Clinical trial results:
A Two-Part Seamless, Multi-Center, Randomized, Placebo-Controlled, Double Blind Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of Risdiplam (RO7034067) in Type 2 and 3 Spinal Muscular Atrophy Patients

Summary

EudraCT number	2016-000750-35
Trial protocol	ES GB IT BE DE FR PL HR BG
Global end of trial date	

Results information

Result version number	v1
This version publication date	13 September 2020
First version publication date	13 September 2020

Trial information

Trial identification

Sponsor protocol code	BP39055

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02908685
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	06 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 September 2019
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

Part 1: To evaluate the safety, tolerability, Pharmacokinetics (PK) and Pharmacodynamics (PD) of risdiplam in subjects with Type 2 and Type 3 (ambulant or non-ambulant) SMA, and to select the dose for Part 2 of the study;
Part 2: To evaluate efficacy of risdiplam compared to placebo in terms of motor function in Type 2 and non-ambulant Type 3 SMA subjects, as assessed by the change from baseline in the total score of the Motor Function Measure (MFM) at 12 months

Protection of trial subjects:

All study subjects, parent or legal guardian were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 October 2016
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	Belgium: 19
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	France: 25
Country: Number of subjects enrolled	Italy: 51
Country: Number of subjects enrolled	Brazil: 2
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	China: 16
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	Croatia: 11
Country: Number of subjects enrolled	Japan: 15
Country: Number of subjects enrolled	Poland: 32
Country: Number of subjects enrolled	Russian Federation: 4
Country: Number of subjects enrolled	Serbia: 8
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	231
EEA total number of subjects	163

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 months)	0
Children (2-11 years)	143
Adolescents (12-17 years)	62
Adults (18-64 years)	26
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study Part 1 was conducted at 5 investigational sites across 4 countries, and Part 2 was conducted at 42 investigational sites across 14 countries.

Pre-assignment

Screening details:

The Screening in both Part 1 and 2 was up to 30 days prior to first dose.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1 Group A: Adolescents and Adults (Risdiplam)

Arm description:

Adolescent and adult subjects aged 12-25 years received risdiplam for at least 12 weeks. Once the placebo-controlled period was completed and Part 2 dose was selected, subjects switched to Part 2 dose and were treated in an open-label phase.

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

Dosage and administration details:

Part 1 was a does-finding exploratory part. Risdiplam was administered once daily with meal orally or through gastric tube. Subjects receiving risdiplam orally followed this by rinsing their mouth with water and swallowing. Subjects unable to swallow were to receive risdiplam by bolus via their naso-gastric or gastrostomy tube. This was followed by a bolus flush of water through the tube.

Arm title	Part 1 Group A: Adolescents and Adults (Placebo)

Arm description:

Adolescent and adult subjects aged 12-25 years received placebo matching to risdiplam for at least 12 weeks. Once the placebo-controlled period was completed, subjects first switched to their cohort risdiplam dose. After the Part 2 dose was selected, subjects switched to Part 2 dose and were treated in an open-label phase.

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

Dosage and administration details:

Part 1 was a dose-finding exploratory part. Risdiplam matching placebo was administered once daily with meal orally or through gastric tube. Subjects receiving risdiplam matching placebo orally followed this by rinsing their mouth with water and swallowing. Subjects unable to swallow were to receive risdiplam matching placebo by bolus via their naso-gastric or gastrostomy tube. This was followed by a bolus flush of water through the tube.

Arm title	Part 1 Group B: Children (Risdiplam)

Arm description:

Children aged 2-11 years received risdiplam for at least 12 weeks. Once the placebo-controlled period was completed and Part 2 dose was selected, subjects switched to Part 2 dose and were treated in an open-label phase.

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

Dosage and administration details:

Part 1 was a dose-finding exploratory part. Risdiplam was administered once daily with meal orally or through gastric tube. Subjects receiving risdiplam orally followed this by rinsing their mouth with water and swallowing. Subjects unable to swallow were to receive risdiplam by bolus via their naso-gastric or gastrostomy tube. This was followed by a bolus flush of water through the tube.

Arm title	Part 1 Group B: Children (Placebo)

Arm description:

Children aged 2-11 years received placebo matching to risdiplam for at least 12 weeks. Once the placebo-controlled period was completed, subjects first switched to their cohort risdiplam dose. After the Part 2 dose was selected, subjects switched to Part 2 dose and were treated in an open-label phase.

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

Dosage and administration details:

Part 1 was a dose-finding exploratory part. Risdiplam matching placebo was administered once daily with meal orally or through gastric tube. Subjects receiving risdiplam matching placebo orally followed this by rinsing their mouth with water and swallowing. Subjects unable to swallow were to receive risdiplam matching placebo by bolus via their naso-gastric or gastrostomy tube. This was followed by a bolus flush of water through the tube.

Arm title	Part 2: Risdiplam

Arm description:

Subjects aged 2-25 years received risdiplam at the dose of 5 mg once daily for subjects with a body weight (BW) >/=20kg or 0.25 mg/kg for subjects with a BW <20 kg for 12 months.

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

Dosage and administration details:

Risdiplam was administered once daily with meal orally or through gastric tube at 5 mg for subjects with body weight (BW) >/=20 kg and 0.25 mg/kg for subjects with BW <20 kg. Subjects receiving risdiplam orally followed this by rinsing their mouth with water and swallowing. Subjects unable to swallow were to receive risdiplam by bolus via their naso-gastric or gastrostomy tube. This was followed by a bolus flush of water through the tube.

Arm title	Part 2: Placebo

Arm description:

Subjects aged 2-25 years received placebo matching to risdiplam for 12 months. After 12 months of treatment with placebo, subjects switched to risdiplam (5 mg once daily for subjects with a body weight (BW) >/=20kg or 0.25 mg/kg for subjects with a BW <20) in a blinded manner and subjects will continue with treatment and observations.

Arm type	Placebo

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

Dosage and administration details:

Risdiplam matching placebo was administered once daily with meal orally or through gastric tube. Subjects receiving risdiplam matching placebo orally followed this by rinsing their mouth with water and swallowing. Subjects unable to swallow were to receive risdiplam matching placebo by bolus via their naso-gastric or gastrostomy tube. This was followed by a bolus flush of water through the tube.

Number of subjects in period 1	Part 1 Group A: Adolescents and Adults (Risdiplam)	Part 1 Group A: Adolescents and Adults (Placebo)	Part 1 Group B: Children (Risdiplam)
Started	14	6	21
Completed	13	6	21
Not completed	1	0	0
Consent withdrawn by subject	1	-	-
Changed to other treatment	-	-	-
Changed to Spinraza	-	-	-

Number of subjects in period 1	Part 1 Group B: Children (Placebo)	Part 2: Risdiplam	Part 2: Placebo
Started	10	120	60
Completed	10	117	59
Not completed	0	3	1
Consent withdrawn by subject	-	-	-
Changed to other treatment	-	1	-
Changed to Spinraza	-	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Part 1 Group A: Adolescents and Adults (Risdiplam)
Reporting group description:	
Adolescent and adult subjects aged 12-25 years received risdiplam for at least 12 weeks. Once the placebo-controlled period was completed and Part 2 dose was selected, subjects switched to Part 2 dose and were treated in an open-label phase.	
Reporting group title	Part 1 Group A: Adolescents and Adults (Placebo)
Reporting group description:	
Adolescent and adult subjects aged 12-25 years received placebo matching to risdiplam for at least 12 weeks. Once the placebo-controlled period was completed, subjects first switched to their cohort risdiplam dose. After the Part 2 dose was selected, subjects switched to Part 2 dose and were treated in an open-label phase.	
Reporting group title	Part 1 Group B: Children (Risdiplam)
Reporting group description:	
Children aged 2-11 years received risdiplam for at least 12 weeks. Once the placebo-controlled period was completed and Part 2 dose was selected, subjects switched to Part 2 dose and were treated in an open-label phase.	
Reporting group title	Part 1 Group B: Children (Placebo)
Reporting group description:	
Children aged 2-11 years received placebo matching to risdiplam for at least 12 weeks. Once the placebo-controlled period was completed, subjects first switched to their cohort risdiplam dose. After the Part 2 dose was selected, subjects switched to Part 2 dose and were treated in an open-label phase.	
Reporting group title	Part 2: Risdiplam
Reporting group description:	
Subjects aged 2-25 years received risdiplam at the dose of 5 mg once daily for subjects with a body weight (BW) >/=20kg or 0.25 mg/kg for subjects with a BW <20 kg for 12 months.	
Reporting group title	Part 2: Placebo
Reporting group description:	
Subjects aged 2-25 years received placebo matching to risdiplam for 12 months. After 12 months of treatment with placebo, subjects switched to risdiplam (5 mg once daily for subjects with a body weight (BW) >/=20kg or 0.25 mg/kg for subjects with a BW <20) in a blinded manner and subjects will continue with treatment and observations.	

Reporting group values	Part 1 Group A: Adolescents and Adults (Risdiplam)	Part 1 Group A: Adolescents and Adults (Placebo)	Part 1 Group B: Children (Risdiplam)
Number of subjects	14	6	21
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)	0	0	21
Adolescents (12-17 years)	11	5	0
Adults (18-64 years)	3	1	0
From 65-84 years	0	0	0
85 years and over	0	0	0

Age Continuous			
Units: Years			
arithmetic mean	15.7	16.0	5.5
standard deviation	± 4.1	± 3.7	± 2.5
Sex: Female, Male			
Units: Participants			
Female	10	3	12
Male	4	3	9
Race/Ethnicity, Customized			
Units: Subjects			
Asian	0	0	1
White	14	6	19
Multiple	0	0	1
Black or African American	0	0	0
Not stated	0	0	0
Race/Ethnicity, Customized			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	14	6	20
Unknown	0	0	1

Reporting group values	Part 1 Group B: Children (Placebo)	Part 2: Risdiplam	Part 2: Placebo
Number of subjects	10	120	60
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	76	36
Adolescents (12-17 years)	0	30	16
Adults (18-64 years)	0	14	8
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	4.6	9.9	10.3
standard deviation	± 2.0	± 5.8	± 6.1
Sex: Female, Male			
Units: Participants			
Female	2	61	30
Male	8	59	30
Race/Ethnicity, Customized			
Units: Subjects			
Asian	0	23	12
White	9	80	41
Multiple	1	1	0
Black or African American	0	2	0
Not stated	0	14	7
Race/Ethnicity, Customized			

Units: Subjects			
Hispanic or Latino	0	5	2
Not Hispanic or Latino	10	114	57
Unknown	0	1	1

Reporting group values	Total		
Number of subjects	231		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	143		
Adolescents (12-17 years)	62		
Adults (18-64 years)	26		
From 65-84 years	0		
85 years and over	0		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Participants			
Female	118		
Male	113		
Race/Ethnicity, Customized Units: Subjects			
Asian	36		
White	169		
Multiple	3		
Black or African American	2		
Not stated	21		
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	7		
Not Hispanic or Latino	221		
Unknown	3		

End points

End points reporting groups

Reporting group title	Part 1 Group A: Adolescents and Adults (Risdiplam)

Reporting group description:

Adolescent and adult subjects aged 12-25 years received risdiplam for at least 12 weeks. Once the placebo-controlled period was completed and Part 2 dose was selected, subjects switched to Part 2 dose and were treated in an open-label phase.

Reporting group title	Part 1 Group A: Adolescents and Adults (Placebo)

Reporting group description:

Adolescent and adult subjects aged 12-25 years received placebo matching to risdiplam for at least 12 weeks. Once the placebo-controlled period was completed, subjects first switched to their cohort risdiplam dose. After the Part 2 dose was selected, subjects switched to Part 2 dose and were treated in an open-label phase.

Reporting group title	Part 1 Group B: Children (Risdiplam)

Reporting group description:

Children aged 2-11 years received risdiplam for at least 12 weeks. Once the placebo-controlled period was completed and Part 2 dose was selected, subjects switched to Part 2 dose and were treated in an open-label phase.

Reporting group title	Part 1 Group B: Children (Placebo)

Reporting group description:

Children aged 2-11 years received placebo matching to risdiplam for at least 12 weeks. Once the placebo-controlled period was completed, subjects first switched to their cohort risdiplam dose. After the Part 2 dose was selected, subjects switched to Part 2 dose and were treated in an open-label phase.

Reporting group title	Part 2: Risdiplam

Reporting group description:

Subjects aged 2-25 years received risdiplam at the dose of 5 mg once daily for subjects with a body weight (BW) >/=20kg or 0.25 mg/kg for subjects with a BW <20 kg for 12 months.

Reporting group title	Part 2: Placebo

Reporting group description:

Subjects aged 2-25 years received placebo matching to risdiplam for 12 months. After 12 months of treatment with placebo, subjects switched to risdiplam (5 mg once daily for subjects with a body weight (BW) >/=20kg or 0.25 mg/kg for subjects with a BW <20) in a blinded manner and subjects will continue with treatment and observations.

Subject analysis set title	Part 1: All Risdiplam
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Children aged 2-11 years and adolescent and adult subjects aged 12-25 years received risdiplam or risdiplam matching placebo.

Subject analysis set title	Part 1 Intent-to Treat (ITT)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population in Part 1 is defined as all randomized subjects. Subjects were grouped by treatment and by age group of 2-11 or 12-25 years old.

Subject analysis set title	Part 1 Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects in Part 1 who received at least one dose of study medication (risdiplam or placebo) whether prematurely withdrawn or not were included in the safety population.

Subject analysis set title	Part 2 ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population defined as all randomized subjects in Part 2 are the primary analysis population for all efficacy analyses. Subjects under the ITT population are reported according to the treatment they were randomized to.

Subject analysis set title	Part 2 Safety Population

Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects in Part 2 who received at least one dose of study medication (risdiplam or placebo) were included in the safety population. Subjects were grouped according to the treatment received.

Primary: Part 1: Selected Part 2 Dose of Risdiplam for Subjects with a Body Weight (BW) of >/=20kg

End point title	Part 1: Selected Part 2 Dose of Risdiplam for Subjects with a Body Weight (BW) of >/=20kg[1]

End point description:

The Internal Monitoring Committee (IMC) was responsible for selecting the dose for Part 2 of the study (pivotal dose). An external Independent Data Monitoring Committee (iDMC) reviewed data from Part 1 and confirmed the dose-selection decision of the IMC. The dose for Part 2 selected by the IMC was a dose that: 1.Was judged to be safe and well-tolerated, based on all available safety data from Part 1 and as confirmed by the iDMC; 2. Resulted in an exposure at steady-state below the exposure cap (mean value) of AUC0-24h,ss 2000 ng*h/mL (adjusted for free-fraction, if required); 3. Resulted in an SMN protein increase that was expected to be clinically relevant.

End point type	Primary

End point timeframe:

Day 1 up to at least 4 weeks on study (Up to CCOD of 25 July 2017)

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: Only descriptive statistics was planned to be reported in the endpoint.

End point values	Part 1: All Risdiplam			
Subject group type	Subject analysis set			
Number of subjects analysed	51			
Units: milligram (mg)	5			

Statistical analyses

No statistical analyses for this end point

Primary: Part 1: Selected Part 2 Dose of Risdiplam for Subjects with BW of <20kg

End point title	Part 1: Selected Part 2 Dose of Risdiplam for Subjects with BW of <20kg[2]

End point description:

The Internal Monitoring Committee (IMC) was responsible for selecting the dose for Part 2 of the study (pivotal dose). An external Independent Data Monitoring Committee (iDMC) reviewed data from Part 1 and confirmed the dose-selection decision of the IMC. The dose for Part 2 selected by the IMC was a dose that: 1.Was judged to be safe and well-tolerated, based on all available safety data from Part 1 and as confirmed by the iDMC; 2. Resulted in an exposure at steady-state below the exposure cap (mean value) of AUC0-24h,ss 2000 ng*h/mL (adjusted for free-fraction, if required); 3. Resulted in an SMN protein increase that was expected to be clinically relevant.

End point type	Primary

End point timeframe:

Day 1 up to at least 4 weeks on study (Up to CCOD of 25 July 2017)

Notes:

[2] - 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: Only descriptive statistics was planned to be reported in the endpoint.

End point values	Part 1: All Risdiplam			
Subject group type	Subject analysis set			
Number of subjects analysed	51			
Units: milligram/kilogramm (mg/kg)				
number (not applicable)	0.25			

Statistical analyses

No statistical analyses for this end point

Primary: Part 2: Change from Baseline in the Total Motor Function Measure 32 (MFM-32) Total Score at Month 12

End point title	Part 2: Change from Baseline in the Total Motor Function Measure 32 (MFM-32) Total Score at Month 12[3]

End point description:

The Motor Function Measure 32 (MFM32) is a scale constructed for use in neuromuscular disorders. It comprises 32 items that evaluate physical function in three dimensions: D1 function related to standing and transfer; D2 axial and proximal function; D3 distal motor function. Tasks are scored with a 4-point Likert scale: 0 - cannot initiate the task or maintain the starting position; 1 - performs the task partially; 2 - performs the task incompletely or imperfectly; 3 - performs the task fully and "normally". The 32 scores are summed and expressed on a 0-100 scale for the MFM32 total score. Higher scores indicate increased motor function. A positive change from Baseline indicates improvement. MMRM analysis was performed based on primary efficacy hypothetical estimand, which included subjects data assuming no prohibited medication intended for treatment of SMA was received and subjects continued on their randomized treatment until the analysis time point at Month 12.

End point type	Primary

End point timeframe:

Baseline (Day -1) and Month 12

Notes:

[3] - 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: Data for this endpoint was provided only for those arms which were planned to be reported.

End point values	Part 2: Risdiplam	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115[4]	59[5]		
Units: Scores on a Scale				
least squares mean (confidence interval 95%)	1.36 (0.61 to 2.11)	-0.19 (-1.22 to 0.84)		

Notes:

[4] - Subjects with missing MFM32 total score at Baseline were not included in the analysis.

[5] - Subjects with missing MFM32 total score at Baseline were not included in the analysis.

Statistical analyses

Statistical analysis title	Risdiplam vs Placebo

Statistical analysis description:

This is the first end point and first family tested in the hierarchical testing. The variables included in the MMRM model are: baseline total score, treatment, age group, visit, treatment-by-visit and baseline score-by-visit interaction.

Comparison groups	Part 2: Risdiplam v Part 2: Placebo

Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0156
Method	Mixed Model Repeated Measure Analysis
Parameter estimate	Least Square Mean Difference
Point estimate	1.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	2.81

Secondary: Part 2: Percentage of Subjects with Marked Improvement (Defined as >= 3) in the Total Motor Function Measure (MFM32) Score at Month 12

End point title	Part 2: Percentage of Subjects with Marked Improvement (Defined as >= 3) in the Total Motor Function Measure (MFM32) Score at Month 12[6]

End point description:

The MFM32 comprises 32 items that evaluate physical function. The scoring of each task uses a 4-point Likert scale: 0 - cannot initiate the task or maintain the starting position; 1 - performs the task partially; 2 - performs the task incompletely or imperfectly; 3 - performs the task fully and "normally". The 32 scores are summed and expressed on a 0-100 scale for the MFM32 total score. A change in MFM32 total score of threshold >/=3 represents marked improvement in this measure. Logistic regression analysis was performed based on efficacy hypothetical estimand, which included subjects data assuming no prohibited medication intended for treatment of SMA was received and subjects continued on their randomized treatment until the analysis time point at Month 12. Missing results at Month 12 are considered as non-responders.

End point type	Secondary

End point timeframe:

At Month 12

Notes:

[6] - 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: Data for this endpoint was provided only for those arms which were planned to be reported.

End point values	Part 2: Risdiplam	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115[7]	59[8]		
Units: Percentage of Subjects				
least squares mean (confidence interval 95%)	38.3 (28.94 to 47.58)	23.7 (12.03 to 35.43)		

Notes:

[7] - Subjects with missing MFM32 total score at Baseline were not included in the analysis.

[8] - Subjects with missing MFM32 total score at Baseline were not included in the analysis.

Statistical analyses

Statistical analysis title	Risdiplam vs Placebo

Statistical analysis description:

This is the second end point and second family tested in the hierarchical testing. Logistic Regression Model.The variables included in the logistic regression are: baseline total score, treatment and age

group.

Comparison groups	Part 2: Risdiplam v Part 2: Placebo
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0469 [9]
Method	Wald test
Parameter estimate	Odds ratio (OR)
Point estimate	2.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	5.44

Notes:

[9] - Adjusted p-Value
The adjusted p-values were derived based on all the p-values from end points in order of the hierarchical testing up to the current endpoint.

Secondary: Part 2: Change from Baseline in the Total Score of the Revised Upper Limb Module (RULM) at Month 12

End point title	Part 2: Change from Baseline in the Total Score of the Revised Upper Limb Module (RULM) at Month 12[10]

End point description:

The RULM is a 20 items scale that assesses the proximal and distal motor functions of the arm. There is an entry item and the remaining 18 items are scored on the 3 point scale of : 0: cannot complete task independently; 1: modified method but can complete task independently; 2: completes task without any assistance, and with 1 item scored on a 2 point scale of as a can/cannot score with 1 as the highest score. The RULM total score is the sum of 19 items scores with range of 0-37, and the entry item does not contribute to the total score. Higher scores indicate greater upper limb function. A positive change from Baseline indicates improvement. MMRM analysis was performed based on the efficacy hypothetical estimand, which included subjects data assuming no prohibited medication intended for treatment of SMA was received and subjects continued on their randomized treatment until the analysis time point at Month 12.

End point type	Secondary

End point timeframe:

Baseline (Day-1) and Month 12

Notes:

[10] - 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: Data for this endpoint was provided only for those arms which were planned to be reported.

End point values	Part 2: Risdiplam	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119[11]	58[12]		
Units: Scores on a Scale				
least squares mean (confidence interval 95%)	1.61 (1.00 to 2.22)	0.02 (-0.83 to 0.87)		

Notes:

[11] - Subjects with missing RULM total score at Baseline were not included in the analysis.

[12] - Subjects with missing RULM total score at Baseline were not included in the analysis.

Statistical analyses

Statistical analysis title	Risdiplam vs Placebo

Statistical analysis description:

This is the third end point and third family tested in the hierarchical testing. The variables included in the MMRM model are: baseline total score, treatment, age group, visit, treatment-by-visit and baseline score-by-visit interaction.

Comparison groups	Part 2: Risdiplam v Part 2: Placebo
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0469 [13]
Method	Mixed Model Repeated Measure Analysis
Parameter estimate	Least Square Mean Difference
Point estimate	1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	2.62

Notes:

[13] - Adjusted p-Value
The adjusted p-values were derived based on all the p-values from end points in order of the hierarchical testing up to the current endpoint.

Secondary: Part 2: Change from Baseline in Total Score of Hammersmith Functional Motor Scale Expanded (HFMSE) at Month 12

End point title	Part 2: Change from Baseline in Total Score of Hammersmith Functional Motor Scale Expanded (HFMSE) at Month 12[14]

End point description:

The HFMSE scale contains 33 items, which are scored on a 3-point Likert-type scale (0-2) and summed to derive the total score, with lower scores indicating greater impairment. The HFMSE contains a series of assessments designed to assess important functional abilities, including standing, transfers, ambulation, and proximal and axial function. The overall score is the sum of the scores for all activities with a maximum achievable score of 66. Higher scores indicate greater motor function. A positive change from Baseline indicates improvement. MMRM analysis was performed based on the efficacy hypothetical estimand, which included subjects data assuming no prohibited medication intended for treatment of SMA was received and subjects continued on their randomized treatment until the analysis time point at Month 12.

End point type	Secondary

End point timeframe:

Baseline (Day-1) and Month 12

Notes:

[14] - 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: Data for this endpoint was provided only for those arms which were planned to be reported.

End point values	Part 2: Risdiplam	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	60		
Units: Scores on a Scale				
least squares mean (confidence interval 95%)	0.95 (0.29 to 1.61)	0.37 (-0.54 to 1.28)		

Statistical analyses

Statistical analysis title	Risdiplam vs Placebo

Statistical analysis description:

This is one of the two end points in family four in the hierarchical testing. The variables included in the MMRM model are: baseline total score, treatment, age group, visit, treatment-by-visit and baseline score-by-visit interaction.

Comparison groups	Part 2: Risdiplam v Part 2: Placebo
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3902 [15]
Method	Mixed Model Repeated Measure Analysis
Parameter estimate	Least Square Mean Difference
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	1.69

Notes:

[15] - Adjusted p-Value
The adjusted p-values were derived based on all the p-values from end points in order of the hierarchical testing up to the current endpoint.

Secondary: Part 2: Change from Baseline in Forced Vital Capacity (FVC) at Month 12 in Subjects Aged 6-25 Years

End point title	Part 2: Change from Baseline in Forced Vital Capacity (FVC) at Month 12 in Subjects Aged 6-25 Years[16]

End point description:

Spirometry is a pulmonary function test that assesses how the lungs work by measuring how much air moves through the airways. Spirometry was performed by all subjects aged 6 or older. Forced vital capacity (FVC) is the total volume that can be exhaled after inhaling maximally. The best % predicted value out of all attempts were used for the analysis. MMRM analysis was performed based on the efficacy hypothetical estimand, which included subjects data assuming no prohibited medication intended for treatment of SMA was received and subjects continued on their randomized treatment until the analysis time point at Month 12.

End point type	Secondary

End point timeframe:

Baseline (Day-1) and Month 12

Notes:

[16] - 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: Data for this endpoint was provided only for those arms which were planned to be reported.

End point values	Part 2: Risdiplam	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83[17]	40[18]		
Units: Percentage Predicted				
least squares mean (confidence interval 95%)	-5.16 (-7.93 to -2.39)	-3.11 (-6.59 to 0.74)		

Notes:

[17] - Subjects with missing FVC data at Baseline were not included in the analysis.

[18] - Subjects with missing FVC data at Baseline were not included in the analysis.

Statistical analyses

Statistical analysis title	Risdiplam vs Placebo

Statistical analysis description:

This is one of the two end points in family four in the hierarchical testing. The variables included in the MMRM model are: baseline total score, treatment, age group, visit, treatment-by-visit and baseline score-by-visit interaction.

Comparison groups	Part 2: Risdiplam v Part 2: Placebo
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3902 [19]
Method	Mixed Model Repeated Measure Analysis
Parameter estimate	Least Square Mean Difference
Point estimate	-2.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.67
upper limit	2.56

Notes:

[19] - Adjusted p-Value
The adjusted p-values were derived based on all the p-values from end points in order of the hierarchical testing up to the current endpoint.

Secondary: Part 2: Change from Baseline in the Caregiver-Reported SMA Independence Scale (SMAIS) Total Score at Month 12

End point title	Part 2: Change from Baseline in the Caregiver-Reported SMA Independence Scale (SMAIS) Total Score at Month 12[20]

End point description:

The SMA Independence Scale (SMAIS) was developed specifically for SMA subjects in order to assess function-related independence. The SMAIS contains 29 items, assessing the amount of assistance required from another individual to perform daily activities such as eating, or bathing. Each item is scored on a 0-4 scale (with an additional option to indicate that an item is non-applicable). The SMAIS total score ranging from 0-44 is obtained based on 22 items with each item on the 0-2 scale. Lower scores indicate greater dependence on another individual. The SMAIS was completed by subjects aged 12 years or older and caregivers of subjects aged 2-25 years. MMRM analysis was performed based on efficacy hypothetical estimand, which included subjects data assuming no prohibited medication intended for treatment of SMA was received and subjects continued on their randomized treatment until the analysis time point at Month 12.

End point type	Secondary

End point timeframe:

Baseline (Day-1) and Month 12

Notes:

[20] - 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: Data for this endpoint was provided only for those arms which were planned to be reported.

End point values	Part 2: Risdiplam	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116[21]	60		
Units: Scores on a Scale				
least squares mean (confidence interval 95%)	1.65 (0.66 to 2.63)	-0.91 (-2.23 to 0.42)		

Notes:

[21] - Subjects with missing SMAIS total score at Baseline were not included in the analysis.

Statistical analyses

Statistical analysis title	Risdiplam vs Placebo

Statistical analysis description:

This is the sixth endpoint and the fifth family tested in the hierarchical testing. The variables included in the MMRM model are: baseline total score, treatment, age group, visit, treatment-by-visit and baseline score-by-visit interaction.

Comparison groups	Part 2: Risdiplam v Part 2: Placebo
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3902 [22]
Method	Mixed Model Repeated Measure Analysis
Parameter estimate	Least Square Mean Difference
Point estimate	2.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	4.17

Notes:

[22] - Adjusted p-Value
The adjusted p-values were derived based on all the p-values from end points in order of the hierarchical testing up to the current endpoint.

Secondary: Part 2: Percentage of Subjects Rated by Clinicians as Improved in the Clinical Global Impression of Change (CGI-C) Scale Ratings at Month 12

End point title	Part 2: Percentage of Subjects Rated by Clinicians as Improved in the Clinical Global Impression of Change (CGI-C) Scale Ratings at Month 12[23]

End point description:

The Clinical Global Impression of Change (CGI-C) is used to score a clinician’s impression of a subject’s change in global health. The CGI-C is a single item measure of change in global health, using seven response options: “very much improved”, “much improved”, “minimally improved”, “no change”, “minimally worse”, “much worse”, and “very much worse”. Subjects considered as "improved" included responses of "very much improved, "much improved" and "minimally improved". Logistic regression analysis was performed based on efficacy hypothetical estimand, which included subjects data assuming no prohibited medication intended for treatment of SMA was received and subjects continued on their randomized treatment until the analysis time point at Month 12.

End point type	Secondary

End point timeframe:

At Month 12

Notes:

[23] - 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: Data for this endpoint was provided only for those arms which were planned to be

reported.

End point values	Part 2: Risdiplam	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120[24]	60[25]		
Units: Percentage of Subjects				
number (confidence interval 95%)	47.5 (38.15 to 56.86)	40.0 (26.77 to 53.23)		

Notes:

[24] - Missing results at Month 12 are considered as non-responders.

[25] - Missing results at Month 12 are considered as non-responders.

Statistical analyses

Statistical analysis title	CGI Improved

Statistical analysis description:

This is the seventh endpoint and the sixth family tested in the hierarchical testing. Logistic Regression Model. The variables included in the logistic regression are: baseline total score, treatment and age group.

Comparison groups	Part 2: Risdiplam v Part 2: Placebo
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3902 [26]
Method	Wald-test
Parameter estimate	Odds ratio (OR)
Point estimate	1.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	2.74

Notes:

[26] - Adjusted p-Value
The adjusted p-values were derived based on all the p-values from end points in order of the hierarchical testing up to the current endpoint.

Secondary: Part 2: Percentage of Subjects who Achieve Stabilization or Improvement (Defined as >= 0) in the Total Motor Function Measure (MFM) Score at Month 12

End point title	Part 2: Percentage of Subjects who Achieve Stabilization or Improvement (Defined as >= 0) in the Total Motor Function Measure (MFM) Score at Month 12[27]

End point description:

The MFM32 comprises 32 items that evaluate physical function in three dimensions: D1 function related to standing and transfer; D2 axial and proximal function; D3 distal motor function. Tasks are scored with a 4-point Likert scale: 0 - cannot initiate the task or maintain the starting position; 1 - performs the task partially; 2 - performs the task incompletely or imperfectly; 3 - performs the task fully and "normally". The 32 scores are summed and expressed on a 0-100 scale for the MFM32 total score. Higher scores indicate increased motor function. Logistic regression analysis was performed based on efficacy hypothetical estimand, which included subjects data assuming no prohibited medication intended for treatment of SMA was received and subjects continued on their randomized treatment until the analysis time point at Month 12. Missing results at Month 12 are considered as non-responders.

End point type	Secondary

End point timeframe:

At Month 12

Notes:

[27] - 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: Data for this endpoint was provided only for those arms which were planned to be reported.

End point values	Part 2: Risdiplam	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115[28]	59[29]		
Units: Percentage of Subjects				
number (confidence interval 95%)	69.6 (60.72 to 78.41)	54.2 (40.68 to 67.80)		

Notes:

[28] - Subjects with missing MFM32 total score at Baseline were not included in the analysis.

[29] - Subjects with missing MFM32 total score at Baseline were not included in the analysis.

Statistical analyses

Statistical analysis title	Risdiplam vs Placebo

Statistical analysis description:

Logistic Regression Model. The variables included in the logistic regression are: baseline total score, treatment and age group.

Comparison groups	Part 2: Risdiplam v Part 2: Placebo
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.043
Method	Wald test
Parameter estimate	Odds ratio (OR)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	3.93

Secondary: Part 2: Percentage of Subjects who Achieve an Improvement of at Least One Standard Error of Measurement (SEM) on the Total MFM Score at Month 12

End point title	Part 2: Percentage of Subjects who Achieve an Improvement of at Least One Standard Error of Measurement (SEM) on the Total MFM Score at Month 12[30]

End point description:

The MFM32 comprises 32 items that evaluate physical function in three dimensions: D1 standing and transfer; D2 axial and proximal function; D3 distal motor function. Tasks are scored with a 4-point Likert scale: 0-cannot initiate the task or maintain the starting position; 1-performs the task partially; 2-performs the task incompletely or imperfectly; 3-performs the task fully and "normally". The 32 scores are summed and expressed on a 0-100 scale for the total score. Higher scores indicate increased motor function. Standard error of measurement (SEM) is derived using 32 items scores and total scores at baseline. Change from baseline >= one SEM is equivalent to a change >= 4. Logistic regression analysis was performed based on efficacy hypothetical estimand included subjects data assuming no prohibited

medication intended for treatment of SMA was received and subjects continued on their randomized treatment until the analysis time point at Month 12.

End point type	Secondary

End point timeframe:

At Month 12

Notes:

[30] - 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: Data for this endpoint was provided only for those arms which were planned to be reported.

End point values	Part 2: Risdiplam	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115[31]	59[32]		
Units: Percentage of Subjects				
number (confidence interval 95%)				
Week 52	28.7 (20.65 to 37.88)	16.9 (8.44 to 28.97)		

Notes:

[31] - Subjects with missing MFM32 total score at Baseline were not included in the analysis.

[32] - Subjects with missing MFM32 total score at Baseline were not included in the analysis.

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Change from Baseline in the MFM Domain 1 (D1) Score at Month 12

End point title	Part 2: Change from Baseline in the MFM Domain 1 (D1) Score at Month 12[33]

End point description:

The MFM32 comprises 32 items that evaluate physical function in three dimensions: D1 function related to standing and transfer; D2 axial and proximal function; D3 distal motor function. Tasks are scored with a 4-point Likert scale: 0 - cannot initiate the task or maintain the starting position; 1 - performs the task partially; 2 - performs the task incompletely or imperfectly; 3 - performs the task fully and "normally". The D1 items score are summed and expressed on 0-100 scale for the MFM D1 total score. Higher scores indicate increased motor function. A positive change from Baseline indicates improvement. MMRM analysis was performed based on efficacy hypothetical estimand, which included subjects data assuming no prohibited medication intended for treatment of SMA was received and subjects continued on their randomized treatment until the analysis time point at Month 12.

End point type	Secondary

End point timeframe:

Baseline (Day-1) and Month 12

Notes:

[33] - 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: Data for this endpoint was provided only for those arms which were planned to be reported.

End point values	Part 2: Risdiplam	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118[34]	60		
Units: Scores on a Scale				
least squares mean (confidence interval 95%)	0.37 (-0.12 to 0.87)	-0.26 (-0.94 to 0.42)		

Notes:

[34] - Subjects with missing MFM32 D1 score at Baseline were not included in the analysis.

Statistical analyses

Statistical analysis title	Risdiplam vs Placebo

Statistical analysis description:

The variables included in the MMRM model are: baseline total score, treatment, age group, visit, treatment-by-visit and baseline score-by-visit interaction.

Comparison groups	Part 2: Risdiplam v Part 2: Placebo
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1328
Method	Mixed Model Repeated Measure Analysis
Parameter estimate	Least Square Mean Difference
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	1.47

Secondary: Part 2: Change from Baseline in the MFM Domain 2 (D2) Score at Month 12

End point title	Part 2: Change from Baseline in the MFM Domain 2 (D2) Score at Month 12[35]

End point description:

The MFM32 comprises 32 items that evaluate physical function in three dimensions: D1 function related to standing and transfer; D2 axial and proximal function; D3 distal motor function. Tasks are scored with a 4-point Likert scale: 0 - cannot initiate the task or maintain the starting position; 1 - performs the task partially; 2 - performs the task incompletely or imperfectly; 3 - performs the task fully and "normally". The D2 items score are summed and expressed on 0-100 scale for the MFM D2 total score. Higher scores indicate increased motor function. A positive change from Baseline indicates improvement. MMRM analysis was performed based on efficacy hypothetical estimand, which included subjects data assuming no prohibited medication intended for treatment of SMA was received and subjects continued on their randomized treatment until the analysis time point at Month 12.

End point type	Secondary

End point timeframe:

Baseline (Day-1) and Month 12

Notes:

[35] - 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: Data for this endpoint was provided only for those arms which were planned to be reported.

End point values	Part 2: Risdiplam	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118[36]	60		
Units: Scores on a Scale				
least squares mean (confidence interval 95%)	1.04 (-0.38 to 2.46)	-0.93 (-2.87 to 1.02)		

Notes:

[36] - Subjects with missing MFM32 D2 total score at Baseline were not included in the analysis.

Statistical analyses

Statistical analysis title	Risdiplam vs Placebo

Statistical analysis description:

The variables included in the MMRM model are: baseline total score, treatment, age group, visit, treatment-by-visit and baseline score-by-visit interaction.

Comparison groups	Part 2: Risdiplam v Part 2: Placebo
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.103
Method	Mixed Model Repeated Measure Analysis
Parameter estimate	Least Square Mean Difference
Point estimate	1.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	4.34

Secondary: Part 2: Change from Baseline in the MFM Domain 3 (D3) Score at Month 12

End point title	Part 2: Change from Baseline in the MFM Domain 3 (D3) Score at Month 12[37]

End point description:

The MFM32 comprises 32 items that evaluate physical function in three dimensions: D1 function related to standing and transfer; D2 axial and proximal function; D3 distal motor function. Tasks are scored with a 4-point Likert scale: 0 - cannot initiate the task or maintain the starting position; 1 - performs the task partially; 2 - performs the task incompletely or imperfectly; 3 - performs the task fully and "normally". The D3 items score are summed and expressed on 0-100 scale for the MFM D3 total score. Higher scores indicate increased motor function. A positive change from Baseline indicates improvement. MMRM analysis was performed based on efficacy hypothetical estimand, which included subjects data assuming no prohibited medication intended for treatment of SMA was received and subjects continued on their randomized treatment until the analysis time point at Month 12.

End point type	Secondary

End point timeframe:

Baseline (Day-1) and Month 12

Notes:

[37] - 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: Data for this endpoint was provided only for those arms which were planned to be reported.

End point values	Part 2: Risdiplam	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115[38]	59[39]		
Units: Scores on a Scale				
least squares mean (confidence interval 95%)	3.68 (2.31 to 5.04)	1.34 (-0.54 to 3.22)		

Notes:

[38] - Subjects with missing MFM32 D3 total score at Baseline were not included in the analysis.

[39] - Subjects with missing MFM32 D3 total score at Baseline were not included in the analysis.

Statistical analyses

Statistical analysis title	Risdiplam vs Placebo

Statistical analysis description:

The variables included in the MMRM model are: baseline total score, treatment, age group, visit, treatment-by-visit and baseline score-by-visit interaction.

Comparison groups	Part 2: Risdiplam v Part 2: Placebo
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0451
Method	Mixed Model Repeated Measure Analysis
Parameter estimate	Least Square Mean Difference
Point estimate	2.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.05
upper limit	4.62

Secondary: Part 2: Change from Baseline in the Total Combined Scores of MFM Domains 1 and 2 at Month 12

End point title	Part 2: Change from Baseline in the Total Combined Scores of MFM Domains 1 and 2 at Month 12[40]

End point description:

The MFM32 comprises 32 items that evaluate physical function in three dimensions: D1 function related to standing and transfer; D2 axial and proximal function; D3 distal motor function. Tasks are scored with a 4-point Likert scale: 0 - cannot initiate the task or maintain the starting position; 1 - performs the task partially; 2 - performs the task incompletely or imperfectly; 3 - performs the task fully and "normally". The D1+D2 items score are summed and expressed on 0-100 scale for the MFM D1+D2 total score. Higher scores indicate increased motor function. A positive change from Baseline indicates improvement. MMRM analysis was performed based on efficacy hypothetical estimand, which included subjects data assuming no prohibited medication intended for treatment of SMA was received and subjects continued on their randomized treatment until the analysis time point at Month 12.

End point type	Secondary

End point timeframe:

Baseline (Day-1) and Month 12

Notes:

[40] - 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: Data for this endpoint was provided only for those arms which were planned to be reported.

End point values	Part 2: Risdiplam	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118[41]	60		
Units: Scores on a Scale				
least squares mean (confidence interval 95%)	0.69 (-0.07 to 1.45)	-0.59 (-1.64 to 0.45)		

Notes:

[41] - Subjects with missing MFM32 D1+D2 total score at Baseline were not included in the analysis.

Statistical analyses

Statistical analysis title	Risdiplam vs Placebo

Statistical analysis description:

The variables included in the MMRM model are: baseline total score, treatment, age group, visit, treatment-by-visit and baseline score-by-visit interaction.

Comparison groups	Part 2: Risdiplam v Part 2: Placebo
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0489
Method	Mixed Model Repeated Measure Analysis
Parameter estimate	Least Square Mean Difference
Point estimate	1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.01
upper limit	2.56

Secondary: Part 2: Change from Baseline in Forced Expiratory Volume in 1 Second (FEV1) at Month 12 in Subjects Aged 6-25 Years

End point title	Part 2: Change from Baseline in Forced Expiratory Volume in 1 Second (FEV1) at Month 12 in Subjects Aged 6-25 Years[42]

End point description:

Spirometry is a pulmonary function test that assesses how the lungs work by measuring how much air moves through the airways. Spirometry was performed by all subjects aged 6 or older. Forced expiratory volume (FEV1) is the volume forcefully exhaled in the first second of the forced vital capacity test. The best % predicted value out of all attempts were used for the analysis. MMRM analysis was performed based on efficacy hypothetical estimand, which included subjects data assuming no prohibited medication intended for treatment of SMA was received and subjects continued on their randomized treatment until the analysis time point at Month 12.

End point type	Secondary

End point timeframe:

Baseline (Day-1) and Month 12

Notes:

[42] - 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: Data for this endpoint was provided only for those arms which were planned to be reported.

End point values	Part 2: Risdiplam	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83[43]	40[44]		
Units: Percentage Predicted				
least squares mean (confidence interval 95%)	-4.22 (-7.49 to -0.96)	-1.35 (-5.91 to 3.20)		

Notes:

[43] - Subjects with missing FEV1 data at Baseline were not included in the analysis.

[44] - Subjects with missing FEV1 data at Baseline were not included in the analysis.

Statistical analyses

Statistical analysis title	Risdiplam vs Placebo

Statistical analysis description:

The variables included in the MMRM model are: baseline total score, treatment, age group, visit, treatment-by-visit and baseline score-by-visit interaction.

Comparison groups	Part 2: Risdiplam v Part 2: Placebo
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3029
Method	Mixed Model Repeated Measure Analysis
Parameter estimate	Least Square Mean Difference
Point estimate	-2.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.36
upper limit	2.62

Secondary: Part 2: Change from Baseline in the Peak Cough Flow (PCF) at Month 12 in Subjects Aged 6-25 Years

End point title	Part 2: Change from Baseline in the Peak Cough Flow (PCF) at Month 12 in Subjects Aged 6-25 Years[45]

End point description:

Spirometry is a pulmonary function test that assesses how the lungs work by measuring how much air moves through the airways. Spirometry was performed by all subjects aged 6 or older. Peak cough flow (PCF) is an assessment of cough strength. The best % predicted value out of all attempts were used for the analysis MMRM analysis was performed based on efficacy hypothetical estimand, which included subjects data assuming no prohibited medication intended for treatment of SMA was received and subjects continued on their randomized treatment until the analysis time point at Month 12.

End point type	Secondary

End point timeframe:

Baseline (Day-1) and Month 12

Notes:

[45] - 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: Data for this endpoint was provided only for those arms which were planned to be reported.

End point values	Part 2: Risdiplam	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83[46]	42[47]		
Units: Percent Predicted				
least squares mean (confidence interval 95%)	1.06 (-1.18 to 3.31)	-0.22 (-3.27 to 2.83)		

Notes:

[46] - Subjects with missing PCF data at Baseline were not included in the analysis.

[47] - Subjects with missing PCF data at Baseline were not included in the analysis.

Statistical analyses

Statistical analysis title	Risdiplam vs Placebo

Statistical analysis description:

The variables included in the MMRM model are: baseline total score, treatment, age group, visit, treatment-by-visit and baseline score-by-visit interaction.

Comparison groups	Part 2: Risdiplam v Part 2: Placebo
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4937
Method	Mixed Model Repeated Measure Analysis
Parameter estimate	Least Square Mean Difference
Point estimate	1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.42
upper limit	4.99

Secondary: Part 2: Change from Baseline in the Best Sniff Nasal Inspiratory Pressure (SNIP) at Month 12

End point title	Part 2: Change from Baseline in the Best Sniff Nasal Inspiratory Pressure (SNIP) at Month 12[48]

End point description:

The Sniff Nasal Inspiratory Pressure (SNIP) is a volitional, non-invasive test of inspiratory muscle strength that has been successfully applied to children > 2 years of age. Advantages include the simplicity of the maneuver and the absence of a mouthpiece, which is particularly helpful for subjects with SMA, who may have bulbar weakness. SNIP also has the advantage of measuring inspiratory pressure during a natural maneuver that is easily performed even by young children with neuromuscular disorders. The best % predicted value out of all attempts were used for the analysis. MMRM analysis was performed based on efficacy hypothetical estimand, which included subjects data assuming no prohibited medication intended for treatment of SMA was received and subjects continued on their randomized treatment until the analysis time point at Month 12.

End point type	Secondary

End point timeframe:

Baseline (Day-1) and Month 12

Notes:

[48] - 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: Data for this endpoint was provided only for those arms which were planned to be reported.

End point values	Part 2: Risdiplam	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118[49]	59[50]		
Units: Percentage Predicted				
least squares mean (confidence interval 95%)	3.42 (0.22 to 6.62)	1.07 (-3.42 to 5.57)		

Notes:

[49] - Subjects with missing SNIP data at Baseline were not included in the analysis.

[50] - Subjects with missing SNIP data at Baseline were not included in the analysis.

Statistical analyses

Statistical analysis title	Risdiplam vs Placebo

Statistical analysis description:

The variables included in the MMRM model are: baseline total score, treatment, age group, visit, treatment-by-visit and baseline score-by-visit interaction.

Comparison groups	Part 2: Risdiplam v Part 2: Placebo
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3967
Method	Mixed Model Repeated Measure Analysis
Parameter estimate	Least Square Mean Difference
Point estimate	2.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.11
upper limit	7.8

Secondary: Part 2: Change from Baseline in Maximal Inspiratory Pressure (MIP) at Month 12 in Subjects Aged 6-25 Years

End point title	Part 2: Change from Baseline in Maximal Inspiratory Pressure (MIP) at Month 12 in Subjects Aged 6-25 Years[51]

End point description:

The maximal inspiratory pressure (MIP) is a non-invasive test of muscle strength, which measures the maximum strength of the diaphragm and other inspiratory muscles. MIP was measured in subjects aged 6 or older. Subjects were asked to perform a forceful inspiration against an occluded mouth piece. The best % predicted value out of all attempts were used for the analysis. MMRM analysis was performed based on efficacy hypothetical estimand, which included subjects data assuming no prohibited medication intended for treatment of SMA was received and subjects continued on their randomized treatment until the analysis time point at Month 12.

End point type	Secondary

End point timeframe:

Baseline (Day-1) and Month 12

Notes:

[51] - 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: Data for this endpoint was provided only for those arms which were planned to be reported.

End point values	Part 2: Risdiplam	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81[52]	40[53]		
Units: Percentage Predicted				
least squares mean (confidence interval 95%)	1.99 (-6.13 to 10.11)	-0.97 (-12.33 to 10.38)		

Notes:

[52] - Subjects with missing MIP data at Baseline were not included in the analysis.

[53] - Subjects with missing MIP data at Baseline were not included in the analysis.

Statistical analyses

Statistical analysis title	Risdiplam vs Placebo

Statistical analysis description:

The variables included in the MMRM model are: baseline total score, treatment, age group, visit, treatment-by-visit and baseline score-by-visit interaction.

Comparison groups	Part 2: Risdiplam v Part 2: Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6704
Method	Mixed Model Repeated Measure Analysis
Parameter estimate	Least Square Mean Difference
Point estimate	2.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.78
upper limit	16.7

Secondary: Part 2: Change from Baseline in Maximal Expiratory Pressure (MEP) at Month 12 in Subjects Aged 6-25 Years

End point title	Part 2: Change from Baseline in Maximal Expiratory Pressure (MEP) at Month 12 in Subjects Aged 6-25 Years[54]

End point description:

The maximal expiratory pressure (MEP) is a non-invasive test of muscle strength, which measures the maximum strength of the abdominal muscles and other expiratory muscles. MEP was measured in subjects aged 6 or older. Subjects were asked to perform a forceful inspiration against an occluded mouth piece. The best % predicted value out of all attempts were used for the analysis. MMRM analysis was performed based on efficacy hypothetical estimand, which included subjects data assuming no prohibited medication intended for treatment of SMA was received and subjects continued on their randomized treatment until the analysis time point at Month 12.

End point type	Secondary

End point timeframe:

Baseline (Day-1) and Month 12

Notes:

[54] - 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: Data for this endpoint was provided only for those arms which were planned to be reported.

End point values	Part 2: Risdiplam	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83[55]	41[56]		
Units: Percentage Predicted				
least squares mean (confidence interval 95%)	-2.75 (-6.22 to 0.72)	-2.33 (-7.21 to 2.56)		

Notes:

[55] - Subjects with missing MEP data at Baseline were not included in the analysis.

[56] - Subjects with missing MEP data at Baseline were not included in the analysis.

Statistical analyses

Statistical analysis title	Risdiplam vs Placebo

Statistical analysis description:

The variables included in the MMRM model are: baseline total score, treatment, age group, visit, treatment-by-visit and baseline score-by-visit interaction.

Comparison groups	Part 2: Risdiplam v Part 2: Placebo
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8856
Method	Mixed Model Repeated Measure Analysis
Parameter estimate	Least Square Mean Difference
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.3
upper limit	5.45

Secondary: Part 2: Change from Baseline in the Subject-Reported SMA Independence Scale (SMAIS) Total Score at Month 12

End point title	Part 2: Change from Baseline in the Subject-Reported SMA Independence Scale (SMAIS) Total Score at Month 12[57]

End point description:

The SMAIS was developed specifically for SMA subjects in order to assess function-related independence. It contains 29 items, assessing the amount of assistance required from another individual to perform daily activities such as eating, or bathing. Each item is scored on a 0-4 scale (with an additional option to indicate that an item is non-applicable). The SMAIS total score ranging from 0-44 is obtained based on 22 items with each item on the 0-2 scale. Lower scores indicate greater dependence on another individual. The SMAIS was completed by subjects aged 12 years or older and caregivers of subjects aged 2-25 years. MMRM analysis was performed based on efficacy hypothetical estimand, which included subjects data assuming no prohibited medication intended for treatment of SMA was received and subjects continued on their randomized treatment until the analysis time point at Month 12.

End point type	Secondary

End point timeframe:

Baseline (Day-1) and Month 12

Notes:

[57] - 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: Data for this endpoint was provided only for those arms which were planned to be

reported.

End point values	Part 2: Risdiplam	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43[58]	23[59]		
Units: Scores on a Scale				
least squares mean (confidence interval 95%)	1.04 (-0.26 to 2.35)	-0.40 (-2.13 to 1.32)		

Notes:

[58] - Subjects with missing SMAIS total score at Baseline were not included in the analysis.

[59] - Subjects with missing SMAIS total score at Baseline were not included in the analysis.

Statistical analyses

Statistical analysis title	Risdiplam vs Placebo

Statistical analysis description:

The variables included in the MMRM model are: baseline total score, treatment, age group, visit, treatment-by-visit and baseline score-by-visit interaction.

Comparison groups	Part 2: Risdiplam v Part 2: Placebo
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1778
Method	Mixed Model Repeated Measure Analysis
Parameter estimate	Least Square Mean Difference
Point estimate	1.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	3.57

Secondary: Part 2: Percentage of Subjects Rated by Clinicians as No Change or Improved in the Clinical Global Impression of Change (CGI-C) Scale Ratings at Month 12

End point title	Part 2: Percentage of Subjects Rated by Clinicians as No Change or Improved in the Clinical Global Impression of Change (CGI-C) Scale Ratings at Month 12[60]

End point description:

The CGI-C is used to score a clinician’s impression of a participant’s change in global health. It is a single item measure of change in global health, using seven response options: “very much improved”, “much improved”, “minimally improved”, “no change”, “minimally worse”, “much worse”, and “very much worse”. Participants considered as "no change or improved" included responses of "no change", "very much improved", "much improved" and "minimally improved". Logistic regression analysis was performed based on efficacy hypothetical estimand, which included participants data assuming no prohibited medication intended for treatment of SMA was received and participants continued on their randomized treatment until the analysis time point at Month 12.

End point type	Secondary

End point timeframe:

At Month 12

Notes:

[60] - 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: Data for this endpoint was provided only for those arms which were planned to be reported.

End point values	Part 2: Risdiplam	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120[61]	60[62]		
Units: Percentage of Subjects				
number (confidence interval 95%)	85.8 (79.18 to 92.49)	83.3 (73.07 to 93.60)		

Notes:

[61] - Missing results at Month 12 are considered as non-responders.

[62] - Missing results at Month 12 are considered as non-responders.

Statistical analyses

Statistical analysis title	CGI No Change or Improved

Statistical analysis description:

Logistic Regression Model. The variables included in the logistic regression are: baseline total score, treatment and age group.

Comparison groups	Part 2: Risdiplam v Part 2: Placebo
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6636
Method	Wald-test
Parameter estimate	Odds ratio (OR)
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	2.83

Secondary: Part 2: Percentage of Subjects who Experience at Least One Disease-Related Adverse Event at Month 12

End point title	Part 2: Percentage of Subjects who Experience at Least One Disease-Related Adverse Event at Month 12[63]

End point description:

Disease-related adverse events (AEs) were identified by applying two different types of baskets to the AE dataset: Narrow prospectively defined baskets of MedDRA lowest level terms. This basket was defined based on a group of CDC terms selected from an age and gender matched case control study comparing CDC code rates observed in subjects with and without SMA using commercially available insurance claim data (CLAIMS and Market scan data). The lowest level terms included in each basket, coded using the latest version of MedDRA; Broad prospectively defined basket with events selected at preferred term level from all AEs reported in ongoing clinical trials up to January 2019, i.e., prior to unblinding of Part 2 of Study BP39055.

End point type	Secondary

End point timeframe:

Baseline up to Month 12 (Week 52; up to CCOD of 06 September 2019)

Notes:

[63] - 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: Data for this endpoint was provided only for those arms which were planned to be reported.

End point values	Part 2: Risdiplam	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	60		
Units: Percentage of Subjects				
number (confidence interval 95%)				
Narrow Basket AEs	46.7 (37.51 to 55.99)	53.3 (40.00 to 66.33)		
Broad Basket AEs	65.0 (55.76 to 73.48)	60.0 (46.54 to 72.44)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Number of Disease-Related Adverse Events Per Patient-Years at Month 12

End point title	Part 2: Number of Disease-Related Adverse Events Per Patient-Years at Month 12[64]

End point description:

Disease-related AEs were collected through the AE reporting of the study, and the disease-related AE rate was adjusted for patient years (AE rate per 100 patient-years). They were identified by applying two different types of baskets to the AE dataset: Narrow prospectively defined baskets of MedDRA lowest level terms and Broad prospectively defined basket with events selected at preferred term level from all AEs reported in ongoing clinical trials up to January 2019, i.e., prior to unblinding of Part 2 of Study BP39055.

End point type	Secondary

End point timeframe:

Baseline up to Month 12 (Week 52; up to CCOD of 06 September 2019)

Notes:

[64] - 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: Data for this endpoint was provided only for those arms which were planned to be reported.

End point values	Part 2: Risdiplam	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	60		
Units: Number of Events per 100 Patient-Years				
number (confidence interval 95%)				
Narrow Basket AEs	101.51 (84.23 to 121.29)	119.77 (93.71 to 150.82)		
Broad Basket AEs	217.29 (191.63 to 245.42)	199.61 (165.50 to 238.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 1: Percentage of Subjects with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Part 1: Percentage of Subjects with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An adverse event (AE) is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. All subjects in Part 1 who received at least one dose of study medication (risdiplam or placebo) whether prematurely withdrawn or not were included in the safety population.

End point type	Secondary

End point timeframe:

Day 1 on risdiplam up to at least 12 months (up to CCOD of 09 January 2019)

End point values	Part 1: All Risdiplam			
Subject group type	Subject analysis set			
Number of subjects analysed	51			
Units: Percentage of Subjects				
number (not applicable)				
With at Least One AE	94.1			
With at Least One SAE	17.6			

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Percentage of Subjects with Adverse Events (AEs) and Serious Adverse Events (SAEs) in the Placebo-Controlled Period

End point title	Part 2: Percentage of Subjects with Adverse Events (AEs) and Serious Adverse Events (SAEs) in the Placebo-Controlled Period[65]

End point description:

An adverse event (AE) is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which

worsen during a study are also considered as adverse events. All subjects in Part 2 who receive at least one dose of study medication (risdiplam or placebo) were included in the safety population.

End point type	Secondary

End point timeframe:

Day 1 up to 12 months of the placebo-controlled period

Notes:

[65] - 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: Data for this endpoint was provided only for those arms which were planned to be reported.

End point values	Part 2: Risdiplam	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	60		
Units: Percentage of Subjects				
number (not applicable)				
With at Least One AE	92.5	91.7		
With at Least One SAE	20.0	18.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Percentage of Subjects with Treatment Discontinuation due to Adverse Events (AEs) and Serious Adverse Events (SAEs) in the Placebo-Controlled Period

End point title	Part 2: Percentage of Subjects with Treatment Discontinuation due to Adverse Events (AEs) and Serious Adverse Events (SAEs) in the Placebo-Controlled Period[66]

End point description:

An adverse event (AE) is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. All subjects in Part 2 who receive at least one dose of study medication (risdiplam or placebo) were included in the safety population.

End point type	Secondary

End point timeframe:

Day 1 up to 12 months of the placebo-controlled period

Notes:

[66] - 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: Data for this endpoint was provided only for those arms which were planned to be reported.

End point values	Part 2: Risdiplam	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	60		
Units: Percentage of Subjects				
number (not applicable)				
Due to AE	0.0	0.0		
Due to SAE	0.0	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Number of Subjects Aged 6-25 Years with Suicidal Ideation Based on Columbia-Suicide Severity Rating Scale (C-SSRS) in the Placebo-Controlled Period

End point title	Part 2: Number of Subjects Aged 6-25 Years with Suicidal Ideation Based on Columbia-Suicide Severity Rating Scale (C-SSRS) in the Placebo-Controlled Period[67]

End point description:

The Columbia Suicide Severity Rating Scale (C-SSRS) is used to assess the lifetime suicidality of a subject (C-SSRS baseline) as well as any new instances of suicidality (C-SSRS since last visit). The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior, and attempts with actual/potential lethality. The C-SSRS assessments results were collected for subjects aged 6 years and older.

End point type	Secondary

End point timeframe:

Day 1 up to 12 months of the placebo-controlled period

Notes:

[67] - 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: Data for this endpoint was provided only for those arms which were planned to be reported.

End point values	Part 2: Risdiplam	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83[68]	42[69]		
Units: Number of Subjects				
number (not applicable)				
Wish to be Dead	1	1		
Non-specific Active Suicidal Thoughts	1	1		
Ideation with Any Methods, No Intent to Act	1	1		
Ideation with Some Intent to Act, No Plan	0	1		
Ideation with Specific Plan and Intent	0	1		

Notes:

[68] - Data were collected for subjects aged 6-25 years.

[69] - Data were collected for subjects aged 6-25 years.

Statistical analyses

No statistical analyses for this end point

Secondary: Part 2: Number of Subjects Aged 6-25 Years with Suicidal Behavior Based on Columbia-Suicide Severity Rating Scale (C-SSRS) in the Placebo-Controlled Period

End point title	Part 2: Number of Subjects Aged 6-25 Years with Suicidal Behavior Based on Columbia-Suicide Severity Rating Scale (C-SSRS) in the Placebo-Controlled Period[70]

End point description:

The Columbia Suicide Severity Rating Scale (C-SSRS) is used to assess the lifetime suicidality of a subject (C-SSRS baseline) as well as any new instances of suicidality (C-SSRS since last visit). The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior, and attempts with actual/potential lethality. The C-SSRS assessments results were collected for subjects aged 6 years and older.

End point type	Secondary

End point timeframe:

Day 1 up to 12 months of the placebo-controlled period

Notes:

[70] - 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: Data for this endpoint was provided only for those arms which were planned to be reported.

End point values	Part 2: Risdiplam	Part 2: Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83[71]	42[72]		
Units: Number of Subjects				
number (not applicable)				
Preparatory Acts or Behavior	0	0		
Aborted Attempt	0	0		
Interrupted Attempt	0	0		
Actual Attempt (non-fatal)	0	0		
Completed Suicide	0	0		

Notes:

[71] - Data were collected for subjects aged 6-25 years.

[72] - Data were collected for subjects aged 6-25 years.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Part 1: Day 1 up to at least 12 months (up to CCOD of 09 January 2019); Part 2: At least 12 months (up to CCOD of 06 September 2019)

Adverse event reporting additional description:

All subjects in Part 1 who received at least one dose of study medication (risdiplam or placebo) whether prematurely withdrawn or not were included in the safety population. All subjects in Part 2 who receive at least one dose of study medication (risdiplam or placebo) were included in the safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Part 1 Group A: Adolescents and Adults (Risdiplam)

Reporting group description:

Adolescent and adult participants aged 12-25 years received Risdiplam for 12 weeks. Once 12-week treatment was completed and Part 2 dose was selected, participants switched to Part 2 dose and were followed up in open-label extension (OLE) phase.

Reporting group title	Part 1 Group A: Adolescents and Adults (Placebo)

Reporting group description:

Adolescent and adult participants aged 12-25 years received placebo matching to Risdiplam for 12 weeks. Once 12-week treatment was completed and Part 2 dose was selected, participants switched to Part 2 dose and were followed up in OLE phase.

Reporting group title	Part 1 Group B: Children (Risdiplam)

Reporting group description:

Children aged 2-11 years received Risdiplam for 12 weeks. Once 12-week treatment was completed and Part 2 dose was selected, participants switched to Part 2 dose and were followed up in OLE phase.

Reporting group title	Part 2: Risdiplam

Reporting group description:

Participants aged 2-25 years received Risdiplam at the dose of 5 mg once daily for participants with a body weight (BW) >/=20kg or 0.25 mg/kg for participants with a BW <20 kg, for 24 months. After 24-month treatment, participants were offered the opportunity to enter the OLE phase.

Reporting group title	Part 1 Group B: Children (Placebo)

Reporting group description:

Children aged 2-11 years received placebo matching to Risdiplam for 12 weeks. Once 12-week treatment was completed and Part 2 dose was selected, participants switched to Part 2 dose and were followed up in OLE phase.

Reporting group title	Part 2: Placebo

Reporting group description:

Participants aged 2-25 years received placebo matching to Risdiplam. After 12 months of treatment with placebo, participants switched to Risdiplam in a blinded manner and treatment then continued until Month 24. After 24-month treatment, participants were offered the opportunity to enter the OLE phase.

Serious adverse events	Part 1 Group A: Adolescents and Adults (Risdiplam)	Part 1 Group A: Adolescents and Adults (Placebo)	Part 1 Group B: Children (Risdiplam)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 14 (14.29%)	2 / 6 (33.33%)	3 / 21 (14.29%)
number of deaths (all causes)	0	0	0
number of deaths resulting from			

adverse events			
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Lung operation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal stone removal			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Febrile convulsion			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Medical device pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 21 (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
Vomiting			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic respiratory failure			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection viral			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymph gland infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	0 / 21 (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
Pneumonia bacterial			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part 2: Risdiplam	Part 1 Group B: Children (Placebo)	Part 2: Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 120 (21.67%)	2 / 10 (20.00%)	11 / 60 (18.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 120 (0.83%)	0 / 10 (0.00%)	0 / 60 (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
Femur fracture			

subjects affected / exposed	1 / 120 (0.83%)	1 / 10 (10.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Lung operation			
subjects affected / exposed	1 / 120 (0.83%)	0 / 10 (0.00%)	0 / 60 (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
Renal stone removal			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Febrile convulsion			
subjects affected / exposed	1 / 120 (0.83%)	0 / 10 (0.00%)	0 / 60 (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
Partial seizures			
subjects affected / exposed	1 / 120 (0.83%)	0 / 10 (0.00%)	0 / 60 (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
General disorders and administration site conditions			
Medical device pain			
subjects affected / exposed	1 / 120 (0.83%)	0 / 10 (0.00%)	0 / 60 (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
Pyrexia			

subjects affected / exposed	2 / 120 (1.67%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 120 (0.83%)	0 / 10 (0.00%)	0 / 60 (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
Nausea			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	1 / 120 (0.83%)	0 / 10 (0.00%)	0 / 60 (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
Asthma			
subjects affected / exposed	1 / 120 (0.83%)	0 / 10 (0.00%)	0 / 60 (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
Atelectasis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 10 (0.00%)	0 / 60 (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
Pneumonia aspiration			
subjects affected / exposed	1 / 120 (0.83%)	0 / 10 (0.00%)	0 / 60 (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

Respiratory failure			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic respiratory failure			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 10 (0.00%)	0 / 60 (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
Nephrolithiasis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 10 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 120 (0.83%)	0 / 10 (0.00%)	0 / 60 (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			
Appendicitis			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			

subjects affected / exposed	2 / 120 (1.67%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 10 (0.00%)	0 / 60 (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
Gastroenteritis			
subjects affected / exposed	2 / 120 (1.67%)	0 / 10 (0.00%)	2 / 60 (3.33%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	2 / 120 (1.67%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 10 (0.00%)	0 / 60 (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
Lower respiratory tract infection viral			
subjects affected / exposed	1 / 120 (0.83%)	0 / 10 (0.00%)	0 / 60 (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
Lung infection			
subjects affected / exposed	1 / 120 (0.83%)	0 / 10 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymph gland infection			

subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	9 / 120 (7.50%)	0 / 10 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 12	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	1 / 120 (0.83%)	0 / 10 (0.00%)	0 / 60 (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
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 120 (0.83%)	0 / 10 (0.00%)	0 / 60 (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
Respiratory tract infection			
subjects affected / exposed	1 / 120 (0.83%)	0 / 10 (0.00%)	0 / 60 (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
Respiratory tract infection viral			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 120 (0.83%)	0 / 10 (0.00%)	0 / 60 (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
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 120 (0.83%)	0 / 10 (0.00%)	0 / 60 (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
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	1 / 60 (1.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Part 1 Group A: Adolescents and Adults (Risdiplam)	Part 1 Group A: Adolescents and Adults (Placebo)	Part 1 Group B: Children (Risdiplam)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 14 (92.86%)	5 / 6 (83.33%)	20 / 21 (95.24%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	1 / 21 (4.76%)
occurrences (all)	0	1	1
Pyrexia			
subjects affected / exposed	3 / 14 (21.43%)	2 / 6 (33.33%)	13 / 21 (61.90%)
occurrences (all)	13	2	16
Asthenia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Fatigue			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences (all)	2	0	3
Hyperpyrexia			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Hyperthermia			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Dysmenorrhoea			
subjects affected / exposed	2 / 14 (14.29%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	12	9	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 14 (21.43%)	1 / 6 (16.67%)	7 / 21 (33.33%)
occurrences (all)	3	1	9
Epistaxis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	5 / 14 (35.71%)	1 / 6 (16.67%)	3 / 21 (14.29%)
occurrences (all)	8	1	4
Productive cough			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	3 / 21 (14.29%)
occurrences (all)	0	0	8
Catarrh			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Dyspnoea			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Respiratory tract inflammation			

subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	3 / 21 (14.29%)
occurrences (all)	0	0	4
Rhinitis allergic			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	5	1	0
Upper respiratory tract inflammation			
subjects affected / exposed	2 / 14 (14.29%)	1 / 6 (16.67%)	3 / 21 (14.29%)
occurrences (all)	4	2	5
Psychiatric disorders			
Initial insomnia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	4
Contusion			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Fall			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Foot fracture			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Ligament sprain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Muscle rupture			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			

Tachycardia			
subjects affected / exposed	2 / 14 (14.29%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	2	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 14 (21.43%)	1 / 6 (16.67%)	3 / 21 (14.29%)
occurrences (all)	13	8	38
Dizziness			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Neutropenia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	2 / 21 (9.52%)
occurrences (all)	1	1	2
Motion sickness			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Vertigo			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Conjunctival hyperaemia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 14 (21.43%)	0 / 6 (0.00%)	2 / 21 (9.52%)
occurrences (all)	3	0	3
Abdominal pain upper			

subjects affected / exposed	2 / 14 (14.29%)	1 / 6 (16.67%)	2 / 21 (9.52%)
occurrences (all)	4	1	3
Constipation			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	3
Diarrhoea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	2 / 21 (9.52%)
occurrences (all)	1	0	3
Nausea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	3 / 21 (14.29%)
occurrences (all)	3	0	4
Vomiting			
subjects affected / exposed	2 / 14 (14.29%)	2 / 6 (33.33%)	8 / 21 (38.10%)
occurrences (all)	2	3	14
Aphthous ulcer			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Faecaloma			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Hyperchlorhydria			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	2	1	0
Oral mucosal erythema			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Tongue oedema			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Rash			
subjects affected / exposed	2 / 14 (14.29%)	0 / 6 (0.00%)	5 / 21 (23.81%)
occurrences (all)	2	0	6

Acne			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Alopecia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Dermatitis			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Dermatitis diaper			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	1 / 21 (4.76%)
occurrences (all)	1	1	1
Erythema			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Hyperhidrosis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Hyperkeratosis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Palmar erythema			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Pruritus			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	0	3	0
Rash papular			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Seborrhoeic dermatitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0

Skin induration			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Urinary tract pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	3
Pain in extremity			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	3 / 21 (14.29%)
occurrences (all)	0	0	5
Back pain			
subjects affected / exposed	3 / 14 (21.43%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences (all)	16	0	1
Fracture pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Groin pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Neck pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	4 / 21 (19.05%)
occurrences (all)	0	0	7
Conjunctivitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0

Gastroenteritis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	3 / 21 (14.29%)
occurrences (all)	1	0	4
Influenza			
subjects affected / exposed	2 / 14 (14.29%)	2 / 6 (33.33%)	1 / 21 (4.76%)
occurrences (all)	2	4	1
Nasopharyngitis			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	5 / 21 (23.81%)
occurrences (all)	1	1	8
Pharyngitis			
subjects affected / exposed	2 / 14 (14.29%)	1 / 6 (16.67%)	2 / 21 (9.52%)
occurrences (all)	2	1	2
Pneumonia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	2 / 14 (14.29%)	1 / 6 (16.67%)	3 / 21 (14.29%)
occurrences (all)	2	1	5
Rhinitis			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	1 / 21 (4.76%)
occurrences (all)	1	1	1
Tonsillitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 14 (7.14%)	1 / 6 (16.67%)	7 / 21 (33.33%)
occurrences (all)	1	2	15
Urinary tract infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Varicella			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Cystitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0

Ear infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Fungal skin infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis viral			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal viral infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Infection			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Laryngitis			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	1 / 21 (4.76%)
occurrences (all)	1	0	1
Laryngitis viral			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Paronychia			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	1	0	0
Scarlet fever			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	2 / 21 (9.52%)
occurrences (all)	0	0	2
Skin infection			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	0	1	0
Tracheitis			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	0 / 14 (0.00%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	0	0	0

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 14 (7.14%)	0 / 6 (0.00%)	0 / 21 (0.00%)
occurrences (all)	2	0	0
Iron deficiency			
subjects affected / exposed	0 / 14 (0.00%)	1 / 6 (16.67%)	0 / 21 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Part 2: Risdiplam	Part 1 Group B: Children (Placebo)	Part 2: Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	102 / 120 (85.00%)	9 / 10 (90.00%)	50 / 60 (83.33%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	1 / 120 (0.83%)	0 / 10 (0.00%)	3 / 60 (5.00%)
occurrences (all)	1	0	3
Pyrexia			
subjects affected / exposed	27 / 120 (22.50%)	6 / 10 (60.00%)	11 / 60 (18.33%)
occurrences (all)	45	16	21
Asthenia			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences (all)	0	2	0
Hyperpyrexia			
subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences (all)	0	2	0
Hyperthermia			
subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Pain			

subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Dysmenorrhoea			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	17 / 120 (14.17%)	7 / 10 (70.00%)	13 / 60 (21.67%)
occurrences (all)	29	21	21
Epistaxis			
subjects affected / exposed	3 / 120 (2.50%)	0 / 10 (0.00%)	3 / 60 (5.00%)
occurrences (all)	4	0	5
Oropharyngeal pain			
subjects affected / exposed	6 / 120 (5.00%)	3 / 10 (30.00%)	8 / 60 (13.33%)
occurrences (all)	6	5	9
Productive cough			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	3 / 60 (5.00%)
occurrences (all)	0	0	3
Rhinorrhoea			
subjects affected / exposed	5 / 120 (4.17%)	0 / 10 (0.00%)	3 / 60 (5.00%)
occurrences (all)	6	0	3
Catarrh			
subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Dyspnoea			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Respiratory tract inflammation			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Rhinitis allergic			

subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract inflammation			
subjects affected / exposed	0 / 120 (0.00%)	3 / 10 (30.00%)	0 / 60 (0.00%)
occurrences (all)	0	5	0
Psychiatric disorders			
Initial insomnia			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Foot fracture			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Muscle rupture			
subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences (all)	0	2	0

Nervous system disorders			
Headache			
subjects affected / exposed	25 / 120 (20.83%)	2 / 10 (20.00%)	11 / 60 (18.33%)
occurrences (all)	139	3	46
Dizziness			
subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Motion sickness			
subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences (all)	0	2	0
Vertigo			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Conjunctival hyperaemia			
subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	9 / 120 (7.50%)	2 / 10 (20.00%)	5 / 60 (8.33%)
occurrences (all)	12	2	8
Abdominal pain upper			
subjects affected / exposed	7 / 120 (5.83%)	1 / 10 (10.00%)	2 / 60 (3.33%)
occurrences (all)	7	1	3
Constipation			

subjects affected / exposed	9 / 120 (7.50%)	1 / 10 (10.00%)	5 / 60 (8.33%)
occurrences (all)	11	1	7
Diarrhoea			
subjects affected / exposed	22 / 120 (18.33%)	1 / 10 (10.00%)	8 / 60 (13.33%)
occurrences (all)	29	4	8
Nausea			
subjects affected / exposed	11 / 120 (9.17%)	1 / 10 (10.00%)	4 / 60 (6.67%)
occurrences (all)	13	1	6
Vomiting			
subjects affected / exposed	18 / 120 (15.00%)	3 / 10 (30.00%)	15 / 60 (25.00%)
occurrences (all)	38	6	29
Aphthous ulcer			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Faecaloma			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Hyperchlorhydria			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Oral mucosal erythema			
subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Tongue oedema			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	6 / 120 (5.00%)	0 / 10 (0.00%)	1 / 60 (1.67%)
occurrences (all)	6	0	1
Rash			
subjects affected / exposed	9 / 120 (7.50%)	0 / 10 (0.00%)	1 / 60 (1.67%)
occurrences (all)	11	0	1
Acne			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0

Alopecia			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Dermatitis			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Dermatitis diaper			
subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 120 (0.00%)	2 / 10 (20.00%)	0 / 60 (0.00%)
occurrences (all)	0	4	0
Hyperhidrosis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Hyperkeratosis			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Palmar erythema			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Rash papular			
subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Skin induration			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0

Renal and urinary disorders			
Urinary tract pain			
subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 120 (5.83%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences (all)	10	2	0
Pain in extremity			
subjects affected / exposed	4 / 120 (3.33%)	3 / 10 (30.00%)	3 / 60 (5.00%)
occurrences (all)	4	3	5
Back pain			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Fracture pain			
subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Groin pain			
subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	7 / 120 (5.83%)	2 / 10 (20.00%)	10 / 60 (16.67%)
occurrences (all)	9	4	12
Conjunctivitis			
subjects affected / exposed	4 / 120 (3.33%)	2 / 10 (20.00%)	4 / 60 (6.67%)
occurrences (all)	6	2	5
Gastroenteritis			
subjects affected / exposed	8 / 120 (6.67%)	2 / 10 (20.00%)	5 / 60 (8.33%)
occurrences (all)	11	2	7

Influenza			
subjects affected / exposed	3 / 120 (2.50%)	1 / 10 (10.00%)	3 / 60 (5.00%)
occurrences (all)	3	1	4
Nasopharyngitis			
subjects affected / exposed	32 / 120 (26.67%)	3 / 10 (30.00%)	16 / 60 (26.67%)
occurrences (all)	57	8	22
Pharyngitis			
subjects affected / exposed	7 / 120 (5.83%)	2 / 10 (20.00%)	3 / 60 (5.00%)
occurrences (all)	9	2	3
Pneumonia			
subjects affected / exposed	4 / 120 (3.33%)	1 / 10 (10.00%)	3 / 60 (5.00%)
occurrences (all)	5	1	3
Respiratory tract infection			
subjects affected / exposed	9 / 120 (7.50%)	0 / 10 (0.00%)	7 / 60 (11.67%)
occurrences (all)	12	0	10
Rhinitis			
subjects affected / exposed	5 / 120 (4.17%)	1 / 10 (10.00%)	3 / 60 (5.00%)
occurrences (all)	9	2	4
Tonsillitis			
subjects affected / exposed	3 / 120 (2.50%)	1 / 10 (10.00%)	3 / 60 (5.00%)
occurrences (all)	4	1	5
Upper respiratory tract infection			
subjects affected / exposed	39 / 120 (32.50%)	3 / 10 (30.00%)	20 / 60 (33.33%)
occurrences (all)	58	7	31
Urinary tract infection			
subjects affected / exposed	6 / 120 (5.00%)	0 / 10 (0.00%)	1 / 60 (1.67%)
occurrences (all)	7	0	1
Varicella			
subjects affected / exposed	3 / 120 (2.50%)	0 / 10 (0.00%)	3 / 60 (5.00%)
occurrences (all)	3	0	3
Cystitis			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Ear infection			
subjects affected / exposed	0 / 120 (0.00%)	2 / 10 (20.00%)	0 / 60 (0.00%)
occurrences (all)	0	3	0

Fungal skin infection			
subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis viral			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal viral infection			
subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Infection			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Laryngitis			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Laryngitis viral			
subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Paronychia			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Scarlet fever			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Skin infection			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0
Tracheitis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Viral infection			
subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	0 / 120 (0.00%)	1 / 10 (10.00%)	0 / 60 (0.00%)
occurrences (all)	0	1	0
Iron deficiency			
subjects affected / exposed	0 / 120 (0.00%)	0 / 10 (0.00%)	0 / 60 (0.00%)
occurrences (all)	0	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 October 2016	Details were added regarding neurological examinations specified in the protocol; Urine and blood pregnancy tests were added to the schedule of assessments for both Part 1 and Part 2 of the study; Stopping rules for cohorts in the dose-escalation part of the study were changed to allow the decision to terminate a cohort to be made by the iDMC
07 March 2017	The randomization ratio was changed from 1:1 to 2 (active):1 (placebo), and the sample size increased to maintain the same statistical power; Subjects initially randomized to placebo were switched to active treatment after 12 months; Age group stratification was subdivided: in place of one group of subjects aged 6 to 17 years, two groups were specified, aged 6 to 11 and 12 to 17 years; A new market formulation was introduced; Clarification that following the dose selection for Part 2, data from the exploratory Part 1 of this study (and the Part 1 extension phase) could be locked at intervals in order to analyze and report the safety, PK/PD and exploratory efficacy of those subjects enrolled into Part 1 only, which does not impact the integrity of Part 2 of the study; Two new scales were added, the SMAIS and CGI-C; The respiratory measures MEP and MIP were added; Based on Study BP29840, no interaction with CYP3A inducers or inhibitors was expected; therefore, some prohibited drugs were removed from the exclusion criteria and prohibited therapy; A summary of Part 1 data was provided. The pivotal dose was incorporated into the protocol; PedsQL subject-reported outcome measurements were included in Part 1 for up to 12 months of risdiplam treatment; Home nursing visits were removed (for U.S. only) as these were not utilized by the sites except to deliver study drug. These visits were replaced with a study drug service; The age limit at time of randomization was clarified for the completion of pulmonary function testing required for the study
01 March 2019	Results from in vitro studies characterizing the inhibition of CYP3A4 by risdiplam were added. This inhibition has the potential to increase the concentration of concomitant medications predominantly metabolized by the CYP3A4 enzyme; Studies in animals have shown that risdiplam is teratogenic and fetotoxic. The "Background on RO7034067" and "Safety Precautions" sections were updated accordingly; Responder analyses for the Hammersmith Functional Motor Scale Expanded (HFMSE) and Revised Upper Limb Module (RULM) were added as secondary objectives; The end of the study was revised. A subject's treatment in the open-label extension phase of the study may continue for 3 years. Thereafter, treatment will continue until the drug is available commercially in the subject's country. The end of the study is when the last patient completes 5 years into the study; An exclusion criterion was added for the use of inhibitors or inducers of FMO1 or FMO3. FMO1 and FMO3 inhibitors and inducers was added to the prohibited therapy section; Chronic treatment was defined as a minimum of 8 weeks to ensure that all sites in the study are applying the same definition;
01 March 2019	The permitted therapy section was updated to state that concomitant medications that are CYP3A4 substrates are permitted if required; however, as per usual clinical practice, potential toxicities should be monitored carefully, in particular for medications with a narrow therapeutic window; Adverse events of skin or subcutaneous reaction, pharyngeal/laryngeal or mucosal reaction, and clinically relevant retinal abnormalities on optical coherence tomography/fundus photography were removed from the list of non-serious adverse events of special interest (AESI) as the independent data monitoring committee (iDMC) provided independent safety surveillance; Blood samples for SMN protein every 26 weeks following the Week 104 visit were added in order to assess whether any increase in SMN protein observed in the first 104 weeks is sustained over the long term

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported