RAINBOWFISH: Preliminary efficacy and safety data in risdiplam-treated infants with presymptomatic SMA

RS Finkel,1 MA Farrar,2 D Vlodavets,3 L Servais,4–6 E Zanotelli,7 M Al-Muhaizea,8 L Nelson,9 A Prufer,10 Y Wang,11 C Fisher,12 M Gerber,13 K Gorni,14 H Kletzl,15 L Palfreeman,12 RS Scalco,16 E Bertini,17 on behalf of the RAINBOWFISH Study Group

1Center for Experimental Neurotherapeutics, St Jude Children’s Research Hospital, Memphis, TN, USA; 2Sydney Children’s Hospital Network and UNSW Medicine, UNSW Sydney, Sydney, Australia; 3Russian Children Neuromuscular Center, Viatassave Clinical Pediatric Research Institute of Pirogov Russian National Research Medical University, Moscow, Russia; 4MDUK Oxford Neuromuscular Centre, Department of Paediatrics, University of Oxford, Oxford, UK; 5Division of Child Neurology, Centre de Références des Maladies Neuromusculaires, Department of Pediatrics, University Hospital Liège & University of Liège, Liège, Belgium; 6M-Motion – Hôpital Armand Trousseau, Paris, France; 7Department of Neurology, Faculdade de Medicina, Universidade de São Paulo (FMUSP), São Paulo, Brazil; 8Department of Neurosciences, King Faisal Specialist Hospital & Research Center-Riyadh, Riyadh, Kingdom of Saudi Arabia; 9UT Southwestern Medical Center, Dallas, TX, USA; 10Federal Uni Rio de Janeiro, Rio de Janeiro, Brazil; 11Children’s Hospital of Fudan University, Shanghai, China; 12Roche Products Ltd, Welwyn Garden City, UK; 13Pharma Development, Safety, F. Hoffmann-La Roche Ltd, Basel, Switzerland; 14PRIMA Neuroscience and Rare Disease, F. Hoffmann-La Roche Ltd, Basel, Switzerland; 15Roche Pharmaceutical Research and Early Development, Roche Innovation Center Basel, Basel, Switzerland; 16Pharma Development Neurology, F. Hoffmann-La Roche Ltd, Basel, Switzerland; 17Department of Neurosciences and Neurorehabilitation, Bambino Gesù Children’s Research Hospital IRCCS, Rome, Italy.

Overview

As of 22 February 2022, worldwide recruitment for RAINBOWFISH is complete

Richard Finkel has participated as an investigator in clinical trials sponsored by AveXis/Novartis Gene Therapies, Biogen, Catabasis, Capricor Therapeutics, Cytokinetics, Ionis Pharmaceuticals, Muscular Dystrophy Association, National Institutes of Health, Lilly, ReveraGen, Roche, Sarepta, Scholar Rock and Summit. He has received honoraria for participating in symposia and on advisory boards for these same pharmaceutical companies. He serves without compensation as an advisor to the n-Lorem and EveryLife Foundations. His institution receives funding from Biogen for the coordination of a USA registry for SMA, iSMAC. RSF has no financial interests in these companies.
Background

- In patients with SMA, motor neuron degeneration begins before the onset of symptoms.
- In clinical studies of SMA, the time from symptom onset to treatment initiation has been established as a predictive factor with regards to the degree of treatment effect. Therefore, the timing of treatment initiation is crucial.
- Risdiplam (EVRYSDI®) is a centrally and peripherally distributed, oral SMN2 pre-mRNA splicing modifier that increases and sustains the levels of functional SMN protein.
  - Risdiplam has been approved for the treatment of patients with SMA aged 2 months and older by the FDA.
- Here we present data from the RAINBOWFISH study (NCT03779334), which assesses the efficacy and safety of risdiplam in infants with genetically diagnosed presymptomatic SMA.
A multicenter, open-label, single-arm study of risdiplam in infants with genetically diagnosed, presymptomatic SMA

**Study design**

**Screening**
- Genetic diagnosis of 5q-autosomal recessive SMA
- Absence of clinical signs or symptoms of SMA at screening
- Up to 6 weeks (42 days) of age at the time of first dose

** PRIMARY ANALYSIS 12 months**

**Risdiplam**
- Primary endpoint (n≥5): Proportion of infants who are sitting without support for ≥5 seconds at Month 12 (BSID-III Gross Motor Scale, Item 22)

**OLE (≥3 years)**
- Secondary endpoints (all infants; n=26):
  - Development of clinically manifested SMA
  - Survival and permanent ventilation
  - Achievement of motor milestones as defined by the HINE-2 and BSID-III Gross Motor Scale
  - CHOP-INTEND total score
  - Growth measures
  - Ability to swallow and feed orally
  - CMAP amplitude
  - PK/PD
  - Safety

*The primary efficacy population includes infants with two copies of the SMN2 gene and CMAP amplitude ≥1.5 mV at baseline. *Final patient number. As of 22 February 2022, worldwide recruitment for RAINBOWFISH is complete.
### Baseline characteristics of 18 infants enrolled in RAINBOWFISH as of 1 July 2021

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Risdiplam (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at first dose, days, median (range)</strong></td>
<td>26.5 (16–40)</td>
</tr>
<tr>
<td><strong>SMN2 copy number, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>7 (39)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>11 (61)*</td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>10 (56)</td>
</tr>
<tr>
<td>Male</td>
<td>8 (44)</td>
</tr>
<tr>
<td><strong>SMA identification method, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Newborn screening</td>
<td>13 (72)</td>
</tr>
<tr>
<td>Family history</td>
<td>5 (28)</td>
</tr>
<tr>
<td><strong>Baseline CMAP amplitude, mV, median (range)</strong></td>
<td></td>
</tr>
<tr>
<td>Baseline value &lt;1.5 mV, n (%)</td>
<td>3.6 (0.5–6.7)</td>
</tr>
<tr>
<td>Baseline value ≥1.5 mV, n (%)</td>
<td>3 (17)</td>
</tr>
<tr>
<td></td>
<td>15 (83)</td>
</tr>
</tbody>
</table>

- Enrolled infants have been treated with risdiplam for a median of 8.7 months (range: 0.5–22.8 months)
  - Seven infants have been treated for ≥12 months (preliminary efficacy data are available for these infants)
  - Four infants have been treated for ≥6 to <12 months
  - Seven infants have been treated for <6 months

*Includes seven infants with three SMN2 copies, and four infants with ≥4 SMN2 copies. *These three infants had baseline CMAP amplitude values of 1.3, 0.6 and 0.46 mV. The primary efficacy population includes infants with two SMN2 copies and CMAP amplitude value ≥1.5 mV at baseline.

Data cut-off: 1 Jul 2021.
RAINBOWFISH: Preliminary efficacy and safety data in risdiplam-treated infants with presymptomatic SMA

RS Finkel,1* MA Farrar,2 D Vlodavets,3 L Servais,4–6 E Zanoteli,7 M Al-Muhaizea,8 L Nelson,9 A Prufer,10 Y Wang,11 C Fisher,12 M Gerber,13 K Gorni,14 H Kletzl,15 L Palfreeman,12 RS Scalco,16 E Bertini,17 on behalf of the RAINBOWFISH Study Group

Overview

Background

Study design

Demographics

Safety results

Efficacy results

References and abbreviations

Acknowledgments

AEs were more reflective of the age of the infants rather than the underlying SMA

<table>
<thead>
<tr>
<th></th>
<th>2 SMN2 copies (n=7)</th>
<th>&gt;2 SMN2 copies (n=11)</th>
<th>Total risdiplam (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teething</td>
<td>2 (29)</td>
<td>4 (36)</td>
<td>6 (33)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>1 (14)</td>
<td>4 (36)</td>
<td>5 (28)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0</td>
<td>5 (45)</td>
<td>5 (28)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>4 (36)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Viral infection</td>
<td>2 (29)</td>
<td>2 (18)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (14)</td>
<td>3 (27)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (29)</td>
<td>1 (9)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Cough</td>
<td>0</td>
<td>3 (27)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Eczema</td>
<td>1 (14)</td>
<td>2 (18)</td>
<td>3 (17)</td>
</tr>
</tbody>
</table>

Most common AEs, n (%) (reported in ≥3 infants)

• Preclinical safety findings were not observed in any infants in RAINBOWFISH:

  - No risdiplam-associated ophthalmologic findings were observed
  - Hematologic parameters remained stable over time
  - No drug-induced skin findings were observed

Multiple occurrences of the same AE in an individual are counted only once. This includes AEs with onset from first dose of study drug up to the cut-off date. Additional AEs that were reported in ≥2 infants were accidental overdose, conjunctivitis, gastroenteritis, papule, rhinitis and rhinorrhea.

Data cut-off: 1 Jul 2021.
RAINBOWFISH: Preliminary efficacy and safety data in risdiplam-treated infants with presymptomatic SMA

RS Finkel,1* MA Farrar,2 D Vlodavets,3 L Servais,4−6 E Zanoteli,7 M Al-Muhaizea,8 L Nelson,9 A Prufer,10 Y Wang,11 C Fisher,12 M Gerber,13 K Gorni,14 H Kletzl,15 L Palfreeman,12 RS Scalco,16 E Bertini,17 on behalf of the RAINBOWFISH Study Group

No SAEs were reported in presymptomatic infants treated with risdiplam*

<table>
<thead>
<tr>
<th>2 SMN2 copies (n=7)</th>
<th>&gt;2 SMN2 copies (n=11)</th>
<th>Total risdiplam (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants with at least one AE, n (%)</td>
<td>5 (71)</td>
<td>9 (82)</td>
</tr>
<tr>
<td>Total number of AEs</td>
<td>22</td>
<td>59</td>
</tr>
<tr>
<td>Total number of deaths, n (%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Number of infants with at least one AE, n (%)

| SAE* | 0 | 0 | 0 |
| Treatment-related SAE | 0 | 0 | 0 |
| Treatment-related AE* | 0 | 2 (18) | 2 (11) |
| AE leading to withdrawal from treatment | 0 | 0 | 0 |
| AE leading to dose modification/interruption | 0 | 2 (18) | 2 (11) |
| Related AE leading to withdrawal from treatment | 0 | 0 | 0 |
| Related AE leading to dose modification/interruption | 0 | 0 | 0 |
| Grade 3–5 AE† | 1 (14) | 1 (9) | 2 (11) |

- Two related AEs were reported in two infants:*
  - diarrhea (reported in one infant)
  - skin discoloration (reported in one infant)
- At the data cut-off,‡ the related AEs had resolved or were resolving with ongoing risdiplam treatment
- Pneumonia had not been reported in any infant

*Since the previous data cut-off (20 Feb 2021), one SAE of gastroenteritis norovirus was reclassified as an AE, and two AEs that were previously classified as related AEs (increased alanine aminotransferase and increased aspartate aminotransferase [both reported in one infant]) were deleted. †Both AEs were Grade 3 and consisted of gastroenteritis norovirus and cystoid macular oedema. Neither were considered to be related to risdiplam treatment. ‡Data cut-off: 1 Jul 2021.

Multiple occurrences of the same AE in one individual are counted only once except for the “Total number of AEs” row, for which multiple occurrences of the same AE are counted separately. Includes AEs with onset from first dose of study drug up to the cut-off date.
As of the data cut-off, seven infants have been treated with risdiplam for ≥12 months

4/7 infants have 2 SMN2 copies
- Two infants had a baseline CMAP amplitude ≥1.5 mV
- Two infants had a baseline CMAP amplitude <1.5 mV

3/7 infants have >2 SMN2 copies
- All three infants had a baseline CMAP amplitude ≥1.5 mV

These seven infants have received risdiplam for 12.2–22.8 months. Preliminary exploratory efficacy data (CHOP-INTEND and HINE-2) are available for these seven infants.

*Data cut-off: 1 Jul 2021. †The two infants with baseline CMAP amplitude ≥1.5 mV had baseline values of 0.6 mV and 0.46 mV. ‡Two infants have 3 SMN2 copies and one infant has ‘atypical’ (when a patient’s SMN2 copy number result falls in between two values) 3–4 SMN2 copies. §The primary endpoint will be assessed when the primary efficacy population has been enrolled and has completed 12 months of treatment with risdiplam. The primary efficacy population includes infants with two copies of the SMN2 gene and CMAP amplitude ≥1.5 mV at baseline.
Most infants treated with risdiplam for ≥12 months (n=7) reached near-maximum CHOP-INTEND scores by 4–5 months of age

*The two infants with baseline CMAP <1.5 mV had baseline values of 0.6 mV (square symbols) and 0.46 mV (triangles). At the data cut-off, only seven infants had received treatment with risdiplam for ≥12 months and were included in this analysis. Data cut-off: 1 Jul 2021.
Rainbowfish: Preliminary efficacy and safety data in risdiplam-treated infants with presymptomatic SMA
RS Finkel,1* MA Farrar,2 D Vlodavets,3 L Servais,4–6 E Zanoteli,7 M Al-Muhaizea,8 L Nelson,9 A Prufer,10 Y Wang,11 C Fisher,12 M Gerber,13 K Gorni,14 H Kletzl,15 L Palfreeman,12 RS Scalco,16 E Bertini,17 on behalf of the Rainbowfish Study Group

References and abbreviations
Acknowledgments
Overview
Background
Study design
Demographics
Safety results
Efficacy results

Most of the infants with 2 SMN2 copies treated for ≥12 months achieved motor milestones within the WHO windows for healthy children

<table>
<thead>
<tr>
<th>Study visit:</th>
<th>Month 6</th>
<th>Month 9</th>
<th>Month 12</th>
<th>Month 15</th>
<th>Month 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting without support</td>
<td><img src="image" alt="Standing unaided" /></td>
<td><img src="image" alt="Walking independently" /></td>
<td><img src="image" alt="Crawling on hands and knees" /></td>
<td><img src="image" alt="Sitting without support" /></td>
<td><img src="image" alt="Standing unaided" /></td>
</tr>
</tbody>
</table>

*One infant achieved ‘stable sit’. All other patients achieved ‘pivots’, the most difficult sitting motor milestone according to the HINE-2. *White bars represent the 1st–99th percentile window for achievement of motor milestones based on the WHO Motor Development Study.† The age at the visit that infants first achieved the milestone up to the data cut-off is shown. Motor milestones were measured at given study visits and thus achievements are not plotted as continuum. Data cut-off: 1 Jul 2021.

All four infants achieved sitting independently
Two infants achieved sitting within the WHO window
Two infants achieved sitting outside the WHO window

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting without support</td>
<td><img src="image" alt="Standing unaided" /></td>
<td><img src="image" alt="Walking independently" /></td>
<td><img src="image" alt="Crawling on hands and knees" /></td>
<td><img src="image" alt="Sitting without support" /></td>
<td><img src="image" alt="Standing unaided" /></td>
<td><img src="image" alt="Walking independently" /></td>
<td><img src="image" alt="Crawling on hands and knees" /></td>
</tr>
</tbody>
</table>

2. SMN2 copies, ≥1.5 mV CMAP (n=2)
2. SMN2 copies, <1.5 mV CMAP (n=2)
WHO window of achievement in healthy children

†White bars represent the 1st–99th percentile window for achievement of motor milestones based on the WHO Motor Development Study.
RAINFOWISH: Preliminary efficacy and safety data in risdiplam-treated infants with presymptomatic SMA

RS Finkel,1* MA Farrar,2 D Vlodavets,3 L Servais,4–6 E Zanoteli,7 M Al-Muhaizea,8 L Nelson,9 A Prufer,10 Y Wang,11 C Fisher,12 M Gerber,13 K Gorni,14 H Kletzl,15 L Palfreeman,12 RS Scalco,16 E Bertini,17 on behalf of the RAINBOWFISH Study Group

References and abbreviations

Acknowledgments

Overview

Background

Study design

Demographics

Safety results

Efficacy results

Most of the infants with 2 SMN2 copies treated for ≥12 months achieved motor milestones within the WHO windows for healthy children1

<table>
<thead>
<tr>
<th>Study visit</th>
<th>Month 6</th>
<th>Month 9</th>
<th>Month 12</th>
<th>Month 15</th>
<th>Month 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting without support</td>
<td><img src="image.png" alt="Graph" /></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crawling on hands and knees</td>
<td><img src="image.png" alt="Graph" /></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standing unaided</td>
<td><img src="image.png" alt="Graph" /></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking independently</td>
<td><img src="image.png" alt="Graph" /></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*One infant achieved ‘stable sit’. All other patients achieved ‘pivots’, the most difficult sitting motor milestone according to the HINE-2. †White bars represent the 1st–99th percentile window for achievement of motor milestones based on the WHO Motor Development Study.1 The age at the visit that infants first achieved the milestone up to the data cut-off is shown. Motor milestones were measured at given study visits and thus achievements are not plotted as continuum. Data cut-off: 1 Jul 2021.
Most of the infants with 2 SMN2 copies treated for ≥12 months achieved motor milestones within the WHO windows for healthy children\(^1\)

---

**Sitting without support**
- All four infants achieved sitting independently
- Two infants achieved standing – one within the WHO window and one outside the WHO window

**Crawling on hands and knees**
- Two infants achieved crawling within the WHO window

**Standing unaided**
- Two infants achieved standing – one within the WHO window and one outside the WHO window

**Walking independently**
- Two infants did not achieve standing, but were still within the WHO window at their last visit

---

*One infant achieved 'stable sit'. All other patients achieved 'pivots', the most difficult sitting motor milestone according to the HINE-2. \(^1\)White bars represent the 1st–99th percentile window for achievement of motor milestones based on the WHO Motor Development Study. The age at the visit that infants first achieved the milestone up to the data cut-off is shown. Motor milestones were measured at given study visits and thus achievements are not plotted as continuum. Data cut-off: 1 Jul 2021.*
Most of the infants with 2 SMN2 copies treated for ≥12 months achieved motor milestones within the WHO windows for healthy children¹

---

*One infant achieved ‘stable sit’. All other patients achieved ‘pivots’, the most difficult sitting motor milestone according to the HINE-2. *White bars represent the 1st–99th percentile window for achievement of motor milestones based on the WHO Motor Development Study.¹ **This infant achieved the ‘cruising’ milestone. The age at the visit that infants first achieved the milestone up to the data cut-off is shown. Motor milestones were measured at given study visits and thus achievements are not plotted as continuum. Data cut-off: 1 Jul 2021.

---

References and abbreviations

Acknowledgments
Most infants with >2 SMN2 copies who were treated for ≥12 months achieved motor milestones within the WHO windows for healthy children\(^1\)

- Sitting without support
  - *This infant missed the Month 6 visit due to Covid restrictions.
  - White bars represent the 1st–99th percentile window for achievement of motor milestones based on the WHO Motor Development Study.\(^1\)
  - The age at the visit that infants first achieved the milestone up to the data cut-off is shown. Motor milestones were measured at given study visits and thus achievements are not plotted as continuum. Data cut-off: 1 Jul 2021.

All infants achieved all milestones:
- **SITTING**
  - 2 infants achieved sitting outside the WHO window for healthy children
- **CRAWLING**
- **STANDING**
- **WALKING**

References and abbreviations ▸
Acknowledgments ▸
All infants treated with risdiplam for ≥12 months (n=7) maintained the ability to swallow and were able to feed exclusively by mouth.
RAINBOWFISH: Preliminary efficacy and safety data in risdiplam-treated infants with presymptomatic SMA

RS Finkel,1* MA Farrar,2 D Vlodavets,3 L Servais,4–6 E Zanoteli,7 M Al-Muhaizea,8 L Nelson,9 A Prufer,10 Y Wang,11 C Fisher,12 M Gerber,13 K Gorni,14 H Kletzl,15 L Palfreeman,12 RS Scalco,16 E Bertini,17 on behalf of the RAINBOWFISH Study Group

References

1. WHOMGRS. Acta Paediatr Suppl. 2006; 450:86–95;
6. EVRYSDI® FDA prescribing information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213535s000lbl.pdf (Accessed April 2022);

Abbreviations

AE, adverse event; BSID-III, Bayley Scales of Infant and Toddler Development, Third Edition; CHOP-INTEND, Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound muscle action potential; Covid, Coronavirus disease; FDA, US Food and Drug Administration; HINE-2, Hammersmith Infant Neurological Examination, Section 2; mV, millivolt; OLE, open-label extension; PD, pharmacodynamics; PK, pharmacokinetics; SAE, serious AE; SMA, spinal muscular atrophy; SMN, survival of motor neuron; WHO, World Health Organization; WHOMGRS, WHO Multicentre Growth Reference Study Group.

Please scan using your QR reader application to access the graphs and data presented in this presentation. NB: there may be associated costs for downloading data. These costs may be high if you are using your smartphone abroad. Please check your mobile data tariff or contact your service provider for more details. Alternatively this can be accessed at https://bit.ly/3HvULkr
We would like to thank the individuals with SMA and their families, as well as the investigators and trial staff involved in the RAINBOWFISH study.

We would also like to thank our collaborators at PTC Therapeutics and the SMA Foundation.

This study is funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland.

Writing and editorial assistance was provided by Jack Curran (PhD), of Nucleus Global, in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3)