



Clinical trial results:

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

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | BN40703 |
|-----------------------|---------|

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | 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? | Yes |

Notes:

Results analysis stage

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

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

Notes:

Subjects enrolled per age group

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

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

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

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

Arms

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

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|--------------------------|
| Arm title | 3 SMN2 Copies, Risdiplam |
|------------------|--------------------------|

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|-----------------------------|
| Arm title | >/=4 SMN2 Copies, Risdiplam |
|------------------|-----------------------------|

Arm description:

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

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

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

Dosage and administration details:

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

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

Baseline characteristics

Reporting groups

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

| Reporting group values | 2 SMN2 Copies, Risdiplam | 3 SMN2 Copies, Risdiplam | >/=4 SMN2 Copies, Risdiplam |
|------------------------------------|--------------------------|--------------------------|-----------------------------|
| Number of subjects | 8 | 13 | 5 |
| Age categorical Units: Subjects | | | |

| | | | |
|--|---------------|---------------|---------------|
| Age Continuous Units: days arithmetic mean standard deviation | 22.8 ± 5.0 | 28.9 ± 7.5 | 31.2 ± 6.1 |
| Sex: Female, Male Units: participants | | | |
| Female | 4 | 9 | 3 |
| Male | 4 | 4 | 2 |

| Reporting group values | Total | | |
|------------------------------------|-------|--|--|
| Number of subjects | 26 | | |
| Age categorical Units: Subjects | | | |

| | | | |
|--|----|--|--|
| Age Continuous Units: days arithmetic mean standard deviation | - | | |
| Sex: Female, Male Units: participants | | | |
| Female | 16 | | |
| Male | 10 | | |

End points

End points reporting groups

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

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

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

End point description:

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

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

At Month 12

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Data were reported for only one arm and no statistical analysis could be conducted.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only one arm in the study met the requirements for the primary efficacy analysis population of this endpoint.

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

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants developing clinically manifested SMA

| | |
|-----------------|---|
| End point title | Percentage of participants developing clinically manifested SMA |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At Month 12 and 24

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Time to permanent ventilation and/or death

| | |
|-----------------|--|
| End point title | Time to permanent ventilation and/or death |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 7 years

| End point values | 2 SMN2 Copies, Risdiplam | 3 SMN2 Copies, Risdiplam | >/=4 SMN2 Copies, Risdiplam | |
|-------------------------------|--------------------------------|--------------------------------|-----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[6] | 0 ^[7] | 0 ^[8] | |
| Units: months | | | | |
| median (full range (min-max)) | (to) | (to) | (to) | |

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants who are alive without permanent ventilation

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

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At Month 12 and 24

| End point values | 2 SMN2 Copies, Risdiplam | 3 SMN2 Copies, Risdiplam | >/=4 SMN2 Copies, Risdiplam | |
|-----------------------------------|--------------------------------|--------------------------------|-----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[9] | 0 ^[10] | 0 ^[11] | |
| Units: percentage of participants | | | | |
| number (confidence interval 90%) | (to) | (to) | (to) | |

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants alive

| | |
|-----------------|----------------------------------|
| End point title | Percentage of participants alive |
|-----------------|----------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At Month 12 and 24

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At Month 12 and 24

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|---|
| End point title | Percentage of participants with two copies of the SMN2 gene |
|-----------------|---|

sitting without support for 5 seconds (independent of the CMAP value at baseline).^[18]

End point description:

Assessed in Item 22 of the BSID-III Gross Motor Scale. The BSID-III is a commonly used measure of infant and toddler development (0 to 42 months). The normed-scores derived from the BSID-III are used in clinical practice to detect infants with developmental delays, as well as to evaluate developmental progress and the impact of therapeutic interventions. The gross motor scale consists of 72 items scored at 0 (unable to perform the activity) or 1 (criteria for item achieved). Item 22, "sits without support for 5 seconds", is not considered achieved if the infant sits alone for less than 5 seconds before losing balance and falling over, or if the infant uses his or her arms to prop him- or herself up. Intent-to-treat (ITT) population included all enrolled participants, regardless of whether they received risdiplam or not. Only participants with two copies of the SMN2 gene were included in this endpoint. 90% CI for one sample binomial was computed used Clopper-Pearson (exact) method.

End point type Secondary

End point timeframe:

At Month 12

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only one arm in the study met the requirements for the efficacy analysis population of this endpoint.

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

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants sitting without support for 5 seconds

End point title Percentage of participants sitting without support for 5 seconds

End point description:

Assessed with BSID-III Gross Motor Scale

End point type Secondary

End point timeframe:

At Month 24

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants sitting without support for 30 seconds

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

End point description:

Assessed with BSID-III Gross Motor Scale

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At Month 12 and 24

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants standing for at least 3 seconds

| | |
|-----------------|--|
| End point title | Percentage of participants standing for at least 3 seconds |
|-----------------|--|

End point description:

Assessed with BSID-III Gross Motor Scale

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At Month 24

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|--|---|
| End point title | Percentage of participants walking (takes at least 3 steps) |
| End point description: Assessed with BSID-III Gross Motor Scale | |
| End point type | Secondary |
| End point timeframe: At Month 24 | |

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|---|--|
| End point title | Percentage of participants demonstrating the ability to achieve a scaled score on BSID-III Gross Motor Subtests within 1.5 standard deviations of chronological reference standard |
| End point description: Assessed through BSID-III Gross Motor Scale | |
| End point type | Secondary |
| End point timeframe: At Month 24 and 42 | |

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Month 12

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At Month 12

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to Month 24

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At Month 60

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

| | |
|--|-----------|
| End point description: | |
| Based on the WHO Child Growth Standards (WHO 2019) | |
| End point type | Secondary |
| End point timeframe: | |
| At Month 12, 24, 36, 48 and 60 | |

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Based on the WHO Child Growth Standards (WHO 2019)

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| At Month 12 and 24 | |

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|--------------------------------|--|
| End point title | Change from baseline percentiles for weight-for-age, length/height-for-age, and weight-for-length/height |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| At Month 12, 24, 36, 48 and 60 | |

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|------------------------|--|
| End point title | Change from baseline percentiles for head circumference- for-age |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| At Month 12 and 24 | |

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in chest circumference

| | |
|-----------------|---|
| End point title | Change from baseline in chest circumference |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At Month 12 and 24

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Ratio between chest and head circumferences

| | |
|-----------------|---|
| End point title | Ratio between chest and head circumferences |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At Month 12 and 24

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|--|---|
| End point title | Change from baseline in compound muscle action potential (CMAP) amplitude |
| End point description: Measured by CMAP | |
| End point type | Secondary |
| End point timeframe: At Month 12 and 24 | |

| End point values | 2 SMN2 Copies, Risdiplam | 3 SMN2 Copies, Risdiplam | >/=4 SMN2 Copies, Risdiplam | |
|--------------------------------------|--------------------------|--------------------------|-----------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[58] | 0 ^[59] | 0 ^[60] | |
| Units: mV | | | | |
| arithmetic mean (standard deviation) | () | () | () | |

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|--|---|
| End point title | Percentage of participants with the ability to swallow and to feed orally |
| End point description: | |
| End point type | Secondary |
| End point timeframe: At Month 12, 24, 36, 48 and 60 | |

| End point values | 2 SMN2 Copies, Risdiplam | 3 SMN2 Copies, Risdiplam | >/=4 SMN2 Copies, Risdiplam | |
|-----------------------------------|--------------------------|--------------------------|-----------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[61] | 0 ^[62] | 0 ^[63] | |
| Units: percentage of participants | | | | |
| number (confidence interval 90%) | (to) | (to) | (to) | |

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Measurement of pharmacodynamic marker levels in blood

| | |
|-----------------|---|
| End point title | Measurement of pharmacodynamic marker levels in blood |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

| End point values | 2 SMN2 Copies, Risdiplam | 3 SMN2 Copies, Risdiplam | >/=4 SMN2 Copies, Risdiplam | |
|--------------------------------------|--------------------------------|--------------------------------|-----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[64] | 0 ^[65] | 0 ^[66] | |
| Units: nanograms/milliliter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | () | () | () | |

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 7 years

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with adverse events

| | |
|--|--|
| End point title | Percentage of participants with adverse events |
| End point description: | |
| Adverse event severity is determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5 (NCI CTCAE) v5 | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 7 years | |

| End point values | 2 SMN2 Copies, Risdiplam | 3 SMN2 Copies, Risdiplam | >/=4 SMN2 Copies, Risdiplam | |
|-----------------------------------|--------------------------------|--------------------------------|-----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[70] | 0 ^[71] | 0 ^[72] | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|------------------------|--|
| End point title | Plasma concentration of risdiplam and its metabolites to characterize the PK profile |
| End point description: | |
| | |
| End point type | Secondary |
| End point timeframe: | |
| Up to 7 years | |

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

Notes:

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

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

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline up to the clinical cut off date (a minimum of 12 months and a maximum of 3.5 years)

Adverse event reporting additional description:

The safety population included all participants who received at least one dose of risdiplam, whether prematurely withdrawn from the study or not.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 25.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------------------|
| Reporting group title | 2 SMN2 Copies, Risdiplam |
|-----------------------|--------------------------|

Reporting group description:

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

| | |
|-----------------------|-----------------------------|
| Reporting group title | >/=4 SMN2 Copies, Risdiplam |
|-----------------------|-----------------------------|

Reporting group description:

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

| | |
|-----------------------|--------------------------|
| Reporting group title | 3 SMN2 Copies, Risdiplam |
|-----------------------|--------------------------|

Reporting group description:

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

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

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

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

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported