

**Clinical trial results:****A Two Part Seamless, Open-Label, Multicenter Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of Risdiplam in Infants with Type 1 Spinal Muscular Atrophy****Summary**

EudraCT number	2016-000778-40
Trial protocol	DE ES IT BE FR PL HR
Global end of trial date	

**Results information**

Result version number	v2
This version publication date	23 January 2021
First version publication date	26 November 2020
Version creation reason	

**Trial information****Trial identification**

Sponsor protocol code	BP39056
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02913482
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)	EMA-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?	No

Notes:

## Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	14 November 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 November 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 and pharmacodynamics of risdiplam in infants with Type 1 SMA and to select the dose for Part 2.

Part 2: To assess the efficacy of risdiplam measured as the proportion of infants sitting without support after 12 months of treatment, as assessed in the gross motor scale of the Bayley Scales of Infant and Toddler Development -Third Edition (BSID-III) (defined as sitting without support for 5 seconds).

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	23 December 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: 2
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	United States: 4
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	China: 11
Country: Number of subjects enrolled	Croatia: 1
Country: Number of subjects enrolled	Japan: 1
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Russian Federation: 5
Country: Number of subjects enrolled	Turkey: 1
Worldwide total number of subjects	62
EEA total number of subjects	36

Notes:

### Subjects enrolled per age group

In utero	0
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Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	62
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Part 1 was conducted at 7 investigational sites across 5 countries; Part 2 was conducted at 14 investigational sites across 10 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	Not applicable
Blinding used	Not blinded

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Exploratory Part 1 - Cohort 1

Arm description:

Subjects received risdiplam in a staggered, dose-escalation manner once daily at Dose Level 1 for a minimum of 4 weeks to select the dose for Part 2. Dose Level 1 was targeting an exposure of mean AUC<sub>0-24h,ss</sub> 700 ng\*h/mL.

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

Dosage and administration details:

Throughout the study, risdiplam should be taken orally once daily. In the case of breastfeeding, the subject should be fed prior to dosing, winded, and risdiplam administered.

In subjects able to swallow, risdiplam is administered with a syringe inserted between baby's gum and cheek. Thereafter, water (approx. 10–20 mL) should be administered with a baby's bottle to prevent prolonged contact of study drug with buccal mucosa. Similarly, the peribuccal- area of the SMA infant is washed with water in case of drug drooling or spitting. Subjects unable to swallow the study medication and who have a naso-gastric or gastrostomy tube in situ should receive the study medication by bolus via the tube. This should be followed by a bolus flush of water through the tube.

<b>Arm title</b>	Exploratory Part 1 - Cohort 2
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Arm description:

Subjects received risdiplam in a staggered, dose-escalation manner once daily at Dose Level 2 for a minimum of 4 weeks to select the dose for Part 2. Dose Level 2 was targeting an exposure of mean AUC<sub>0-24h,ss</sub> ≤ 2000 ng\*h/mL. Cohort 2 included one infant who started at Dose Level 1 and was escalated to Dose Level 2 on Day 83.

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

Dosage and administration details:

Throughout the study, risdiplam should be taken orally once daily. In the case of breastfeeding, the subject should be fed prior to dosing, winded, and risdiplam administered. In subjects able to swallow, risdiplam is administered with a syringe inserted between baby's gum and cheek. Thereafter, water (approx. 10–20 mL) should be administered with a baby's bottle to prevent prolonged contact of study

drug with buccal mucosa. Similarly, the peribuccal- area of the SMA infant is washed with water in case of drug drooling or spitting. Subjects unable to swallow the study medication and who have a naso-gastric or gastrostomy tube in situ should receive the study medication by bolus via the tube. This should be followed by a bolus flush of water through the tube.

<b>Arm title</b>	Confirmatory Part 2 - Risdiplam
Arm description:	
Subjects received risdiplam orally once daily at a dose of target exposure cap of a mean AUC <sub>0-24h,ss</sub> of 2000 ng*h/mL, for a duration of 24 months with a primary analysis after 12 months. Starting doses were either 0.04mg/kg, 0.08mg/kg or 0.2mg/kg depending on the subject's age. All subjects had their dose adjusted to 0.2mg/kg within a few months of starting treatment. The dose was adjusted to 0.25mg/kg when subject reached 2 years of age.	
Arm type	Experimental
Investigational medicinal product name	risdiplam
Investigational medicinal product code	
Other name	Evrysdi
Pharmaceutical forms	Powder and solvent for oral solution
Routes of administration	Oral use

**Dosage and administration details:**

Throughout the study, risdiplam should be taken orally once daily. In the case of breastfeeding, the subject should be fed prior to dosing, winded, and risdiplam administered. In subjects able to swallow, risdiplam is administered with a syringe inserted between baby's gum and cheek. Thereafter, water (approx. 10–20 mL) should be administered with a baby's bottle to prevent prolonged contact of study drug with buccal mucosa. Similarly, the peribuccal- area of the SMA infant is washed with water in case of drug drooling or spitting. Subjects unable to swallow the study medication and who have a naso-gastric or gastrostomy tube in situ should receive the study medication by bolus via the tube. This should be followed by a bolus flush of water through the tube.

<b>Number of subjects in period 1</b>	Exploratory Part 1 - Cohort 1	Exploratory Part 1 - Cohort 2	Confirmatory Part 2 - Risdiplam
Started	4	17	41
Completed	3	15	38
Not completed	1	2	3
Adverse event, serious fatal	1	1	2
Progressive Disease	-	1	1

## Baseline characteristics

### Reporting groups

Reporting group title	Exploratory Part 1 - Cohort 1
Reporting group description:	
Subjects received risdiplam in a staggered, dose-escalation manner once daily at Dose Level 1 for a minimum of 4 weeks to select the dose for Part 2. Dose Level 1 was targeting an exposure of mean AUC <sub>0-24h,ss</sub> 700 ng*h/mL.	
Reporting group title	Exploratory Part 1 - Cohort 2
Reporting group description:	
Subjects received risdiplam in a staggered, dose-escalation manner once daily at Dose Level 2 for a minimum of 4 weeks to select the dose for Part 2. Dose Level 2 was targeting an exposure of mean AUC <sub>0-24h,ss</sub> ≤ 2000 ng*h/mL. Cohort 2 included one infant who started at Dose Level 1 and was escalated to Dose Level 2 on Day 83.	
Reporting group title	Confirmatory Part 2 - Risdiplam
Reporting group description:	
Subjects received risdiplam orally once daily at a dose of target exposure cap of a mean AUC <sub>0-24h,ss</sub> of 2000 ng*h/mL, for a duration of 24 months with a primary analysis after 12 months. Starting doses were either 0.04mg/kg, 0.08mg/kg or 0.2mg/kg depending on the subject's age. All subjects had their dose adjusted to 0.2mg/kg within a few months of starting treatment. The dose was adjusted to 0.25mg/kg when subject reached 2 years of age.	

Reporting group values	Exploratory Part 1 - Cohort 1	Exploratory Part 1 - Cohort 2	Confirmatory Part 2 - Risdiplam
Number of subjects	4	17	41
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)	4	17	41
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous			
Units: months			
arithmetic mean	6.84	5.56	5.20
standard deviation	± 0.10	± 1.43	± 1.47
Sex: Female, Male			
Units:			
Male	0	6	19
Female	4	11	22
Race/Ethnicity, Customized			
Units: Subjects			
Not Hispanic or Latino	4	17	36
Hispanic or Latino	0	0	5
Race/Ethnicity, Customized			
Units: Subjects			
Asian	0	4	14

White	4	9	22
Unknown	0	4	5

<b>Reporting group values</b>	Total		
Number of subjects	62		
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)	62		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age Continuous Units: months arithmetic mean standard deviation	-		
Sex: Female, Male Units:			
Male	25		
Female	37		
Race/Ethnicity, Customized Units: Subjects			
Not Hispanic or Latino	57		
Hispanic or Latino	5		
Race/Ethnicity, Customized Units: Subjects			
Asian	18		
White	35		
Unknown	9		

## End points

### End points reporting groups

Reporting group title	Exploratory Part 1 - Cohort 1
Reporting group description: Subjects received risdiplam in a staggered, dose-escalation manner once daily at Dose Level 1 for a minimum of 4 weeks to select the dose for Part 2. Dose Level 1 was targeting an exposure of mean AUC <sub>0-24h,ss</sub> 700 ng*h/mL.	
Reporting group title	Exploratory Part 1 - Cohort 2
Reporting group description: Subjects received risdiplam in a staggered, dose-escalation manner once daily at Dose Level 2 for a minimum of 4 weeks to select the dose for Part 2. Dose Level 2 was targeting an exposure of mean AUC <sub>0-24h,ss</sub> ≤ 2000 ng*h/mL. Cohort 2 included one infant who started at Dose Level 1 and was escalated to Dose Level 2 on Day 83.	
Reporting group title	Confirmatory Part 2 - Risdiplam
Reporting group description: Subjects received risdiplam orally once daily at a dose of target exposure cap of a mean AUC <sub>0-24h,ss</sub> of 2000 ng*h/mL, for a duration of 24 months with a primary analysis after 12 months. Starting doses were either 0.04mg/kg, 0.08mg/kg or 0.2mg/kg depending on the subject's age. All subjects had their dose adjusted to 0.2mg/kg within a few months of starting treatment. The dose was adjusted to 0.25mg/kg when subject reached 2 years of age.	
Subject analysis set title	Part 1: Intent-to-Treat (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description: The intent-to-treat (ITT) population was defined as all subjects enrolled in Part 1 of the study, regardless of whether they received treatment or not.	
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) 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 intent-to-treat (ITT) population for Part 2 was defined as all subjects enrolled in Part 2 of the study, regardless of whether they received treatment or not. The ITT population was the primary analysis population for all efficacy analyses, with the exception of weight-for-age and length/height-for-age percentiles, which were analyzed based on the safety population.	
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) were included in the safety population.	
Subject analysis set title	Exploratory Part 1 - Risdiplam
Subject analysis set type	Sub-group analysis
Subject analysis set description: Infants aged between 28 days (1 month) of life and 210 days (7 months) received at least one dose of risdiplam orally or by bolus via naso-gastric or gastrostomy tube, and had available data at the time of the data snapshot for selecting the Part 2 dose.	

### Primary: Part 1: Selected Part 2 Dose of Risdiplam

End point title	Part 1: Selected Part 2 Dose of Risdiplam <sup>[1]</sup>
End point description: All safety, tolerability, PK and PD data available up to the clinical cut-off date of 5 January 2018, plus data that became available prior to the database snapshot on 6 February 2018 were included in the Internal Monitoring Committee (IMC) review. The 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 AUC<sub>0-24h,ss</sub> 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
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End point timeframe:

Minimum of 2 weeks at steady state exposure

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.

<b>End point values</b>	Exploratory Part 1 - Risdiplam			
Subject group type	Subject analysis set			
Number of subjects analysed	18			
Units: mg/kg				
number (not applicable)	0.2			

## Statistical analyses

No statistical analyses for this end point

### **Primary: Part 2: Percentage of Infants who are Sitting Without Support for at least 5 Seconds as Assessed by Item 22 of the Gross Motor Scale of the Bayley Scales of Infant and Toddler development Third Edition (BSID-III) at Month 12**

End point title	Part 2: Percentage of Infants who are Sitting Without Support for at least 5 Seconds as Assessed by Item 22 of the Gross Motor Scale of the Bayley Scales of Infant and Toddler development Third Edition (BSID-III) at Month 12 <sup>[2]</sup> <sup>[3]</sup>
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End point description:

The BSID-III is a standardized assessment commonly used to evaluate development across five domains in infants and young children aged between 1 and 42 months. The gross motor subscale of the BSID-III is evaluated based on the linear and hierarchical attainment of motor skills, as seen in typically developing children. The gross motor scale consists of 72 items scored at 0 (unable to perform the activity) or 1 (criteria for item achieved). Item 22 is not considered achieved if the infant sits alone for less than 5 seconds before losing balance and falling over, or if the infant uses his or her arms to prop him- or herself up. The assessment was video recorded at study sites and reviewed/scored by two independent raters. 90% CI for one sample binomial was computed using Clopper-Pearson (exact) method. The result was compared to a performance criterion of 5% derived from natural history data ( $p < 0.0001$ ).

End point type	Primary
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End point timeframe:

At Month 12 (Up to the Clinical Cut-off Date (CCOD) of 14 November 2019)

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.

[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.

<b>End point values</b>	Confirmatory Part 2 - Risdiplam			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Percentage of Subjects				
number (confidence interval 90%)	29.3 (17.84 to 43.07)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Part 2: Percentage of Infants who Achieve a Score of 40 or Higher in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) at Month 12

End point title	Part 2: Percentage of Infants who Achieve a Score of 40 or Higher in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) at Month 12 <sup>[4]</sup>
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End point description:

The CHOP-INTEND instrument was developed to evaluate motor function in infants with SMA from the ages of 1.4 to 37.9 months. It consists of 16 items, where each item assesses a specific motor task graded on a scale of 0 to 4, where zero is no response and 4 is a complete response. The total score ranges from 0 to 64, with higher scores consistent with better motor function. 90% CI for one sample binomial was computed using Clopper-Pearson (exact) method. The result was compared to a performance criterion of 17% derived from natural history data ( $p < 0.0001$ ).

End point type	Secondary
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End point timeframe:

At Month 12 (Up to the Clinical Cut-off Date (CCOD) of 14 November 2019)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data for this endpoint was provided only for those arms which were planned to be reported.

<b>End point values</b>	Confirmatory Part 2 - Risdiplam			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Percentage of Subjects				
number (confidence interval 90%)	56.1 (42.13 to 69.38)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Part 2: Percentage of Infants Achieving an Increase of $\geq 4$ Points in their CHOP-INTEND Score from Baseline at Month 8 and 12

End point title	Part 2: Percentage of Infants Achieving an Increase of $\geq 4$ Points in their CHOP-INTEND Score from Baseline at Month 8
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## End point description:

The CHOP-INTEND instrument was developed to evaluate motor function in infants with SMA from the ages of 1.4 to 37.9 months. It consists of 16 items, where each item assesses a specific motor task graded on a scale of 0 to 4, where zero is no response and 4 is a complete response. The total score ranges from 0 to 64, with higher scores consistent with better motor function. 90% CI for one sample binomial was computed using Clopper-Pearson (exact) method. The result was compared to a performance criterion of 17% derived from natural history data ( $p < 0.0001$ ). Statistical analysis was only performed for Month 12 data.

End point type	Secondary
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## End point timeframe:

At Month 8 and Month 12 (Up to the CCOD of 14 November 2019)

## Notes:

[5] - 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	Confirmatory Part 2 - Risdiplam			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Percentage of Subjects				
number (confidence interval 90%)				
Month 8	87.8 (76.05 to 95.07)			
Month 12	90.2 (79.05 to 96.60)			

## Statistical analyses

No statistical analyses for this end point

**Secondary: Part 2: Percentage of Infants Achieving Head Control (Defined as a Score of  $\geq 3$  for CHOP-INTEND Item 12) at Month 8 and 12**

End point title	Part 2: Percentage of Infants Achieving Head Control (Defined as a Score of $\geq 3$ for CHOP-INTEND Item 12) at Month 8 and 12 <sup>[6]</sup>
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## End point description:

The CHOP-INTEND instrument was developed to evaluate motor function in infants with SMA from the ages of 1.4 to 37.9 months. It consists of 16 items, where each item assesses a specific motor task graded on a scale of 0 to 4, where zero is no response and 4 is a complete response. The total score ranges from 0 to 64, with higher scores consistent with better motor function. 90% CI for one sample binomial was computed using Clopper-Pearson (exact) method.

End point type	Secondary
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## End point timeframe:

At Month 8 and Month 12 (Up to the CCOD of 14 November 2019)

## 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	Confirmatory Part 2 - Risdiplam			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Percentage of Subjects				
number (confidence interval 90%)				
Month 8	46.3 (32.87 to 60.23)			
Month 12	53.7 (39.77 to 67.13)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 2: Change From Baseline in the Total Raw Score of the BSID-III Gross Motor Scale at Month 12

End point title	Part 2: Change From Baseline in the Total Raw Score of the BSID-III Gross Motor Scale at Month 12 <sup>[7]</sup>
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End point description:

The BSID-III is a standardized assessment commonly used to evaluate development across five domains in infants and young children aged between 1 and 42 months. The gross motor subscale of the BSID-III is evaluated based on the linear and hierarchical obtainment of motor skills, as seen in typically developing children. The gross motor scale consists of 72 items scored at 0 (unable to perform the activity) or 1 (criteria for item achieved). In this study the gross motor scale was assessed in a modified way compared with the standard administration. A total raw score was calculated by summing the item scores to give a maximum possible score of 72.

End point type	Secondary
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End point timeframe:

At Month 12 (Up to the CCOD of 14 November 2019)

Notes:

[7] - 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	Confirmatory Part 2 - Risdiplam			
Subject group type	Reporting group			
Number of subjects analysed	38 <sup>[8]</sup>			
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Month 12	7.21 (± 5.71)			

Notes:

[8] - Only subjects for whom data were collected are included in the analysis.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 2: Percentage of Infants who Achieve the Attainment Levels of a Subset of Motor Milestones Assessed in the Hammersmith Infant Neurological

## Examination Module 2 (HINE-2) at Month 8

End point title	Part 2: Percentage of Infants who Achieve the Attainment Levels of a Subset of Motor Milestones Assessed in the Hammersmith Infant Neurological Examination Module 2 (HINE-2) at Month 8 <sup>[9]</sup>
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### End point description:

The HINE was designed to evaluate infants between 2 months and 24 months of age. It is a simple and standardized instrument that includes 26 items assessing different aspects of neurological examinations, such as cranial nerves, posture, movements, tone, and reflexes. In this study, Module 2 of the HINE (HINE-2) was assessed. The HINE-2 evaluates 8 developmental milestones (head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking) scored on a 3, 4, or 5-point scale, with 0 indicating inability to perform a task and a score of 2, 3, or 4 (depending on the task) indicating full milestone development. The total score is calculated by summing the item scores to give a maximum possible score of 26. This measure represents subset numbers at Month 8 for head control, ability to kick and rolling milestones only.

End point type	Secondary
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### End point timeframe:

At Month 8 (Up to the CCOD of 14 November 2019)

### Notes:

[9] - 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	Confirmatory Part 2 - Risdiplam			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Percentage of Subjects				
number (not applicable)				
Unable to maintain head upright (Head Control)	36.6			
Wobbles (Head Control)	14.6			
All the time maintained upright (Head Control)	39.0			
No kicking (Ability to Kick (supine))	24.4			
Kicks horizontally; legs don't lift (Kick (supine))	58.5			
Upward (vertically) (Ability to Kick (supine))	7.3			
Touches leg (Ability to Kick (supine))	0			
Touches toes (Ability to Kick (supine))	0			
No rolling (Rolling)	56.1			
Rolling to side (Rolling)	29.3			
Prone to supine (Rolling)	2.4			
Supine to prone (Rolling)	2.4			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 2: Percentage of Infants who Achieve the Attainment Levels of the Motor Milestones Assessed in the Hammersmith Infant Neurological Examination Module 2 (HINE-2) at Month 12

End point title	Part 2: Percentage of Infants who Achieve the Attainment Levels of the Motor Milestones Assessed in the Hammersmith Infant Neurological Examination Module 2 (HINE-2) at Month 12 <sup>[10]</sup>
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End point description:

The HINE was designed to evaluate infants between 2 months and 24 months of age. It is a simple and standardized instrument that includes 26 items assessing different aspects of neurological examinations, such as cranial nerves, posture, movements, tone, and reflexes. In this study, Module 2 of the HINE (HINE-2) was assessed. The HINE-2 evaluates 8 developmental milestones (head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking) scored on a 3, 4, or 5-point scale, with 0 indicating inability to perform a task and a score of 2, 3, or 4 (depending on the task) indicating full milestone development. The total score is calculated by summing the item scores to give a maximum possible score of 26.

End point type	Secondary
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End point timeframe:

At Month 12 (Up to the CCOD of 14 November 2019)

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	Confirmatory Part 2 - Risdiplam			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Percentage of Subjects				
number (not applicable)				
Unable to maintain head upright (Head Control)	17.1			
Wobbles (Head Control)	31.7			
All the time maintained upright (Head Control)	43.9			
Cannot sit (Sitting)	31.7			
Sits with support at hips (Sitting)	17.1			
Props (Sitting)	19.5			
Stable sit (Sitting)	14.6			
Pivots (rotates) (Sitting)	9.8			
No grasp (Voluntary Grasp)	2.4			
Uses whole hand (Voluntary Grasp)	29.3			
Index finger & thumb, immature (Voluntary Grasp)	48.8			
Pincer grasp (Voluntary Grasp)	12.2			
No kicking (Ability to Kick (supine))	12.2			
Kicks horizontally; legs don't lift (Kick (supine))	58.5			
Upward (vertically) (Ability to Kick (supine))	7.3			
Touches leg (Ability to Kick (supine))	4.9			
Touches toes (Ability to Kick (supine))	9.8			
No rolling (Rolling)	36.6			
Rolling to side (Rolling)	31.7			
Prone to supine (Rolling)	14.6			
Supine to prone (Rolling)	9.8			
Does not lift head (Crawling)	85.4			
On elbow (Crawling)	2.4			

On outstretched hand (Crawling)	2.4			
Crawling flat on abdomen (Crawling)	0			
Crawling on hands and knees (Crawling)	0			
Cannot test (Crawling)	2.4			
Does not support weight (Standing)	61.0			
Supports weight (Standing)	17.1			
Stands with support (Standing)	4.9			
Stands unaided (Standing)	0			
Cannot test (Standing)	4.9			
Not done (Standing)	4.9			
Bouncing (Walking)	2.4			
Cruising (walks holding on) (Walking)	0			
Walking independently (Walking)	0			
Cannot test (Walking)	82.9			
Not Done (Walking)	7.3			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 2: Percentage of Motor Milestone Responders as Assessed by HINE-2 at Month 12

End point title	Part 2: Percentage of Motor Milestone Responders as Assessed by HINE-2 at Month 12 <sup>[11]</sup>
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End point description:

The HINE-2 evaluates 8 developmental milestones scored on a 3, 4, or 5-point scale, with 0 indicating inability to perform a task and a score of 2, 3, or 4 (depending on the task) indicating full milestone development. For the motor milestone responder definition, an improvement in a motor milestone is defined as at least a 2-point increase in ability to kick (or maximal score) or a 1-point increase in head control, rolling, sitting, crawling, standing, or walking. Worsening is similarly defined as a 2-point decrease in ability to kick (or lowest score) or a 1-point decrease in head control, rolling, sitting, crawling, standing, or walking. Voluntary grasp is excluded from the definition. An infant is classified as a responder if more motor milestones show improvement than show worsening. 90% CI for one sample binomial was computed using Clopper-Pearson (exact) method. The result was compared to a performance criterion of 12% derived from natural history data ( $p < 0.0001$ ).

End point type	Secondary
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End point timeframe:

At Month 12 (Up to the CCOD of 14 November 2019)

Notes:

[11] - 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.

<b>End point values</b>	Confirmatory Part 2 - Risdiplam			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Percentage of Subjects				
number (confidence interval 90%)	78.0 (64.82 to 88.04)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part 2: Highest Motor Milestone Achieved by Month 12 as Assessed in the BSID-III Gross Motor Scale

End point title	Part 2: Highest Motor Milestone Achieved by Month 12 as Assessed in the BSID-III Gross Motor Scale <sup>[12]</sup>
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End point description:

The BSID-III is a standardized assessment commonly used to evaluate development across five domains in infants and young children aged between 1 and 42 months. The gross motor subscale of the BSID-III is evaluated based on the linear and hierarchical obtainment of motor skills, as seen in typically developing children. The gross motor scale consists of 72 items scored at 0 (unable to perform the activity) or 1 (criteria for item achieved). This measure included 6 milestones: Item 9 'Controls head while upright for 15 seconds', Item 14 'Rolls from side to back', Item 22 'Sits without support for 5 seconds', Item 30 'Crawls on stomach', Item 40 'Stands alone' and Item 42 'Walks alone'.

End point type	Secondary
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End point timeframe:

At Month 12 (Up to the CCOD of 14 November 2019)

Notes:

[12] - 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	Confirmatory Part 2 - Risdiplam			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Percentage of Subjects				
number (not applicable)				
Item 9: Controls Head While Upright for 15 sec	0			
Item 14: Rolls from Side to Back	56.1			
Item 22: Sits Without Support for 5 sec	29.3			
Item 30: Crawls on Stomach	0			
Item 40: Stands Alone	0			
Item 42: Walks Alone	0			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part 2: Time to Death

End point title	Part 2: Time to Death <sup>[13]</sup>
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End point description:

The median time to event was estimated using Kaplan-Meier methodology. 90% CI was estimated using the method of Brookmeyer and Crowley. The median time to death was not estimable as few subjects had an event. 9999=not estimable

End point type	Secondary
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End point timeframe:

Baseline up to 12 Months (Up to the CCOD of 14 November 2019)

Notes:

[13] - 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	Confirmatory Part 2 - Risdiplam			
Subject group type	Reporting group			
Number of subjects analysed	41 <sup>[14]</sup>			
Units: Months				
median (confidence interval 90%)				
Month 12	9999 (9999 to 9999)			

Notes:

[14] - The median time to death was not estimable as few subjects had an event.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 2: Time to Death or Permanent Ventilation

End point title	Part 2: Time to Death or Permanent Ventilation <sup>[15]</sup>
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End point description:

Permanent ventilation is defined as  $\geq 16$  hours of non-invasive ventilation per day or intubation for  $>21$  consecutive days in the absence of, or following the resolution of, an acute reversible event; or tracheostomy. Permanent ventilation events were reviewed and confirmed by an independent adjudication committee. The median time to event was estimated using Kaplan-Meier methodology. 90% CI was estimated using the method of Brookmeyer and Crowley. The median time to death or permanent ventilation was not estimable as few subjects had an event. 9999=not estimable

End point type	Secondary
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End point timeframe:

Baseline up to 12 Months (Up to the CCOD of 14 November 2019)

Notes:

[15] - 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	Confirmatory Part 2 - Risdiplam			
Subject group type	Reporting group			
Number of subjects analysed	41 <sup>[16]</sup>			
Units: Months				
median (confidence interval 90%)				

Month 12	9999 (9999 to 9999)			
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Notes:

[16] - The median time to death or permanent ventilation was not estimable as few subjects had an event.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 2: Time to Permanent Ventilation

End point title	Part 2: Time to Permanent Ventilation <sup>[17]</sup>
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End point description:

Permanent ventilation is defined as  $\geq 16$  hours of non-invasive ventilation per day or intubation for  $>21$  consecutive days in the absence of, or following the resolution of, an acute reversible event; or tracheostomy. Permanent ventilation events were reviewed and confirmed by an independent adjudication committee. The median time to event was estimated using Kaplan-Meier methodology. 90% CI was estimated using the method of Brookmeyer and Crowley. The median time to permanent ventilation was not estimable as few subjects had an event. 9999=not estimable

End point type	Secondary
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End point timeframe:

Baseline up to 12 Months (Up to the CCOD of 14 November 2019)

Notes:

[17] - 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	Confirmatory Part 2 - Risdiplam			
Subject group type	Reporting group			
Number of subjects analysed	41 <sup>[18]</sup>			
Units: Months				
median (confidence interval 90%)				
Month 12	9999 (9999 to 9999)			

Notes:

[18] - The median time to permanent ventilation was not estimable as few subjects had an event.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 2: Percentage of Infants who are Alive Without Permanent Ventilation at Month 12

End point title	Part 2: Percentage of Infants who are Alive Without Permanent Ventilation at Month 12 <sup>[19]</sup>
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End point description:

Permanent ventilation is defined as  $\geq 16$  hours of non-invasive ventilation per day or intubation for  $>21$  consecutive days in the absence of, or following the resolution of, an acute reversible event; or tracheostomy. Permanent ventilation events were reviewed and confirmed by an independent adjudication committee. Kaplan-Meier methodology was used to estimate the percentages. 90% CI was computed using the complementary log-log transformation. The result was compared to a performance criterion of 42% derived from natural history data ( $p < 0.0001$ ).

End point type	Secondary			
End point timeframe:				
At Month 12 (Up to the CCOD of 14 November 2019)				
Notes:				
[19] - 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.				
<b>End point values</b>	Confirmatory Part 2 - Risdiplam			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Percentage of Subjects				
number (confidence interval 90%)				
Month 12	85.4 (73.35 to 92.24)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 2: Percentage of Infants Who Are Alive at Month 12

End point title	Part 2: Percentage of Infants Who Are Alive at Month 12 <sup>[20]</sup>			
End point description:				
Kaplan-Meier methodology was used to estimate the percentages. 90% CI was computed using the complementary log-log transformation. The result was compared to a performance criterion of 60% derived from natural history data (p=0.0005).				
End point type	Secondary			
End point timeframe:				
At Month 12 (Up to the CCOD of 14 November 2019)				
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	Confirmatory Part 2 - Risdiplam			
	Reporting group			
	Number of subjects analysed	41		
	Units: Percentage of Subjects			
	number (confidence interval 90%)	92.7 (82.16 to 97.10)		

## Statistical analyses

**Secondary: Part 2: Percentage of Infants Who Are Without Permanent Ventilation at Month 12**

End point title	Part 2: Percentage of Infants Who Are Without Permanent Ventilation at Month 12 <sup>[21]</sup>
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## End point description:

Permanent ventilation is defined as  $\geq 16$  hours of non-invasive ventilation per day or intubation for  $>21$  consecutive days in the absence of, or following the resolution of, an acute reversible event; or tracheostomy. Permanent ventilation events were reviewed and confirmed by an independent adjudication committee. Kaplan-Meier methodology was used to estimate the percentages. 90% CI was computed using the complementary log-log transformation. The result was compared to a performance criterion of 89% derived from natural history data ( $p=0.2595$ ).

End point type	Secondary
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## End point timeframe:

At Month 12 (Up to the CCOD of 14 November 2019)

## Notes:

[21] - 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	Confirmatory Part 2 - Risdiplam			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Percentage of Subjects				
number (confidence interval 90%)				
Month 12	92.3 (81.24 to 96.95)			

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Part 2: Percentage of Infants who Achieve a Reduction of At Least 30 Degrees in Phase Angle From Baseline, as Measured by Respiratory Plethysmography (RP) at Month 12**

End point title	Part 2: Percentage of Infants who Achieve a Reduction of At Least 30 Degrees in Phase Angle From Baseline, as Measured by Respiratory Plethysmography (RP) at Month 12 <sup>[22]</sup>
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## End point description:

RP measures the degree of synchrony between abdominal and thoracic cage-driven breathing. The weakness of intercostal muscles leads to asynchrony of the thorax with the diaphragm, resulting in inefficient and paradoxical breathing patterns. The degree of synchrony between the movement of the chest wall and abdomen during the respiratory cycle can be expressed as the phase angle between the two compartments and measured by placing two RP bands around the thorax and abdomen. In paradoxical breathing, the phase angle is reversed compared with the normal ventilation cycle. A phase angle of 0° indicates perfect in-phase movement, while a value of 180° indicates completely out-of-phase movement between the two compartments. In this measure, 8 or more valid breaths were used to determine the phase angle at each visit; the calculation was not performed if fewer than 8 valid breaths had been measured. 90% CI for one sample binomial was computed using Clopper-Pearson (exact) method.

End point type	Secondary
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End point timeframe:

At Month 12 (Up to the CCOD of 14 November 2019)

Notes:

[22] - 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	Confirmatory Part 2 - Risdiplam			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Percentage of Subjects				
number (confidence interval 90%)	34.1 (21.96 to 48.13)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 2: Percentage of Infants not Requiring Respiratory Support (Invasive or Non-Invasive) at Month 12

End point title	Part 2: Percentage of Infants not Requiring Respiratory Support (Invasive or Non-Invasive) at Month 12 <sup>[23]</sup>
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End point description:

90% CI for one sample binomial was computed using Clopper-Pearson (exact) method

End point type	Secondary
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End point timeframe:

At Month 12 (Up to the CCOD of 14 November 2019)

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	Confirmatory Part 2 - Risdiplam			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Percentage of Subjects				
number (confidence interval 90%)				
Month 12	24.4 (13.87 to 37.85)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 2: Percentage of Infants Able to Feed Orally at Month 12

End point title	Part 2: Percentage of Infants Able to Feed Orally at Month
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End point description:

Able to feed orally includes subjects fed orally and subjects fed via a combination of oral and tube feeding. 90% CI for one sample binomial was computed using Clopper-Pearson (exact) method

End point type	Secondary
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End point timeframe:

At Month 12 (Up to the CCOD of 14 November 2019)

Notes:

[24] - 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	Confirmatory Part 2 - Risdiplam			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Percentage of Subjects				
number (confidence interval 90%)				
Month 12	82.9 (70.31 to 91.70)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 1: Percentage of Subjects With Adverse Events (AE) and Serious Adverse Events (SAEs)

End point title	Part 1: Percentage of Subjects With Adverse Events (AE) and Serious Adverse Events (SAEs) <sup>[25]</sup>
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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.

End point type	Secondary
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End point timeframe:

From first dose of risdiplam up to a minimum of 12 months (Up to CCOD 27 February 2019)

Notes:

[25] - 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	Exploratory Part 1 - Cohort 1	Exploratory Part 1 - Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	17		
Units: Percentage of Subjects				
number (not applicable)				
With at least one AE	100.0	100.0		
With at least one SAE	75.0	41.2		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 2: Percentage of Subjects With Adverse Events (AE) and Serious Adverse Events (SAEs)

End point title	Part 2: Percentage of Subjects With Adverse Events (AE) and Serious Adverse Events (SAEs) <sup>[26]</sup>
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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.

End point type	Secondary
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End point timeframe:

From first dose of risdiplam up to a minimum of 12 months (Up to the CCOD of 14 November 2019)

Notes:

[26] - 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	Confirmatory Part 2 - Risdiplam			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Percentage of Subjects				
number (not applicable)				
With at least one AE	100.0			
With at least one SAE	58.5			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 2: Percentage of Subjects With AEs and SAEs Leading to Treatment Discontinuation

End point title	Part 2: Percentage of Subjects With AEs and SAEs Leading to Treatment Discontinuation <sup>[27]</sup>
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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.

End point type	Secondary
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End point timeframe:

From first dose of risdiplam up to a minimum of 12 months (Up to the CCOD of 14 November 2019)

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.

<b>End point values</b>	Confirmatory Part 2 - Risdiplam			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Percentage of Subjects				
number (not applicable)				
Due to AE	0			
Due to SAE	0			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 2: Percentage of Subjects With AEs and SAEs Leading to Treatment Modification/Interruption

End point title	Part 2: Percentage of Subjects With AEs and SAEs Leading to Treatment Modification/Interruption <sup>[28]</sup>
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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.

End point type	Secondary
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End point timeframe:

From first dose of risdiplam up to a minimum of 12 months (Up to the CCOD of 14 November 2019)

Notes:

[28] - 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	Confirmatory Part 2 - Risdiplam			
Subject group type	Reporting group			
Number of subjects analysed	41			
Units: Percentage of Subjects				
number (not applicable)				
Due to AE	4.9			
Due to SAE	2.4			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 2: Anthropometric Examination of Weight Measured in Kilograms

End point title	Part 2: Anthropometric Examination of Weight Measured in Kilograms <sup>[29]</sup>
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End point description:

Anthropometric examination included weight, height, head circumference and chest circumference. All infants who received at least one dose of study medication (risdiplam) were included in the safety population. Only participants for whom data were collected are included in the analysis.

End point type	Secondary
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End point timeframe:

At Month 12 (Up to the CCOD of 14 November 2019)

Notes:

[29] - 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	Confirmatory Part 2 - Risdiplam			
Subject group type	Reporting group			
Number of subjects analysed	38 <sup>[30]</sup>			
Units: kilogram (kg)				
arithmetic mean (standard deviation)				
Month 12	9.59 (± 1.40)			

Notes:

[30] - Only subjects for whom data were collected are included in the analysis.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 2: Anthropometric Examination of Height, Head Circumference and Chest Circumference Measured in Centimeter

End point title	Part 2: Anthropometric Examination of Height, Head Circumference and Chest Circumference Measured in Centimeter <sup>[31]</sup>
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End point description:

Anthropometric examination included weight, height, head circumference and chest circumference. All

infants who received at least one dose of study medication (risdiplam) were included in the safety population. Only participants for whom data were collected are included in the analysis.

End point type	Secondary
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End point timeframe:

At Month 12 (Up to the CCOD of 14 November 2019)

Notes:

[31] - 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	Confirmatory Part 2 - Risdiplam			
Subject group type	Reporting group			
Number of subjects analysed	38 <sup>[32]</sup>			
Units: centimeter (cm)				
arithmetic mean (standard deviation)				
Month 12 (Height)	80.47 (± 4.00)			
Month 12 (Head Circumference)	47.09 (± 1.72)			
Month 12 (Chest Circumference)	45.77 (± 2.31)			

Notes:

[32] - Only subjects for whom data were collected are included in the analysis.

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Part 1: From first dose of risdiplam up to a minimum of 12 months (Up to CCOD 27 February 2019)

Part 2: From first dose of risdiplam up to a minimum of 12 months (Up to the CCOD of 14 November 2019)

Adverse event reporting additional description:

Part 1 and Part 2 of the study were independent trials with different safety populations. Serious and Non-Serious Adverse Event collection were managed independently. Adverse Events NOT occurring at the 5% threshold in one part of the study does not mean that the event didn't occur, however, it may have occurred at a different frequency threshold.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1; 22.1
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### Reporting groups

Reporting group title	Exploratory Part 1 - Cohort 1
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Reporting group description:

Subjects received risdiplam in a staggered, dose-escalation manner once daily at Dose Level 1 for a minimum of 4 weeks to select the dose for Part 2. Dose Level 1 was targeting an exposure of mean AUC<sub>0-24h,ss</sub> 700 ng\*h/mL.

Reporting group title	Exploratory Part 1 - Cohort 2
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Reporting group description:

Subjects received risdiplam in a staggered, dose-escalation manner once daily at Dose Level 2 for a minimum of 4 weeks to select the dose for Part 2. Dose Level 2 was targeting an exposure of mean AUC<sub>0-24h,ss</sub> ≤ 2000 ng\*h/mL. Cohort 2 included one infant who started at Dose Level 1 and was escalated to Dose Level 2 on Day 83.

Reporting group title	Confirmatory Part 2 - Risdiplam
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Reporting group description:

Subjects received risdiplam orally once daily at a dose of target exposure cap of a mean AUC<sub>0-24h,ss</sub> of 2000 ng\*h/mL, for a duration of 24 months with a primary analysis after 12 months. Starting doses were either 0.04mg/kg, 0.08mg/kg or 0.2mg/kg depending on the subject's age. All subjects had their dose adjusted to 0.2mg/kg within a few months of starting treatment. The dose was adjusted to 0.25mg/kg when subject reached 2 years of age.

Serious adverse events	Exploratory Part 1 - Cohort 1	Exploratory Part 1 - Cohort 2	Confirmatory Part 2 - Risdiplam
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 4 (75.00%)	7 / 17 (41.18%)	24 / 41 (58.54%)
number of deaths (all causes)	1	2	3
number of deaths resulting from adverse events			
Investigations			
Weight decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (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
Congenital, familial and genetic disorders			

Cryptorchism			
subjects affected / exposed	0 / 4 (0.00%)	0 / 17 (0.00%)	1 / 41 (2.44%)
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			
Cardiac arrest			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Sinus tachycardia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 17 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Hydrocephalus			
subjects affected / exposed	0 / 4 (0.00%)	0 / 17 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 17 (0.00%)	2 / 41 (4.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 17 (0.00%)	0 / 41 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	0 / 17 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	1 / 4 (25.00%)	1 / 17 (5.88%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Atelectasis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (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
Pneumonia aspiration			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (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
Pneumothorax			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (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 distress			
subjects affected / exposed	0 / 4 (0.00%)	2 / 17 (11.76%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	2 / 41 (4.88%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Aspiration			
subjects affected / exposed	0 / 4 (0.00%)	0 / 17 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract inflammation			

subjects affected / exposed	0 / 4 (0.00%)	0 / 17 (0.00%)	1 / 41 (2.44%)
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 / 4 (0.00%)	0 / 17 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 4 (25.00%)	0 / 17 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 4 (50.00%)	1 / 17 (5.88%)	13 / 41 (31.71%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Respiratory tract infection			
subjects affected / exposed	1 / 4 (25.00%)	1 / 17 (5.88%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	1 / 4 (25.00%)	1 / 17 (5.88%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (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
Bronchiolitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 17 (0.00%)	2 / 41 (4.88%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 17 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 17 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 17 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 17 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 17 (0.00%)	1 / 41 (2.44%)
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 bacterial			
subjects affected / exposed	0 / 4 (0.00%)	0 / 17 (0.00%)	1 / 41 (2.44%)
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 viral			
subjects affected / exposed	0 / 4 (0.00%)	0 / 17 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 17 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheobronchitis			

subjects affected / exposed	0 / 4 (0.00%)	0 / 17 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Metabolism and nutrition disorders</b>			
Failure to thrive			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (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
<b>Dehydration</b>			
subjects affected / exposed	0 / 4 (0.00%)	0 / 17 (0.00%)	1 / 41 (2.44%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

<b>Non-serious adverse events</b>	Exploratory Part 1 - Cohort 1	Exploratory Part 1 - Cohort 2	Confirmatory Part 2 - Risdiplam
<b>Total subjects affected by non-serious adverse events</b>			
subjects affected / exposed	3 / 4 (75.00%)	17 / 17 (100.00%)	36 / 41 (87.80%)
<b>Injury, poisoning and procedural complications</b>			
Fall			
subjects affected / exposed	0 / 4 (0.00%)	2 / 17 (11.76%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Head injury			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Incorrect dose administered			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Joint dislocation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Stoma site hypergranulation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Thermal burn			



subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 17 (5.88%) 1	0 / 41 (0.00%) 0
Surgical and medical procedures Mechanical ventilation subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 17 (5.88%) 1	0 / 41 (0.00%) 0
Nervous system disorders Loss of consciousness subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 17 (5.88%) 1	0 / 41 (0.00%) 0
Blood and lymphatic system disorders Leukocytosis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 17 (5.88%) 1	0 / 41 (0.00%) 0
Lymphadenopathy subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 17 (5.88%) 1	0 / 41 (0.00%) 0
General disorders and administration site conditions Discomfort subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 17 (5.88%) 1	0 / 41 (0.00%) 0
Ill-defined disorder subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 17 (5.88%) 1	0 / 41 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	3 / 4 (75.00%) 16	8 / 17 (47.06%) 14	16 / 41 (39.02%) 39
Eye disorders Conjunctival hyperaemia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	1 / 17 (5.88%) 1	0 / 41 (0.00%) 0
Macular cyst subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 17 (5.88%) 1	0 / 41 (0.00%) 0
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	1 / 4 (25.00%)	0 / 17 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Abnormal faeces			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Aphthous ulcer			
subjects affected / exposed	1 / 4 (25.00%)	0 / 17 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	1 / 4 (25.00%)	3 / 17 (17.65%)	8 / 41 (19.51%)
occurrences (all)	1	3	8
Diarrhoea			
subjects affected / exposed	0 / 4 (0.00%)	6 / 17 (35.29%)	4 / 41 (9.76%)
occurrences (all)	0	7	4
Dysphagia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Faeces discoloured			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Flatulence			
subjects affected / exposed	1 / 4 (25.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	1	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 4 (0.00%)	2 / 17 (11.76%)	0 / 41 (0.00%)
occurrences (all)	0	3	0
Haematochezia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Infrequent bowel movements			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Salivary hypersecretion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	0	1	0

Teething			
subjects affected / exposed	0 / 4 (0.00%)	3 / 17 (17.65%)	3 / 41 (7.32%)
occurrences (all)	0	4	5
Toothache			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	1 / 4 (25.00%)	4 / 17 (23.53%)	3 / 41 (7.32%)
occurrences (all)	1	10	8
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	0	4	0
Bronchial secretion retention			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	0 / 4 (0.00%)	5 / 17 (29.41%)	0 / 41 (0.00%)
occurrences (all)	0	7	0
Epistaxis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Hypoxia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	0 / 4 (0.00%)	2 / 17 (11.76%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Respiratory tract congestion			
subjects affected / exposed	0 / 4 (0.00%)	2 / 17 (11.76%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Rhinorrhoea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Sleep apnoea syndrome			

subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract congestion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract inflammation			
subjects affected / exposed	2 / 4 (50.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	2	2	0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 17 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Dermatitis allergic			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Dermatitis atopic			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Eczema			
subjects affected / exposed	0 / 4 (0.00%)	3 / 17 (17.65%)	0 / 41 (0.00%)
occurrences (all)	0	3	0
Erythema			
subjects affected / exposed	2 / 4 (50.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	3	1	0
Macule			
subjects affected / exposed	1 / 4 (25.00%)	0 / 17 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Petechiae			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	0	2	0
Rash			
subjects affected / exposed	0 / 4 (0.00%)	2 / 17 (11.76%)	3 / 41 (7.32%)
occurrences (all)	0	3	3
Miliaria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 17 (0.00%)	3 / 41 (7.32%)
occurrences (all)	0	0	3

Rash maculo-papular subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 17 (0.00%) 0	4 / 41 (9.76%) 4
Musculoskeletal and connective tissue disorders			
Kyphosis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 17 (5.88%) 1	0 / 41 (0.00%) 0
Scoliosis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 17 (5.88%) 1	0 / 41 (0.00%) 0
Infections and infestations			
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 17 (5.88%) 1	0 / 41 (0.00%) 0
Ear infection subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	2 / 17 (11.76%) 3	0 / 41 (0.00%) 0
Exanthema subitum subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 17 (0.00%) 0	0 / 41 (0.00%) 0
Folliculitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 17 (5.88%) 1	0 / 41 (0.00%) 0
Gastroenteritis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 17 (5.88%) 2	0 / 41 (0.00%) 0
Lower respiratory tract infection subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 17 (5.88%) 1	0 / 41 (0.00%) 0
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	3 / 17 (17.65%) 5	5 / 41 (12.20%) 9
Oral candidiasis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 17 (5.88%) 1	0 / 41 (0.00%) 0
Otitis media			

subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 17 (0.00%)	0 / 41 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	4 / 41 (9.76%)
occurrences (all)	0	1	4
Pneumonia staphylococcal			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	0	4	0
Rhinitis			
subjects affected / exposed	0 / 4 (0.00%)	3 / 17 (17.65%)	5 / 41 (12.20%)
occurrences (all)	0	3	7
Upper respiratory tract infection			
subjects affected / exposed	1 / 4 (25.00%)	7 / 17 (41.18%)	19 / 41 (46.34%)
occurrences (all)	2	11	33
Urinary tract infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 17 (0.00%)	3 / 41 (7.32%)
occurrences (all)	1	0	4
Varicella post vaccine			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Viral infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 17 (5.88%)	0 / 41 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 4 (0.00%)	2 / 17 (11.76%)	0 / 41 (0.00%)
occurrences (all)	0	3	0

Iron deficiency subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 17 (5.88%) 1	0 / 41 (0.00%) 0
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## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 February 2017	The protocol was updated to clarify the nature of the decisions to be taken by the IMC and the meeting schedule of the IMC; Exclusion criterion #3 was updated to reflect the fact that some subjects may have taken the recently approved drug, Spinraza™, as part of medical care, rather than only in a study; Exclusion criterion #22 was updated to clarify the term 'use' (in relation to prohibited medication use within 90 days prior to enrollment) as administration for at least 8 weeks within 90 days of beginning the study; Details on dilution factors for drug preparation were removed from the protocol as they are provided in the pharmacy manual (referenced in the protocol); The protocol was updated to clarify that subjects could be breastfed and winded if needed, followed by study drug administration.
22 May 2017	A new, optimized formulation was introduced. Subjects participating in the Part 1 extension of the study continued to use the Part 1 clinical formulation until they switched to the Part 2 clinical formulation upon availability of the new formulation. Subjects in Part 2 of the study receive the Part 2 formulation throughout their participation in the study; In Part 2, CMAP acquired from below the elbow stimulation was included following suggestions from different therapeutic area experts. This technical change was expected to give better wave forms in smaller infants, as the size of the hand may be too small for consistent placement of electrodes on the hand and wrist, and ultimately more consistent results.
06 April 2018	The Part 2 dose was incorporated into the protocol based on the Part 1 data, as reviewed by the IMC and the iDMC in February 2018. In addition, the protocol was updated to allow all subjects in Part 1 to receive the dose selected for Part 2, including the first enrolled subject who per protocol thus far remained at the low target exposure of AUC 700 ng*h/mL; Following experience gained in Part 1, some ophthalmology assessments were modified to decrease unnecessary burden to subjects while optimizing quality of the main assessment (OCT); An option to enroll subjects in a specifically extended China enrollment phase after the global enrollment phase at CFDA-recognized sites, was added to ensure approximately 10 subjects are included in the China subpopulation; The definition of permanent ventilation was changed to $\geq 16$ hours of non-invasive ventilation per day or intubation for $> 21$ consecutive days in the absence of, or following the resolution of, an acute reversible event or tracheostomy. This definition better reflects the clinical situation in which an acute but reversible event could necessitate the use of non-invasive ventilation for several hours a day after which the subjects could be weaned, thus not truly meeting the original definition; An independent Permanent Ventilation Adjudication Committee was added to review all pertinent data for subjects who may have met the definition of permanent ventilation. This committee has been added to address the change in the definition of permanent ventilation described above and to provide greater transparency if a patient met this endpoint;
06 April 2018	PK monitoring and dose adjustments as required were added to ensure subjects are within the targeted exposure and are in compliance with the exposure cap; The secondary objective to investigate muscle electrophysiology, as assessed by CMAP was changed to an exploratory objective as it is less well defined with regards to clinical meaningfulness than the multiple motor assessments already being performed; An efficacy outcome measure of ability to swallow and feed orally was added because these data are an important clinical outcome for subjects with SMA Type 1, who in the natural history of the disease lose the ability to swallow; In the context of the independent safety surveillance provided by the iDMC once Part 2 was initiated, AEs of skin or subcutaneous reaction, pharyngeal/laryngeal or mucosal reaction; and clinically relevant retinal abnormalities on OCT/fundus photography were removed from the list of non-serious AEs of special interest (AESI).



27 January 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; 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. If possible, a different concomitant medication should be chosen; The Clinical Domain Level Global Impression assessment was added to collect information on the respiratory function and swallowing ability of subjects which will be compared with their abilities at baseline, with untreated patients with Type 1 SMA, and with typically developing infants. Exploring the effect of treatment with risdiplam on respiratory function and the ability to swallow, as assessed by the clinical domain level items, was added as an exploratory efficacy objective; Evaluation of the change from baseline in weight and height at 12 and 24 months was added as an exploratory efficacy objective; Text was added to clarify that the dose of risdiplam administered may be higher than the dose levels explicitly listed in the protocol in order to maintain the exposure level over time in an individual growing subject.
18 May 2020	Protocol was released but is not effective.
17 June 2020	Given the absence of any risdiplam-induced ophthalmological findings to date in 471 subjects exposed to risdiplam for up to 3 years, the frequency of ophthalmology assessments has been reduced to every 6 months and colour fundus photography will no longer be performed; The length of the open-label extension phase has been defined as 3 years for each subject to allow for a longer safety follow-up period. Continued access to risdiplam will be provided until the end of study, provided that risdiplam is not commercially available in the subject's country. The length of the study has been modified and will not exceed 5 years after the last subject is enrolled in the study; Cautionary language on the concomitant use of CYP3A4 substrates has been removed, based on the recent results of the clinical drug-drug interaction Study BP41361 and subsequent physiologically-based pharmacokinetic modelling for extrapolation to children and infants. The study showed that coadministration with risdiplam led to only a small increase in exposure of the sensitive CYP3A substrate midazolam, which is not considered to be clinically relevant;
17 June 2020	The safety monitoring period has been modified to extend from screening through the open-label extension, the study completion/early withdrawal visit, and follow-up (phone call). Language related to the study completion/early withdrawal visit and follow-up has been clarified to ensure that all assessments are performed at the last visit for each subject, and that the follow-up should occur 30 days after that visit; Safety monitoring and stopping rules for adverse events affecting the skin, mouth, pharynx, and larynx have been removed to align with current data on potential risks updated in the Risdiplam Investigator's Brochure, Version 7; The adverse event reporting period has been reduced to 30 days after the study completion/early withdrawal visit (i.e., at least 30 days after the last dose of study drug), to reflect that adverse events are not expected beyond this reporting period; the elimination half-life of risdiplam will not exceed 30 days.

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported