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

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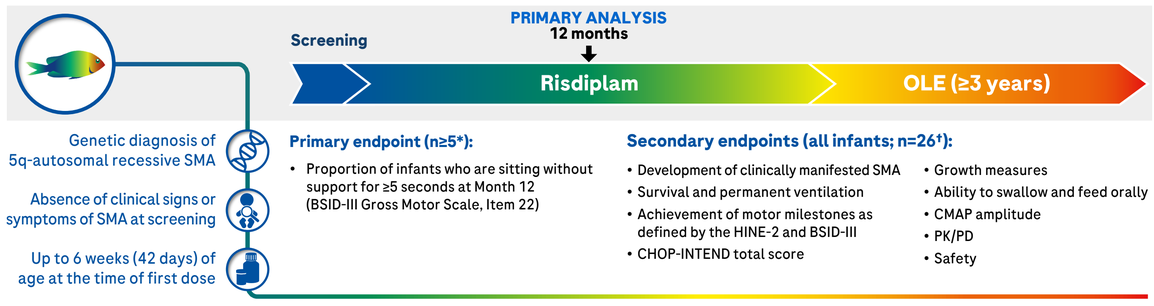
Background

- In patients with SMA, motor neuron degeneration begins before the onset of symptoms.[1]
- 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.[2] 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.[3–6]
  - Risdiplam has been approved for the treatment of patients with SMA aged 2 months and older by the FDA.[7]
- Here we present data from the RAINBOWFISH study (NCT03779334),[8] which assesses the efficacy and safety of risdiplam in infants with genetically diagnosed presymptomatic SMA.

RAINBOWFISH: A multicenter, open-label, single-arm study of risdiplam in infants with genetically diagnosed, presymptomatic SMA[8]



*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 for 18 infants enrolled in RAINBOWFISH as of 1 July 2021

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

*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.

- 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.

No SAEs were reported in presymptomatic infants treated with risdiplam*

		2 *SMN2* copies (n=7)	>2 *SMN2* copies (n=11)	Total risdiplam (n=18)
Most common AEs, n (%) (reported in ≥3 infants)†	Teething	2 (29)	4 (36)	6 (33)
	Nasal congestion	1 (14)	4 (36)	5 (28)
	Pyrexia	0	5 (45)	5 (28)
	Diarrhea	0	4 (36)	4 (22)
	Viral infection	2 (29)	2 (18)	4 (22)
	Vomiting	1 (14)	3 (27)	4 (22)
	Constipation	2 (29)	1 (9)	3 (17)
	Cough	0	3 (27)	3 (17)
	Eczema	1 (14)	2 (18)	3 (17)

- AEs were more reflective of the age of the infants rather than the underlying SMA.
- Two related AEs were reported in two infants (see supplementary data):*
  - diarrhea (reported in one infant)
  - skin discoloration (reported in one infant).
- As of the data cut-off,‡ related AEs had resolved or were resolving with ongoing risdiplam treatment.
- Pneumonia had not been reported in any 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

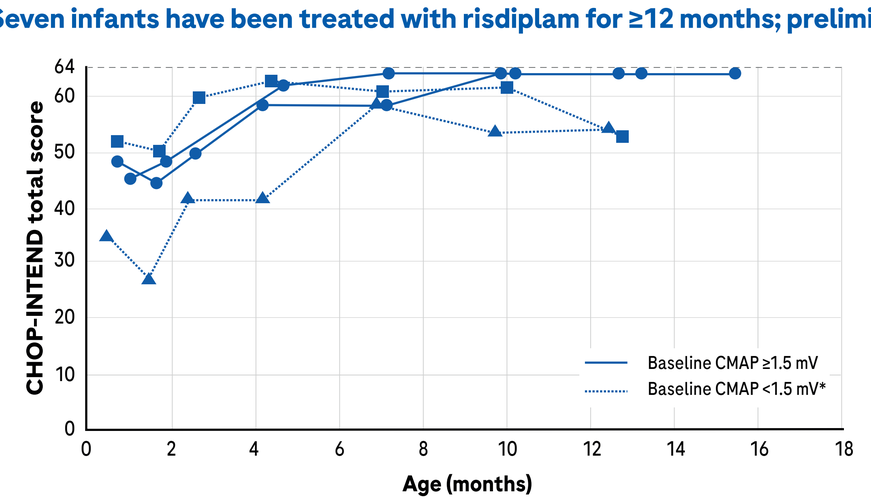
No drug-induced skin findings were observed

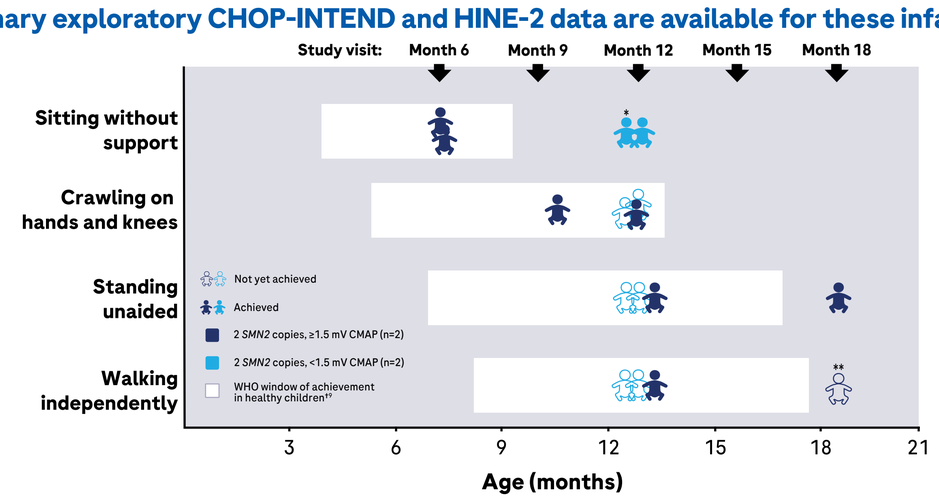
*Since the previous data cut-off (20 Feb 2021), one SAE of gastroenteritis norovirus was reclassified as an AE, and two AEs that were previously classified as related AEs (increased alanine aminotransferase and increased aspartate aminotransferase [both reported in one infant]) were deleted. †Additional AEs that were reported in ≥2 infants were accidental overdose, conjunctivitis, gastroenteritis, papule, rhinitis and rhinorrhea. ‡Data cut-off: 1 Jul 2021. Multiple occurrences of the same AE in an individual are counted only once. Includes AEs with onset from first dose of study drug up to the cut-off date.

Seven infants have been treated with risdiplam for ≥12 months; preliminary exploratory CHOP-INTEND and HINE-2 data are available for these infants

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*

*The two infants with baseline CMAP amplitude <1.5 mV had baseline values of 0.6 mV (square symbols) and 0.46 mV (triangle symbols). Data cut-off: 1 Jul 2021.



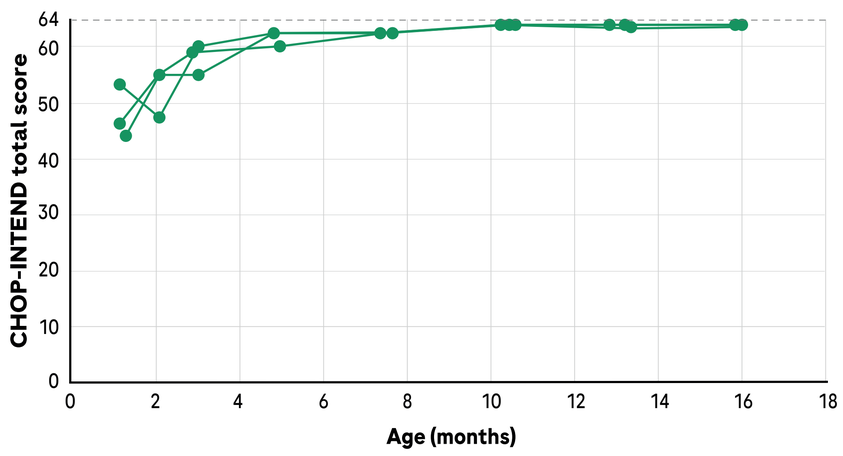


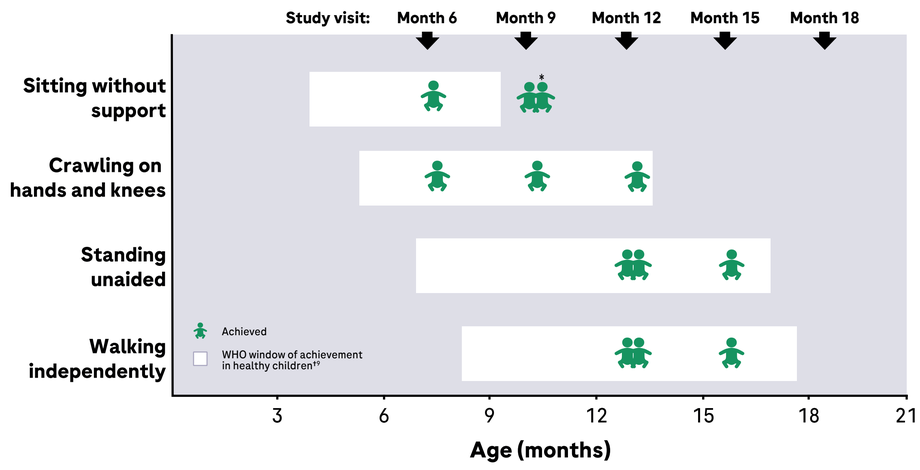
Most infants with 2 *SMN2* copies treated for ≥12 months (n=4) achieved near-maximum CHOP-INTEND scores, and most achieved motor milestones within WHO windows for healthy children[9]

*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.[9] **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. For non-achievers, the age at the last visit prior to the data cut-off is shown.
Motor milestones were measured at given study visits and thus achievements are not plotted as continuum.

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

*Two infants have 3 *SMN2* copies and one infant has atypical 3-4 *SMN2* copies. Data cut-off: 1 Jul 2021.





All infants with >2 *SMN2* copies treated for ≥12 months (n=3) achieved the maximum CHOP-INTEND score, and most achieved motor milestones within WHO windows for healthy children[9]

*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.[9] 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.

Conclusions

- No SAEs were reported in presymptomatic infants treated with risdiplam for up to 22.8 months.
- Most of the infants treated with risdiplam for ≥12 months reached near-maximum CHOP-INTEND scores by 4–5 months of age and achieved motor milestones within the WHO windows for healthy children.[9]
- All seven infants treated for ≥12 months achieved sitting without support by Month 12.
- All seven infants who had received risdiplam for ≥12 months maintained the ability to swallow solid food and were able to feed exclusively by mouth (see supplementary data).
- RAINBOWFISH will help to determine the dose of risdiplam for infants <2 months of age.

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.

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Acknowledgments

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SUPPLEMENTARY INFORMATION – the content below was not in the poster presented at MDA 2022 but is available via a QR code

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Supplementary materials

No SAEs were reported in infants with presymptomatic SMA treated with risdiplam*

		2 *SMN2* copies (n=7)	>2 *SMN2* copies (n=11)	Total risdiplam (n=18)
Infants with at least one AE, n (%)		5 (71)	9 (82)	14 (78)
Total number of AEs		22	59	81
Total number of deaths, n (%)		0	0	0
Number of infants with at least one, 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)

*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 "Total number of AEs" row, for which multiple occurrences of the same are counted separately. Includes AEs with onset from first dose of study drug up to the cut-off date.

All infants treated with risdiplam for ≥12 months (n=7) maintained the ability to swallow and were able to feed exclusively by mouth

Swallowing

100% (7/7) were able to swallow

Swallowing solid food

100% (7/7) were able to swallow solid food

Feeding

100% (7/7) were able to feed exclusively by mouth

Data cut-off: 1 Jul 2021.

Abbreviations

AE, adverse event; SAE, serious AE; SMN survival of motor neuron.