily at a dose selected to achieve the targeted exposure range.	
Reporting group title	>/=4 SMN2 Copies, Risdiplam
Reporting group description:	
Infants with 4 or more copies of SMN2 were enrolled to receive risdiplam orally once daily at a dose selected to achieve the targeted.	
Reporting group title	3 SMN2 Copies, Risdiplam
Reporting group description:	
Infants with 3 copies of SMN2 were enrolled to receive risdiplam orally once daily at a dose selected to achieve the targeted exposure range.	

Serious adverse events	2 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 8 (37.50%)	1 / 5 (20.00%)	0 / 13 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue injury			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			

Jaundice neonatal			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	2 SMN2 Copies, Risdiplam	>/=4 SMN2 Copies, Risdiplam	3 SMN2 Copies, Risdiplam
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	4 / 5 (80.00%)	12 / 13 (92.31%)
Pregnancy, puerperium and perinatal conditions			
Umbilical granuloma			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 8 (12.50%)	2 / 5 (40.00%)	4 / 13 (30.77%)
occurrences (all)	1	5	7
Malaise			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	2 / 13 (15.38%)
occurrences (all)	0	1	2
Epistaxis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	1 / 13 (7.69%)
occurrences (all)	0	3	1
Nasal congestion			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	3 / 13 (23.08%)
occurrences (all)	1	1	3
Rhinitis allergic			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	2 / 8 (25.00%)	0 / 5 (0.00%)	0 / 13 (0.00%)
occurrences (all)	2	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Cardiac murmur			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	3 / 13 (23.08%)
occurrences (all)	0	0	3
Arthropod bite			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Contusion			

subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Expired product administered			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Fall			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Incorrect dose administered			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Intercepted medication error			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Limb injury			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Overdose			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Underdose			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Congenital, familial and genetic disorders			
Cryptorchism			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Eye disorders			
Retinal vascular disorder			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Retinal pigmentation			

subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Cystoid macular oedema			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Gastrointestinal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)	2 / 5 (40.00%)	4 / 13 (30.77%)
occurrences (all)	0	2	4
Constipation			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	3 / 13 (23.08%)
occurrences (all)	2	1	3
Abdominal pain			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 13 (0.00%)
occurrences (all)	2	1	0
Vomiting			
subjects affected / exposed	1 / 8 (12.50%)	2 / 5 (40.00%)	2 / 13 (15.38%)
occurrences (all)	2	2	7
Teething			
subjects affected / exposed	2 / 8 (25.00%)	2 / 5 (40.00%)	6 / 13 (46.15%)
occurrences (all)	2	2	6
Regurgitation			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	2
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Skin discolouration			

subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Dermatitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Dermatitis atopic			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Dermatitis contact			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Dermatitis diaper			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Eczema			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	4 / 13 (30.77%)
occurrences (all)	1	1	5
Erythema			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Papule			
subjects affected / exposed	2 / 8 (25.00%)	0 / 5 (0.00%)	0 / 13 (0.00%)
occurrences (all)	3	0	0
Rash			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	2 / 13 (15.38%)
occurrences (all)	1	0	2
Rash maculo-papular			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Infections and infestations			

Conjunctivitis			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	2 / 13 (15.38%)
occurrences (all)	0	1	2
COVID-19			
subjects affected / exposed	2 / 8 (25.00%)	0 / 5 (0.00%)	7 / 13 (53.85%)
occurrences (all)	2	0	7
Bronchitis			
subjects affected / exposed	0 / 8 (0.00%)	2 / 5 (40.00%)	0 / 13 (0.00%)
occurrences (all)	0	3	0
Bronchiolitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Croup infectious			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Cytomegalovirus infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Suspected COVID-19			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Exanthema subitum			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Gastroenteritis			
subjects affected / exposed	1 / 8 (12.50%)	2 / 5 (40.00%)	2 / 13 (15.38%)
occurrences (all)	1	3	2
Gastroenteritis norovirus			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Gastrointestinal viral infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	2 / 13 (15.38%)
occurrences (all)	0	0	3
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0

Impetigo			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Nasopharyngitis			
subjects affected / exposed	1 / 8 (12.50%)	1 / 5 (20.00%)	3 / 13 (23.08%)
occurrences (all)	1	2	3
Oral candidiasis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	2
Otitis media acute			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Respiratory syncytial virus bronchitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection bacterial			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Respiratory tract infection viral			
subjects affected / exposed	2 / 8 (25.00%)	0 / 5 (0.00%)	2 / 13 (15.38%)
occurrences (all)	4	0	2
Rhinitis			
subjects affected / exposed	1 / 8 (12.50%)	2 / 5 (40.00%)	2 / 13 (15.38%)
occurrences (all)	1	5	2
Skin infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0

Ear infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Tonsillitis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Varicella			
subjects affected / exposed	0 / 8 (0.00%)	2 / 5 (40.00%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Viral infection			
subjects affected / exposed	0 / 8 (0.00%)	1 / 5 (20.00%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Viral rash			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Vulvovaginitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Hyperphosphatasaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Hypoglycaemia			
subjects affected / exposed	1 / 8 (12.50%)	0 / 5 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Vitamin D deficiency			
subjects affected / exposed	0 / 8 (0.00%)	0 / 5 (0.00%)	2 / 13 (15.38%)
occurrences (all)	0	0	2
Iron deficiency			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 5 (0.00%) 0	1 / 13 (7.69%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 February 2019	The protocol was amended primarily based on in vitro data indicating that risdiplam may be a cytochrome P450 3A4 (CYP3A4) inhibitor in humans. This inhibition has the potential to increase the concentration of concomitant medications predominantly metabolized by the CYP3A4 enzyme. For the secondary efficacy objective of achieving motor milestones defined in the BSID-III, an additional endpoint was added at the request of the European Medicines Agency's Paediatric Committee (PDCO). Specifically, the endpoint was to evaluate the percentage of participants demonstrating the ability to achieve a scaled score within 1.5 standard deviations of the chronological reference standard. The option to use a cognition scale other than the BSID-III Cognitive Scale was removed. A new series for the sitting, standing, and walking items was added to the assessments. An additional trial of the BSID-III Gross Motor test was allowed in case the child was uncooperative during the first administration. Additional pharmacokinetic samples were allowed, if required for safety reasons. Dosing could be stopped if safety, tolerability, or efficacy data would suggest risdiplam was not beneficial for the participant, in the investigator's judgment.
18 September 2020	The protocol was amended primarily to include age-appropriate motor function and development milestones beyond Month 24 and to remove some ophthalmological assessments. Major changes were as follows: The pharmacokinetics of risdiplam was updated with data on Type 1 SMA patients, and the very low dose of 0.004 mg/kg will not be required during the study. Given the absence of any risdiplam-induced ophthalmological findings in 470 patients exposed to risdiplam for up to 3 years, intraocular pressure measurement was no longer included and fundus photography did no longer need to be performed after 1 year. Motor function and development milestones were updated throughout: the HFMSE was added as a motor function measure, commencing at Month 24; WHO motor milestones was added as a developmental measure, commencing at Week 208 (Month 48); the six-minute walk test (6MWT) was added as a motor function measure, commencing at Week 182 (Month 42); the stopping criteria for the CHOP-INTEND were amended; the final visit date for BSID-III assessments was clarified as Week 182; it was clarified that after Week 104 in the study, HINE assessment should be stopped for each infant once the maximum score was reached at two consecutive visits; percentage of participants sitting without support at Month 12 of treatment (as assessed in Item 26 of the BSID-III Gross Motor Scale) for 30 seconds was added as a secondary efficacy endpoint; the respiratory plethysmography assessment and associated endpoints were removed; anthropometric and nutritional endpoints were extended to Month 60; the study visit schedule was amended to include a study completion/early withdrawal visit for all participants, and a follow-up call to take place 30 days after the study completion/early withdrawal visit. The 30-day follow-up call replaced the previous 52 weeks of follow-up visits.

30 March 2021	The protocol was amended primarily to reduce the overall number of ophthalmological assessments, including revision of the ophthalmological assessment requirements at baseline, and to modify the conditions for closure of recruitment. Given that ophthalmological monitoring conducted in 461 patients across the risdiplam clinical development program had not revealed any ophthalmological safety concerns, the frequency of ophthalmological assessments was reduced to the following visits: screening, Weeks 8, 28, and 52, and yearly thereafter. In order not to delay the start of treatment in presymptomatic SMA infants, the time window for obtaining high quality screening ophthalmologic assessments was expanded from Day 42 to Day 14. The conditions for the closure of recruitment were updated. The timing of the primary analysis was updated to account for the possibility that recruitment could be completed prior to 10 PE population participants being enrolled. The primary analysis was updated to occur when the last participant enrolled overall reached Month 12 of treatment. The description of the sample size was updated to include the requirements for a statistically significant result in the event that recruitment stopped prior to enrolling 10 participants with two SMN2 copies and a baseline CMAP amplitude >=1.5 mV.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported