

RAINBOWFISH: Preliminary efficacy and safety data in risdiplam-treated infants with presymptomatic spinal muscular atrophy (SMA)

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Disclosures



- LS is a PI of SMA studies for F. Hoffmann-La Roche Ltd, Biogen and AveXis; he has attended scientific advisory boards of F. Hoffmann-La Roche Ltd, Biogen and AveXis and received consultancy fees from Biogen; he serves on the board for Cytokinetics. He is co-inventor of the patent 20190029605 (method for estimating physical activity of the upper limb) from which he has not received any financial interest
- MAF is a PI of SMA studies for F. Hoffmann-La Roche Ltd, Biogen and AveXis; and has received honoraria for participation on scientific advisory boards and educational activities for the same pharmaceutical companies mentioned above
- DV is a PI of SMA studies for F. Hoffmann-La Roche Ltd. He is also a PI for studies for PTC Therapeutics, Novartis, NS Pharma, Sarepta Therapeutics and Pfizer
- EZ is a PI of SMA studies for F. Hoffmann-La Roche Ltd. He has participated on advisory boards for F. Hoffmann-La Roche Ltd, Biogen, Novartis, Sarepta and Sanofi; and has received speaker honoraria and travel support from F. Hoffmann-La Roche Ltd, Biogen, Novartis, Sarepta and Sanofi
- M-AM has participated as an investigator in SMA studies sponsored by F. Hoffmann-La Roche Ltd and PTC Therapeutics. He has received honoraria for participating in symposia and on advisory boards for AveXis/Novartis Gene Therapies, Biogen, F. Hoffmann-La Roche Ltd, Genpharm and PTC Therapeutics. He has no financial interests in these companies
- RSF 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
- LN has served on advisory boards and in consultancy roles for AveXis/Novartis, Roche/Genentech, Biogen and Scholar Rock
- AP is a PI in clinical research sponsored by Roche, PTC Therapeutics and Sarepta. They have received consultancy fees from Biogen, AveXis/Novartis, Roche, PTC Therapeutics and Sarepta
- YW is a PI of SMA studies for F. Hoffmann-La Roche Ltd
- CF, MG, KG, HK, LP and RSS are employees of, and hold shares in, F. Hoffmann-La Roche Ltd
- EB is an advisor/consultant for AveXis, Biogen, Edison, Novartis and Roche; he has received grants from Fondazione Telethon and the Italian Ministry of Health

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- In patients with SMA, motor neuron degeneration begins before the onset of symptoms¹
- 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 is a centrally and peripherally distributed oral *SMN2* pre-mRNA splicing modifier that increases and sustains the levels of functional SMN protein³⁻⁶
 - Risdiplam (EVERYSDI®) has been approved for the treatment of patients with SMA in more than 80 countries worldwide^{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

*Risdiplam has been approved for the treatment of patients of all ages with SMA by the FDA and for patients aged 2 months and older with a clinical diagnosis of Type 1, 2 or 3 SMA or with one to four copies of *SMN2* by the EC.^{9,10}

EC, European Commission; FDA, US Food and Drug Administration; SMA, spinal muscular atrophy; SMN, survival of motor neuron.
1. Kolb SJ, et al. *Ann Neurol*. 2017; 82:883–891; 2. Baranello G, et al. *Clin Pharmacol Ther*. 2021; 110:1435–1454; 3. Ratni H, et al. *J Med Chem*. 2018; 61:6501–6517; 4. Poirier A, et al. *Pharmacol Res Perspect*. 2018; 6:e00447; 5. Chiriboga CA, et al. Data presented at WMS 2021; 6. Day JW, et al. Data presented at WMS 2020; 7. F. Hoffmann-La Roche. May 2022 press release. <https://www.roche.com/media/releases/med-cor-2022-05-31> (Accessed October 2022); 8. ClinicalTrials.gov. NCT03779334 (Accessed October 2022); 9. EVERYSDI® (risdiplam) US prescribing information. https://www.gene.com/download/pdf/evryydi_prescribing.pdf (Accessed October 2022); 10. EVERYSDI® (risdiplam) summary of product characteristics. https://www.ema.europa.eu/en/documents/product-information/evryydi-epar-product-information_en.pdf (Accessed October 2022).



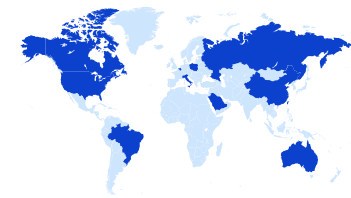
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RAINBOWFISH: A multicentre, open-label, single-arm study of risdiplam in infants with genetically diagnosed, presymptomatic SMA



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 endpoint (n≥5*):

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

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 numbers. As of 22 February 2022, worldwide recruitment for RAINBOWFISH is complete. 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; HINE-2, Hammersmith Infant Neurological Examination, Section 2; mV, millivolt; OLE, open-label extension; PD, pharmacodynamics; PK, pharmacokinetics; SMA, spinal muscular atrophy; SMN, survival of motor neuron. ClinicalTrials.gov. NCT03779334 (Accessed October 2022).



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Baseline characteristics of 18 infants enrolled in RAINBOWFISH*



		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)

- Enrolled infants at the CCOD* had 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**
 - Four infants have been treated for ≥6 to <12 months
 - Seven infants have been treated for <6 months

*Data cut-off: 1 Jul 2021. [†]Includes seven infants with three *SMN2* copies, one infant with 'atypical' (when a patient's *SMN2* copy number result falls in between two values) 3–4 *SMN2* copies, and three infants with ≥4 *SMN2* copies. [‡]These three infants had baseline CMAP values of 1.3, 0.6 and 0.46 mV. RAINBOWFISH enrolled infants with a low baseline CMAP (<1.5 mV) who were not eligible for inclusion in other clinical trials.^{1,2} The primary efficacy population includes infants with two copies of the *SMN2* gene and CMAP amplitude ≥1.5 mV at baseline. CCOD, clinical cut-off date; CMAP, compound muscle action potential; mV, millivolt; SMA, spinal muscular atrophy; SMN, survival of motor neuron.
 1. ClinicalTrials.gov. NCT02386553 (Accessed October 2022); 2. ClinicalTrials.gov. NCT03505099 (Accessed October 2022).



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No SAEs were reported in 18 presymptomatic infants 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)

- Two related AEs were reported in two infants:*
 - Diarrhoea (reported in one infant)
 - Skin discolouration (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.
AE, adverse event; SAE, serious AE; SMN, survival of motor neuron.



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

		2 SMN2 copies (n=7)	>2 SMN2 copies (n=11)	Total risdiplam (N=18)
Most common AEs, n (%) (reported in at least three infants)*	Teething	2 (29)	4 (36)	6 (33)
	Nasal congestion	1 (14)	4 (36)	5 (28)
	Pyrexia	0	5 (45)	5 (28)
	Diarrhoea	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)

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



No risdiplam-associated ophthalmological findings were observed



Haematological parameters remained stable over time



No drug-induced skin findings were observed

*Additional AEs that were reported in ≥ 2 infants were accidental overdose, conjunctivitis, gastroenteritis, papule, rhinitis and rhinorrhoea. 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. Data cut-off: 1 Jul 2021.

AE, adverse event; SMA, spinal muscular atrophy; SMN, survival of motor neuron.

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[‡]

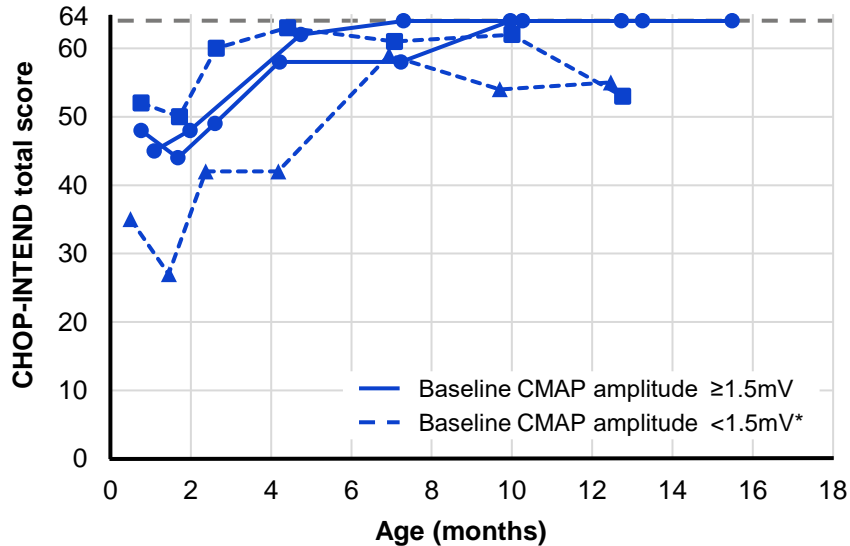
- All three infants had a baseline CMAP amplitude ≥ 1.5 mV

*These seven infants have received risdiplam for 12.2–22.8 months
Preliminary exploratory efficacy data are available for these seven infants[§]*

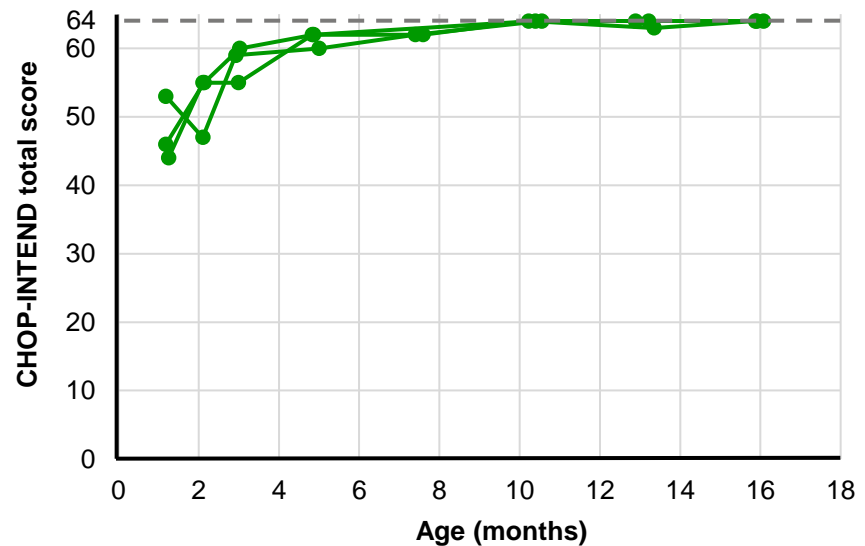
*Data cut-off: 1 Jul 2021. [†]The two infants with baseline CMAP < 1.5 mV had baseline values of 0.6 mV and 0.46 mV. [‡]Two infants have three *SMN2* copies and one infant has 'atypical' (when a patient's *SMN2* copy number result falls in between two values) three to four *SMN2* copies. [§]The primary 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. CMAP, compound muscle action potential; mV, millivolt; SMN, survival of motor neuron.

Most infants treated with risdiplam for ≥ 12 months ($n=7$) achieved the maximum CHOP-INTEND score

**2 SMN2 copies
(n=4 infants)**

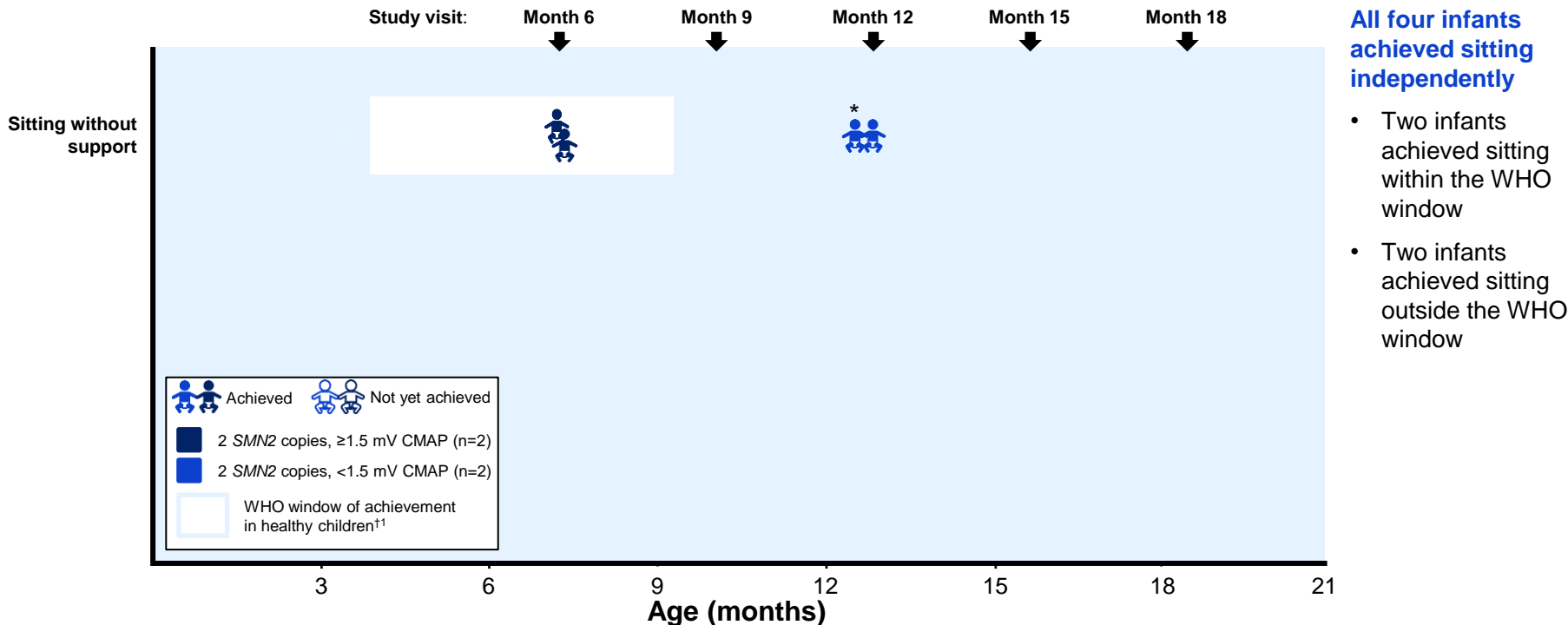


**>2 SMN2 copies
(n=3 infants)**



*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.
 CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound muscle action potential;
 mV, millivolt; SMN, survival of motor neuron.

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



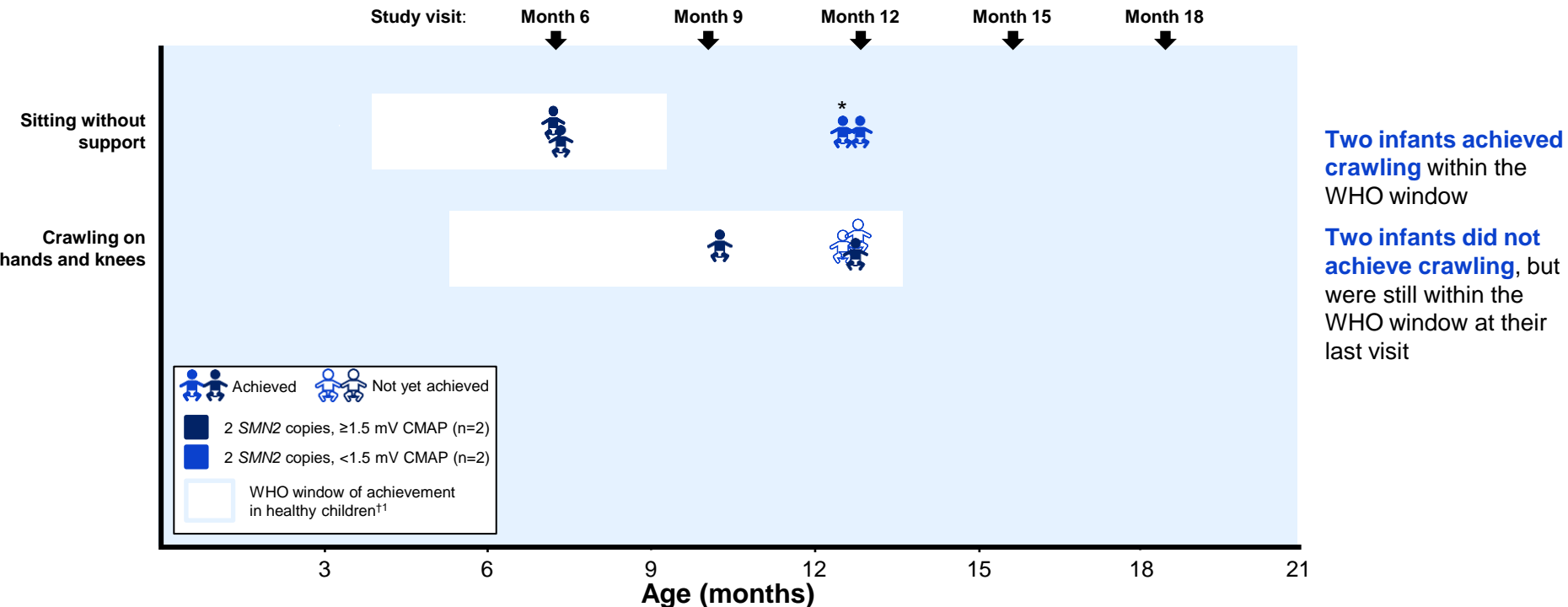
All four infants achieved sitting independently

- Two infants achieved sitting within the WHO window
- Two infants achieved sitting outside the WHO window

*One infant achieved 'stable sit'. All other infants 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. 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 a continuum. Data cut-off: 1 Jul 2021. CMAP, compound muscle action potential; HINE-2, Hammersmith Infant Neurological Examination, Section 2; mV, millivolt; SMN, survival of motor neuron; WHO, World Health Organization.

1. WHO Multicentre Growth Reference Study Group. Acta Paediatr Suppl. 2006; 450:86–95.

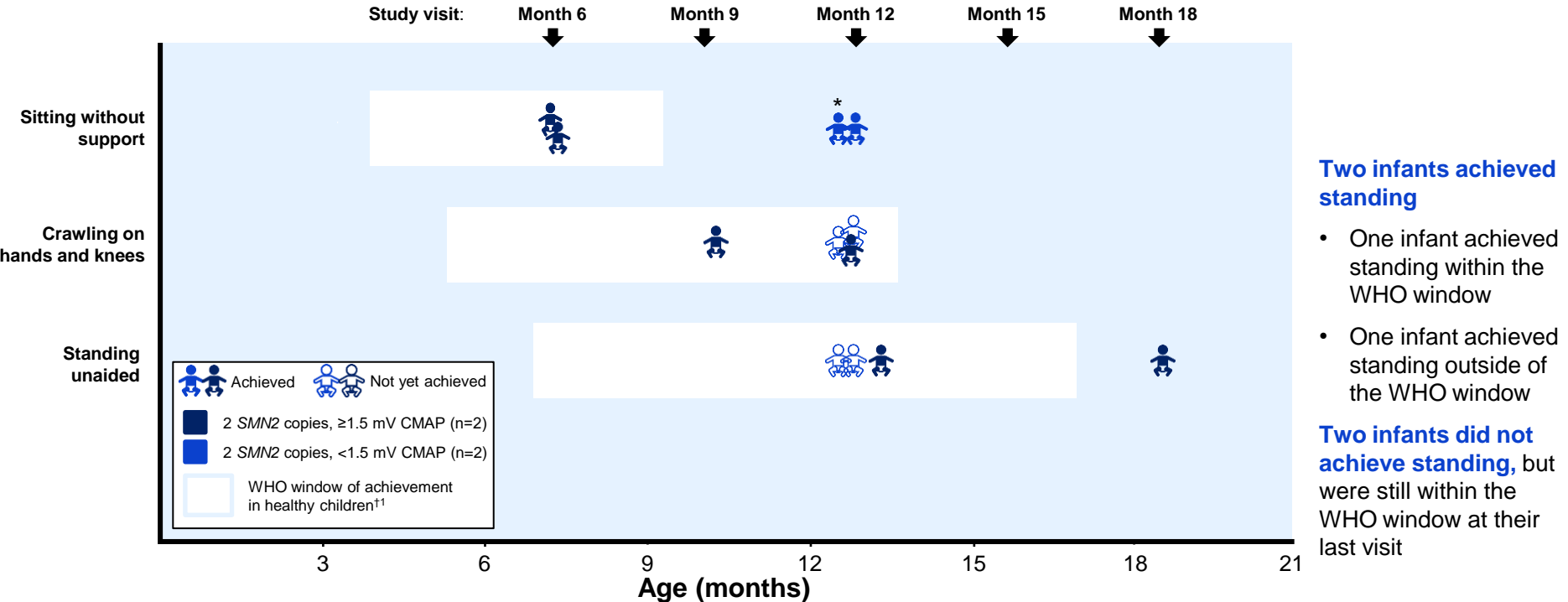
Most of the infants with two *SMN2* copies treated for ≥ 12 months achieved motor milestones within the WHO windows for healthy children



*One infant achieved 'stable sit'. All other infants 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. 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 a continuum. Data cut-off: 1 Jul 2021. CMAP, compound muscle action potential; HINE-2, Hammersmith Infant Neurological Examination, Section 2; mV, millivolt; SMN, survival of motor neuron; WHO, World Health Organization.

1. WHO Multicentre Growth Reference Study Group. Acta Paediatr Suppl. 2006; 450:86-95.

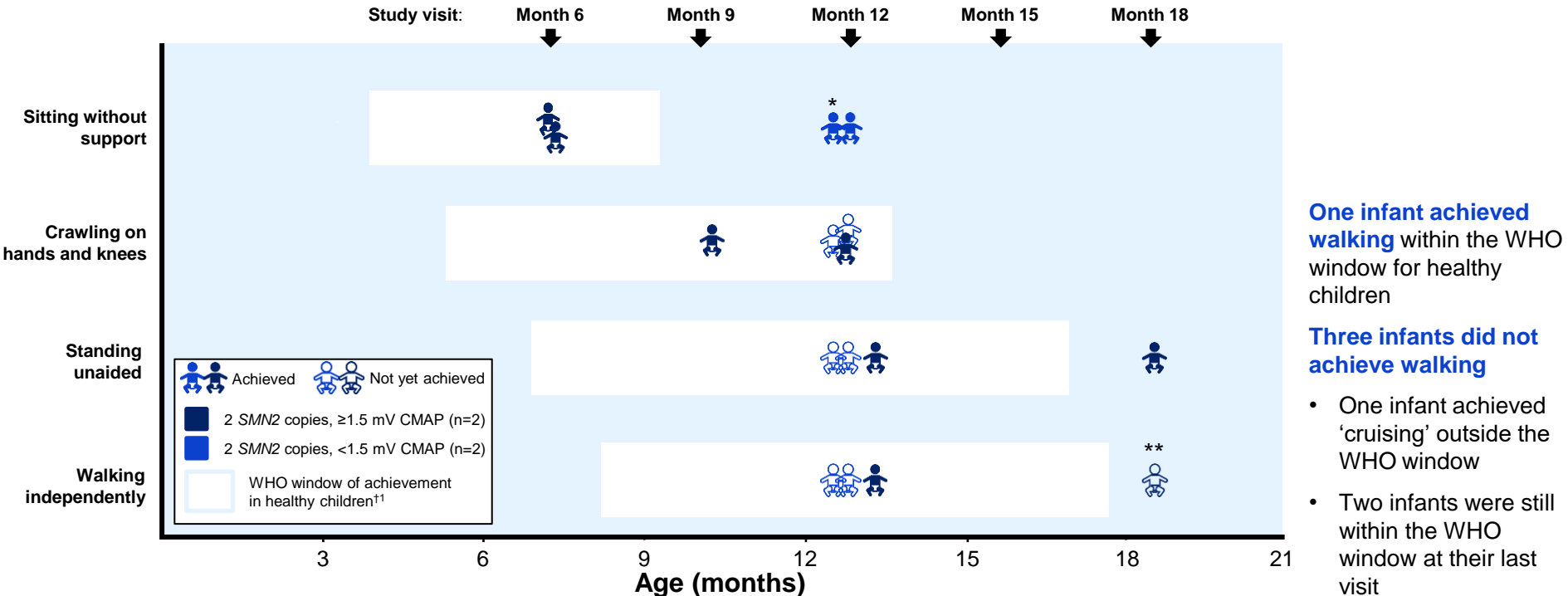
Most of the infants with two *SMN2* copies treated for ≥ 12 months achieved motor milestones within the WHO windows for healthy children



*One infant achieved 'stable sit'. All other infants achieved 'pivots', the most difficult sitting motor milestone according to the HINE-2. ¹White 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. 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 a continuum. Data cut-off: 1 Jul 2021. CMAP, compound muscle action potential; HINE-2, Hammersmith Infant Neurological Examination, Section 2; mV, millivolt; SMN, survival of motor neuron; WHO, World Health Organization.

1. WHO Multicentre Growth Reference Study Group. Acta Paediatr Suppl. 2006; 450:86–95.

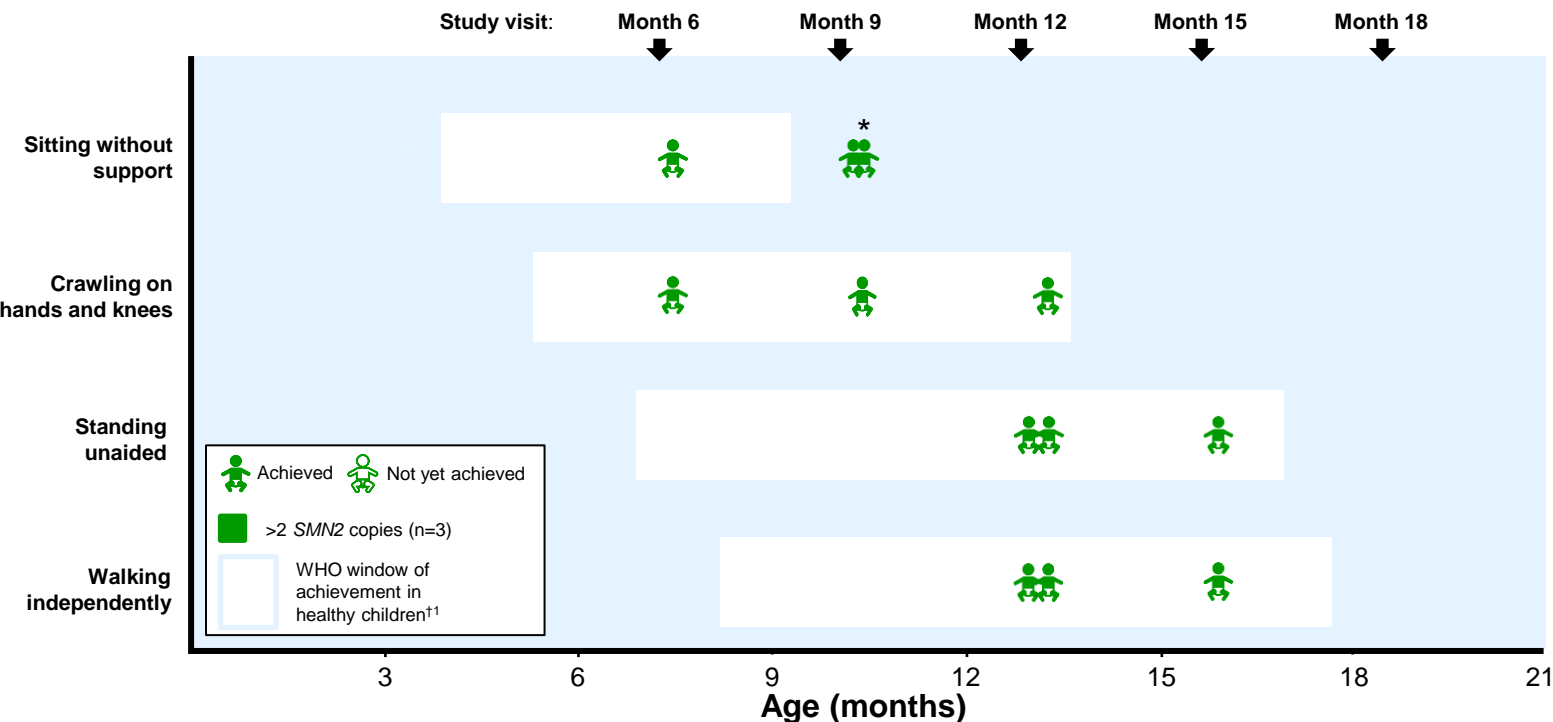
Most of the infants with two *SMN2* copies treated for ≥ 12 months achieved motor milestones within the WHO windows for healthy children



*One infant achieved 'stable sit'. All other infants achieved 'pivots', the most difficult sitting motor milestone according to the HINE-2. ¹White 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. 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 a continuum. Data cut-off: 1 Jul 2021. CMAP, compound muscle action potential; HINE-2, Hammersmith Infant Neurological Examination, Section 2; mV, millivolt; SMN, survival of motor neuron; WHO, World Health Organization.

1. WHO Multicentre Growth Reference Study Group. Acta Paediatr Suppl. 2006; 450:86–95.

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



All infants achieved all milestones

- Two infants achieved sitting outside the WHO window for healthy children

*This infant missed the Month 6 visit due to COVID-19 restrictions. ¹White 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 a continuum. Data cut-off: 1 Jul 2021.

COVID-19, coronavirus 2019; SMN, survival of motor neuron; WHO, World Health Organization.

1. WHO Multicentre Growth Reference Study Group. Acta Paediatr Suppl. 2006; 450:86–95.



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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

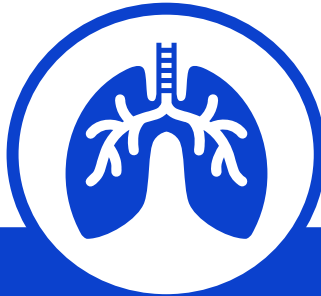
100% (7/7)
were able to swallow
solid food



Feeding

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

No infants who had received risdiplam for at least 12 months (n=7) required permanent ventilation or hospitalisation



No infants who were treated for ≥ 12 months required permanent ventilation



No infants who were treated for ≥ 12 months were hospitalised



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Conclusions



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



All seven infants treated for ≥ 12 months achieved sitting without support by Month 12



Most infants treated with risdiplam for ≥ 12 months reached near-maximum CHOP-INTEND scores by 4–5 months of age



All seven infants treated with risdiplam for ≥ 12 months maintained the ability to swallow and were able to feed exclusively by mouth



Based on RAINBOWFISH PK data, a risdiplam dose of 0.15 mg/kg has been approved by the FDA for infants < 2 months of age^{2,3}

None of the seven infants treated with risdiplam for at least 12 months required hospitalisation or permanent ventilation



No SAEs were reported in presymptomatic infants treated with risdiplam for up to 22.8 months



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

Data cut-off: 1 Jul 2021.

CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; FDA, US Food and Drug Administration; PK, pharmacokinetics; SAE, serious adverse event; WHO, World Health Organization.

1. WHO Multicentre Growth Reference Study Group. Acta Paediatr Suppl. 2006; 450:86–95; 2. F. Hoffmann-La Roche. May 2022 press release. <https://www.roche.com/media/releases/med-cor-2022-05-31> (Accessed October 2022); 3. EVRYSDI® (risdiplam) US prescribing information. https://www.gene.com/download/pdf/evrysdi_prescribing.pdf (Accessed October 2022).

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A patient treated with risdiplam when presymptomatic

