CureSMA Annual meeting 2021

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Basel, 14 June 2021

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Agenda

Welcome
Karl Mahler, Head of Investor Relations and Group Business Planning

JEWELFISH: Safety, pharmacodynamic and exploratory efficacy data in non-naïve patients with spinal muscular atrophy (SMA) receiving treatment with risdiplam

RAINBOWFISH: A study of risdiplam in infants with presymptomatic spinal muscular atrophy (SMA)
Kathryn Wagner, M.D. Ph.D., Vice President of Neuromuscular Disorders Clinical Development

Q&A
Karl Mahler, Head of Investor Relations and Group Business Planning

Welcome

Karl Mahler

Head of Investor Relations and Group Business Planning

2021: Key late-stage news flow*

	Compound	Indication	Milestone		Status
Phase III / pivotal readouts	**faricimab**	nAMD	Ph III TENAYA/LUCERNE	✓	Filing on track for H1 in nAMD and DME
	casirivimab/imdevimab	SARS-CoV-2 Outpatient	Ph III Study 2067	✓	EAU in US, filed in EU
	casirivimab/imdevimab	SARS-CoV-2 Post-exposure prophylaxis	Ph III Study 2069	✓	EAU in US, filed in EU
	Tecentriq	Adjuvant NSCLC	Ph III IMpower010	✓	FDA reviewing under RTOR
	Evrysdi	SMA type 1/2/3 previously treated	Ph II JEWELFISH	✓	Interim data presented at CureSMA
	mosunetuzumab	3L+ FL	Ph Ib GO29781		
	Polivy + R-CHP	1L DLBCL	Ph III POLARIX		
	glofitamab	3L+ DLBCL	Ph Ib NP30179		
	Tecentriq + chemo	Adjuvant SCCHN	Ph III IMvoke010		

Angiogenesis ✓
16 February

Diagnostics Day ✓
23 March

CureSMA ✓
14 June

Roche Pharma Day
14 September

ASH
December TBC

MDA ✓
19 March

ASCO ✓
8 June

ESG event
November TBC

Digital event
November TBC

* Outcome studies are event-driven: timelines may change, RTOR=real time oncology review, EAU=emergency use authorization

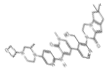
Roche: Broad pipeline leading the way to first/best in class medicines in neuroscience and rare diseases

NeuroImmunology

Multiple Sclerosis
Ocrevus

First B-cell targeted therapy

Multiple Sclerosis
Fenebrutinib



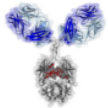
Highly selective and reversible (noncovalent) BTKi

NMOSD
Enspryng

First recycable IL6-mAb, SC q4w dosing

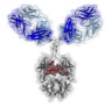
NeuroDegeneration

Alzheimer disease
gantenerumab



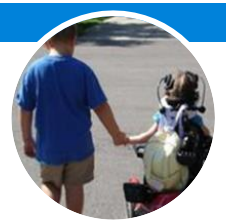
First anti-Aβ mAb with SC convenience

Parkinsons's disease
prasinezumab

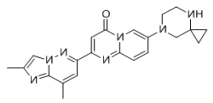


First mAB targeting pathogenic α-synuclein

NeuroMuscular



SMA
Evrysdi



First and only oral DMT in SMA T1/2/3

DMD
SRP-9001
(Sarepta)

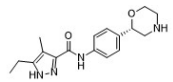
First micro-dystrophin gene therapy to express potentially functional protein

NeuroDevelopment & Psychiatry

Angelman syndrome
UBE3A LNA

First in class antisense oligonucleotide activating paternal gene to produce functional protein

Schizophrenia
ralmitaront

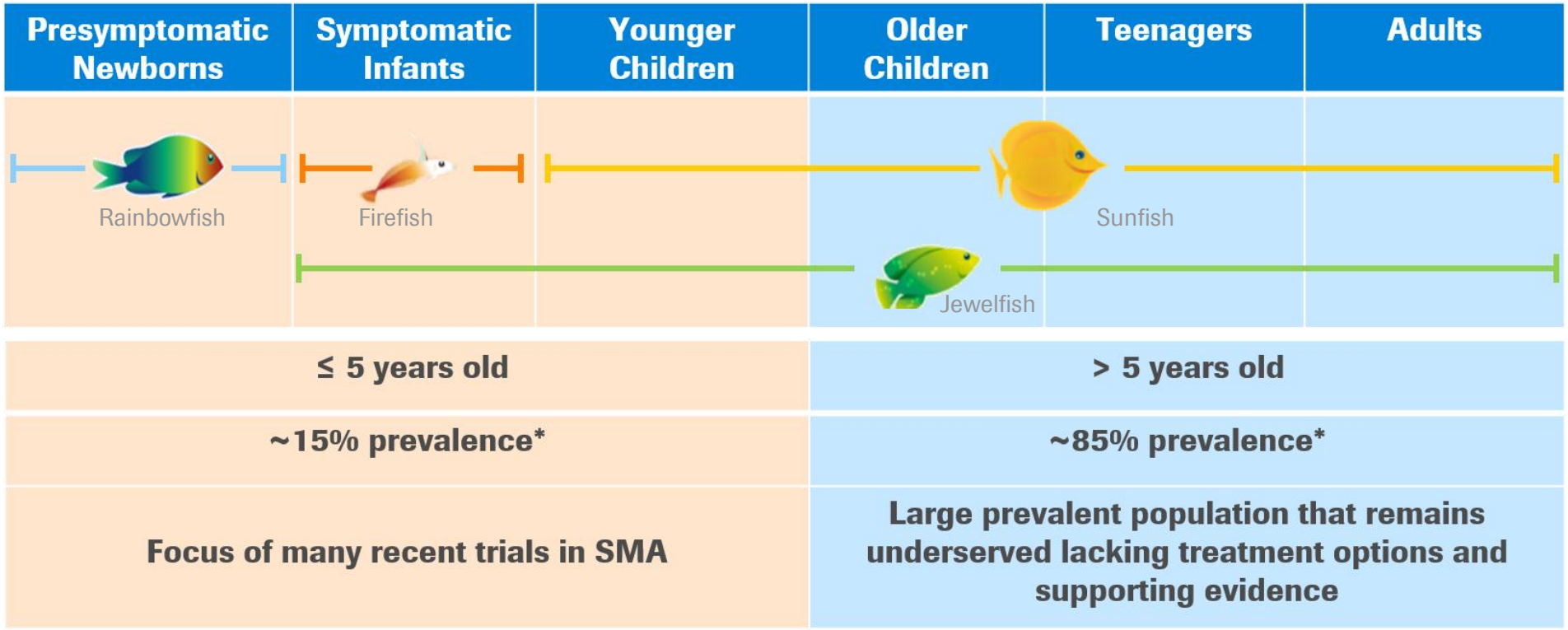


First state-dependent modulator of monoaminergic neurotransmission

Evrysdi: Meaningful evidence being generated across a broad program

Overview of the risdiplam development program

- Spanning types 1, 2, & 3 SMA; naïve and pre-treated
- Newborns to 60 years old; randomized, placebo-controlled data in 2 – 25 years old
- Including real-world spectrum of SMA – scoliosis, joint contractures, low baseline motor scale scores, etc.



* Estimated 2020 prevalence in US and EU5

JEWELFISH: Safety, pharmacodynamic and exploratory efficacy data in non-naïve patients with spinal muscular atrophy (SMA) receiving treatment with risdiplam

RAINBOWFISH: A study of risdiplam in infants with presymptomatic spinal muscular atrophy (SMA)

Kathryn Wagner, M.D. Ph.D.
Vice President of Neuromuscular Disorders Clinical Development

JEWELFISH: Safety, pharmacodynamic and exploratory efficacy data in non-naïve patients with spinal muscular atrophy (SMA) receiving treatment with risdiplam

Claudia A Chiriboga,[1*] Claudio Bruno,[2] Tina Duong,[3] Dirk Fischer,[4] Janbernd Kirschner,[5,6] Eugenio Mercuri,[7] Marianne Gerber,[8] Ksenija Gorni,[9] Heidemarie Kletzl,[10] Imogen Carruthers,[11] Carmen Martin,[11] Francis Warren,[11] Mariacristina Scoto,[12] on behalf of the JEWELFISH Study Group

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*Congress presenter

Introduction

- Risdiplam is a centrally and peripherally distributed oral *SMN2* pre-mRNA splicing modifier that increases the levels of functional SMN protein[1,2]
- Studies are limited for patients with SMA who are more advanced in age, have more severe disease, and who have been previously exposed to other DMTs
- JEWELFISH (NCT03032172)[3] is an ongoing, multicenter, open-label study evaluating risdiplam in the broadest population ever studied in an SMA trial, including patients with Types 1–3 SMA with a wide range of ages (1–60 years), and disease severities and who have previously received other DMTs
  - Patients had been previously treated with RG7800,[4] nusinersen (SPINRAZA®), olesoxime or onasemnogene abeparvovec (ZOLGENSMA®)
- Here we present the 12-month interim analysis on the safety, PD and exploratory efficacy data for the JEWELFISH population

Risdiplam (EVRYSDI™) has been approved for the treatment of patients with SMA, aged 2 months and older by the FDA[5] and EMA[6*]

*Risdiplam is approved by the EC for patients with SMA, aged 2 months and older with a clinical diagnosis of Type 1, Type 2 or Type 3 SMA or with one to four *SMN2* copies.
EMA; European Medicine Agency; DMT, disease-modifying therapy; FDA, US Food and Drug Administration; PD, pharmacodynamics; SMN, survival of motor neuron.
1. Poirier A, et al. Pharmacol Res Perspect. 2018; 6:e00447; 2. Ratni H, et al. J Med Chem. 2018; 61:6501–6517; 3. ClinicalTrials.gov. NCT03032172 (Accessed May 2021); 4. ClinicalTrials.gov. NCT02240355 (Accessed May 2021); 5. EVRYSDI™ prescribing information: https://www.gene.com/download/pdf/evrysdi_prescribing.pdf (Accessed May 2021). 6. EVRYSDI™ summary of product characteristics: https://www.ema.europa.eu/en/documents/product-information/evrysdi-epar-product-information_en.pdf. (Accessed May 2021).

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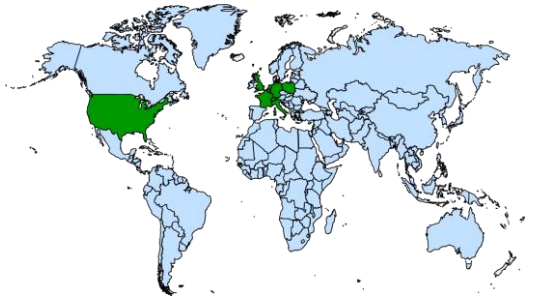
Study design

A multicenter, open-label study of once-daily oral administration of risdiplam in non-treatment-naïve patients with SMA[1]



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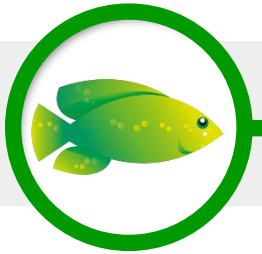

12-month interim analysis

24 months Primary analysis

Risdiplam → OLE

n=174

Inclusion criteria

Confirmed genetic diagnosis of 5q SMA

Aged 6 months–60 years

Non-treatment-naïve patients with SMA*
Previously treated with RG7800,[2] nusinersen, olesoxime, or onasemnogene abeparvovec

Primary endpoint:

- Safety
- PK

Key secondary endpoint:

- PK/PD relationship (*SMN2* mRNA splice forms and SMN protein)

Key exploratory endpoint:

- MFM32

*Nusinersen (defined as having received ≥4 doses of nusinersen, provided that the last dose was received ≥90 days prior to screening), olesoxime (provided that the last dose was received ≤18 months and ≥90 days prior to screening) and onasemnogene abeparvovec (provided that the time of treatment was ≥12 months prior to screening).
AE, adverse event; MFM32, 32-item Motor Function Measure; OLE, open-label extension; PD, pharmacodynamics; PK, pharmacokinetics; SAE, serious AE; SMN, survival of motor neuron.1. ClinicalTrials.gov. NCT03032172 (Accessed May 2021); 2. ClinicalTrials.gov. NCT02240355 (Accessed May 2021).

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The JEWELFISH population is broad and heterogeneous with a high degree of motor impairment at baseline

		Previous treatment				
		RG7800 (MOONFISH) (n=13)	Nusinersen (n=76)*	Olesoxime (n=71)	Onasemnogene abeparvovec (n=14)†	All patients (N=174)
Age at enrollment, years, median (range)		30.0 (16–58)	12.0 (1–60)	16.0 (11–36)	2.0 (1–5)	14.0 (1–60)
≥18 years, n (%)		11 (85)	21 (28)	31 (44)	0	63 (36)
Gender, n (%)	Male	9 (69)	40 (53)	35 (49)	11 (79)	95 (55)
SMA type, n (%)	1	0	9 (12)	2 (3)	4 (29)	15 (9)
	2	5 (39)	43 (57)	50 (70)	10 (71)	108 (62)
	3	8 (62)	24 (32)	19 (27)	0	51 (29)
SMN2 copy number, n (%)	1	0	0	0	1 (7)	1 (1)
	2	0	9 (12)	0	3 (21)	12 (7)
	3	6 (46)	56 (74)	64 (90)	10 (71)	136 (78)
	4	6 (46)	11 (15)	5 (7)	0	22 (13)
	Unknown‡	1 (8)	0	2 (3)	0	3 (2)
Motor function at baseline, n (%)§	Non-sitters	7 (54)	21 (28)‖	29 (41)	2 (14)‖	59 (34)‖
	Sitters	3 (23)	42 (55)‖	42 (59)	12 (86)‖	99 (57)‖
	Walkers	3 (23)	13 (17)	0	0	16 (9)
Baseline HFMSE total score <10, n (%)	Yes	8 (62)	35 (48)¶**	59 (83)	3 (27)¶††	105 (63)¶‡‡
Scoliosis, n (%)	Yes	9 (69)	61 (84)¶ **	66 (93)	3 (27)¶††	139 (83)¶‡‡
	>40 degrees curvature	3 (23)	27 (37)¶**	36 (51)	0	66 (39)¶‡‡
Hip subluxation or dislocation, n (%)	Yes	2 (15)	25 (34)¶**	20 (28)	4 (36)¶††	51 (30)¶‡‡

*Three patients in the nusinersen group had also received olesoxime previously. †One patient in the onasemnogene abeparvovec group received treatment with onasemnogene abeparvovec first followed by nusinersen. Ten patients were enrolled in STRONG, three patients in STR1VE and one patient in STR1VE-EU prior to enrollment in JEWELFISH. ‡Unknown *SMN2* copy number is pending confirmation by genotyping. §Non-sitters are defined as scoring 0 on Item 9 of the MFM while sitters scored ≥1 on Item 9 of the MFM but did not qualify as ambulant. Ambulant patients are defined as walkers. ‖For patients <2 years, baseline motor milestones were evaluated by the Hammersmith Infant Neurological Examination, Module 2. ¶Only reported for patients aged 2–60 years. **n=73. ††n=11. ‡‡n=168. Data cut-off: 29 Jan 2021. Intent-to-treat patients.
HFMSE, Hammersmith Functional Motor Score – Expanded; MFM, Motor Function Measure; SMN, survival of motor neuron.

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Patient- and caregiver-reported reasons why patients began treatment with risdiplam following previous treatments*

Primary reasons to enroll in JEWELFISH	Patients previously treated with nusinersen[†] (n=77) n (%)
Treatment-related tolerability concerns[‡]	24 (31)
Treatment response: Lack of efficacy	14 (18)
Treatment response: Loss of efficacy	8 (10)
Caregiver preference	7 (9)[§]
Patient preference	6 (8)
Other[‖]	18 (23)

Primary reasons to enroll in JEWELFISH	Patients previously treated with onasemnogene abeparvovec[¶] (n=14) n (%)
Hopes of additional benefit	8 (57)
Caregiver preference	4 (29)
Treatment response: lack of efficacy	2 (14)

- RG7800 and olesoxime are no longer in development as investigational treatments for patients with SMA

*Reasons were self-reported for patients aged ≥5 years and caregiver reported for patients aged <5 years. [†]Three patients in the nusinersen group had also received olesoxime previously. [‡]Tolerability generally refers to challenges associated with intrathecal administration in patients with scoliosis or those who have undergone spinal surgery and the inability to receive a lumbar puncture. [§]One patient was treated with onasemnogene abeparvovec and nusinersen. [‖]Other reasons include treatment-related safety concerns, treatment reimbursement/insurance policy challenge, access infrastructure challenges (e.g. accessibility to sites), injection procedures, inconvenience of treatment, or missing. [¶]One patient in the onasemnogene abeparvovec group received treatment with onasemnogene abeparvovec first followed by nusinersen. Data cut-off: 29 Jan 2021.

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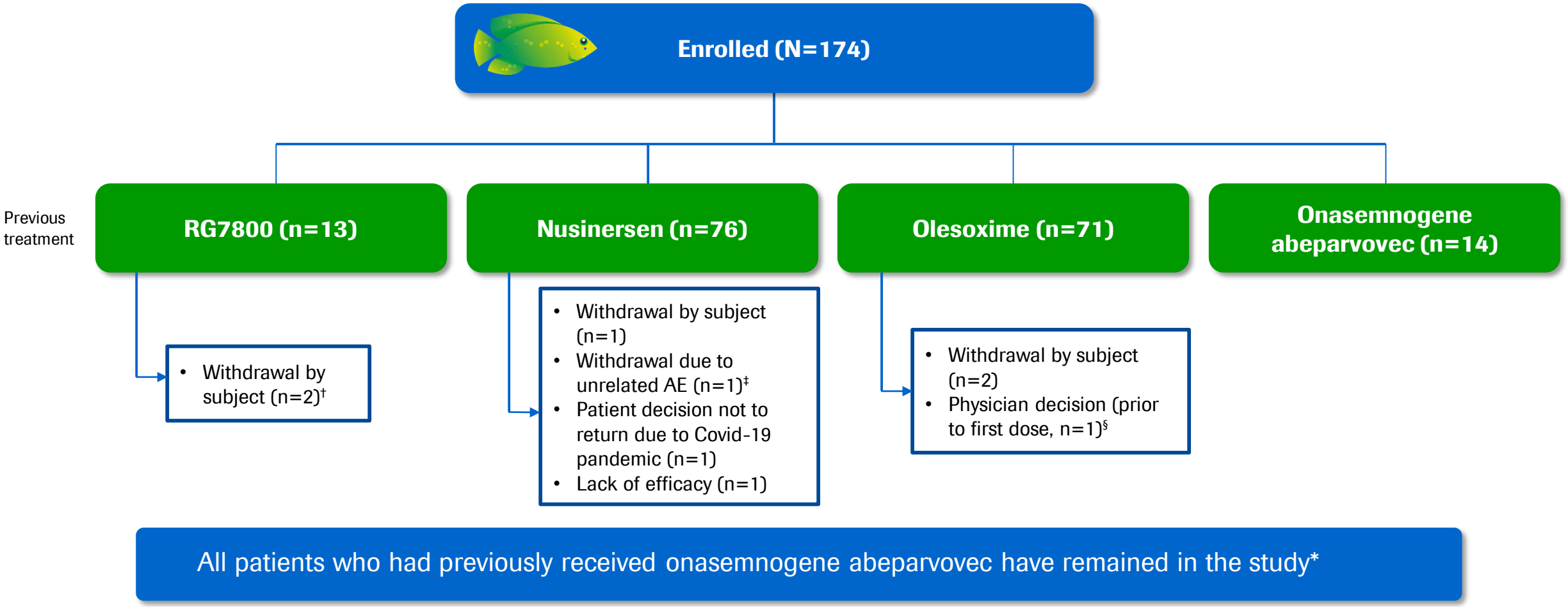
Low rates of discontinuation (5% [9/174]) were observed in the JEWELFISH study*



*Data cut-off: 29 Jan 2021. †One patient withdrew consent. ‡Irritable bowel syndrome and panic attack which were unrelated to risdiplam. §Patient presented poor venous access. AE, adverse event.

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No treatment-related safety findings have led to withdrawal in any JEWELFISH patients

		Previous treatment				
		RG7800 (MOONFISH) (n=13)	Nusinersen (n=76)	Olesoxime (n=70)	Onasemnogene abeparvovec (n=14)	All patients (N=173)*
Patients with at least one AE, n (%)		12 (92)	71 (93)	63 (90)	13 (93)	159 (92)
Total number of AEs		66	450	357	50	923
Total number of deaths		0	0	0	0	0
Total number of patients with at least one, n (%)	SAE	3 (23)	11 (15)	8 (11)	2 (14)	24 (14)
	Treatment-related SAE	0	0	1 (1)†	0	1 (1)†
	SAE leading to dose-modification/interruption	1 (8)	3 (4)	2 (3)	0	6 (4)
	AE leading to withdrawal from treatment	0	1 (1)‡	0	0	1 (1)‡
	Treatment-related AE	6 (46)	19 (25)	8 (11)	0	33 (19)
	Related AE leading to withdrawal from treatment	0	0	0	0	0

*One patient withdrew from the study at baseline, therefore 173 patients received risdiplam. Includes AEs with onset from first dose of study drug up to the clinical cut-off date. Data cut-off: 29 Jan 2021. As follow-up duration is different between groups, the overall rate of AEs and SAEs cannot be compared. Risdiplam treatment duration for all patients in months, median (range): 15.2 (0.9–47.0). †An SAE of supraventricular tachycardia was considered related to risdiplam treatment by the investigator (in the context of hypoxia) and resolved with ongoing treatment with risdiplam. ‡Irritable bowel syndrome and panic attack, which were unrelated to risdiplam, led to the withdrawal of one patient who was previously treated with nusinersen. 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 AE are counted separately. AE, adverse event; SAE, serious AE.

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AEs and SAEs were reflective of underlying disease

		Previous treatment				
		RG7800 (MOONFISH) (n=13)	Nusinersen (n=76)	Olesoxime (n=70)	Onasemnogene abeparvovec (n=14)	All patients (N=173)*
Most common AEs† n (number of patients [%])	URTI	0	14 (18)	14 (20)	2 (14)	30 (17)
	Pyrexia	1 (8)	17 (22)	8 (11)	4 (29)	30 (17)
	Headache	1 (8)	15 (20)	12 (17)	0	28 (16)
	Nausea	0	14 (18)	5 (7)	1 (7)	20 (12)
	Diarrhea	0	14 (18)	4 (6)	1 (7)	19 (11)
	Nasopharyngitis	2 (15)	7 (9)	6 (9)	2 (14)	17 (10)
	Vomiting	1 (8)	5 (7)	6 (9)	2 (14)	14 (8)
Most common SAEs‡ n (number of patients [%])	Pneumonia	0	2 (3)	1 (1)	1 (7)	4 (2)
	LRTI	0	1 (1)	2 (3)	0	3 (2)
	URTI	0	3 (4)	0	0	3 (2)
	Respiratory failure	0	3 (4)	0	0	3 (2)

AEs observed in patients who have been treated with onasemnogene abeparvovec after 12 months of treatment with risdiplam were similar to those in the overall population

*One patient withdrew from the study at baseline, therefore 173 patients received risdiplam. Includes AEs with onset from first dose of study drug up to the clinical cut-off date. Data cut-off: 29 Jan 2021. As follow-up duration is different between groups, the overall rate of AEs and SAEs cannot be compared. Risdiplam treatment duration in months, median (range): 15.2 (0.9–47.0). †AEs reported in ≥8% of all patients. ‡SAEs reported in >2% of all patients. There were 14 skin adverse events that were reported as related to risdiplam in 8 patients at the clinical cut-off date (29 Jan 2021). Multiple occurrences of the same AE in one individual are counted only once. AE, adverse event; CCOD, clinical cut-off date; LRTI, lower respiratory tract infection; SAE, serious AE; URTI, upper respiratory tract infection.

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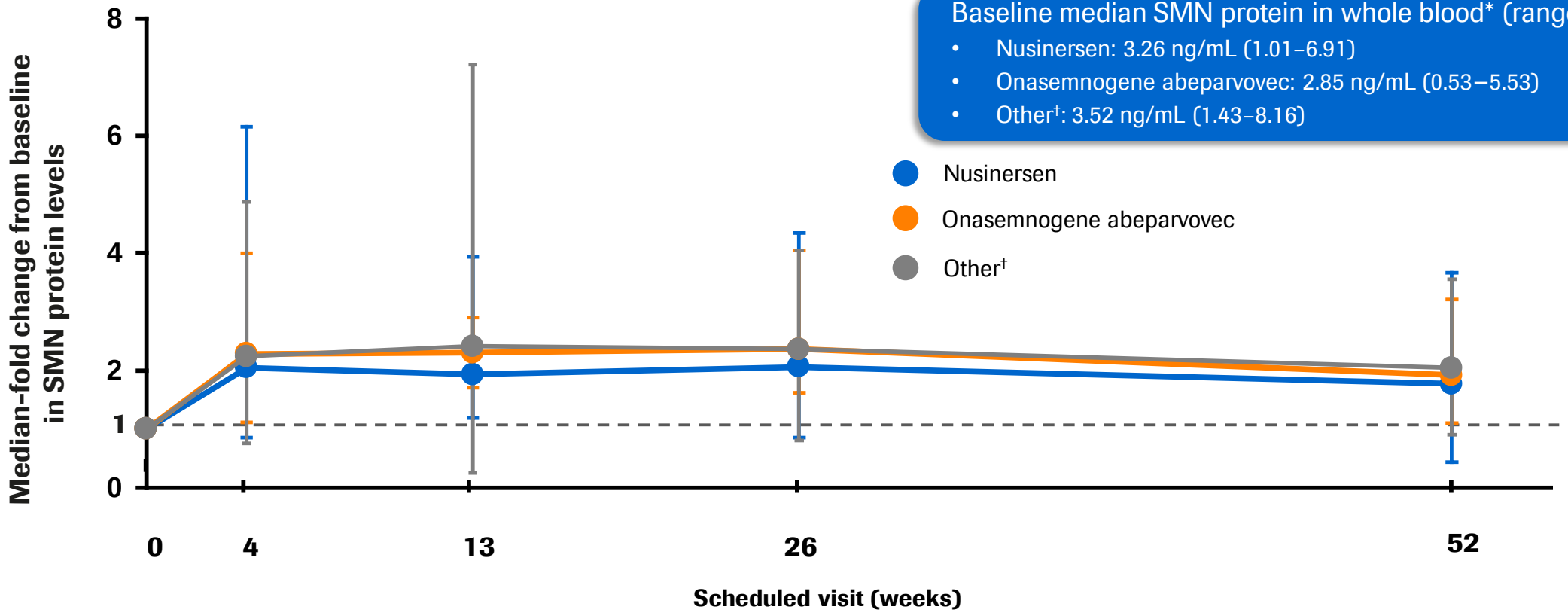
Risdiplam treatment led to rapid and sustained increases in SMN protein levels in patients previously treated with nusinersen or onasemnogene abeparvovec

Baseline median SMN protein in whole blood* (range):
- Nusinersen: 3.26 ng/mL (1.01–6.91)
- Onasemnogene abeparvovec: 2.85 ng/mL (0.53–5.53)
- Other†: 3.52 ng/mL (1.43–8.16)



Patients (n)						
Nusinersen	67	57	53	43		51
Onasemnogene abeparvovec	13	13	6	5		9
Other†	64	60	45	38		48

*Blood mixed with lysis buffer 1:1. †Patients previously treated with RG7800 (MOONFISH) and olesoxime. Error bars represent range (minimum–maximum values).
Data cut-off: 29 Jan 2021.SMN, survival of motor neuron.

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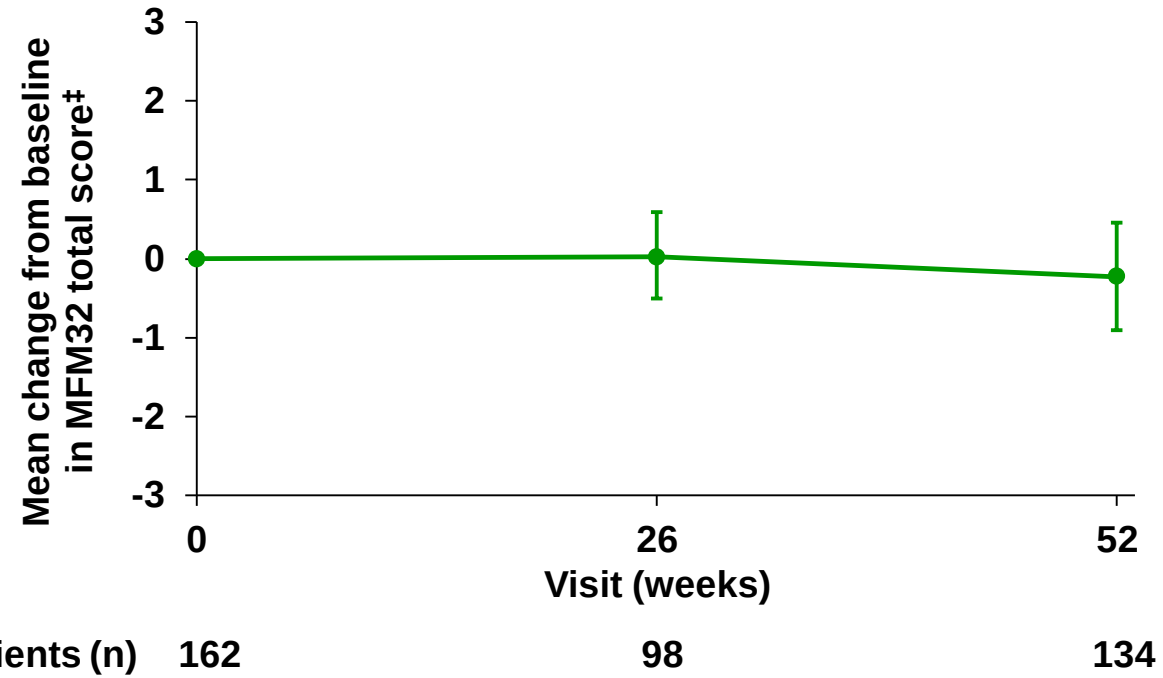
Interim exploratory efficacy data demonstrated overall stabilization in motor function at Month 12 in patients who began treatment with risdiplam following previous treatments

JEWELFISH
MFM32 in patients aged 2–60 years*



The JEWELFISH population is broad and heterogeneous, with a high degree of motor impairment at baseline

In a recent survey of patients† with SMA in Europe >96%, considered stabilization of SMA important progress[1]

*Motor function in patients aged <2 years was measured using the BSID-III. †n=1474. Patient numbers at clinic visits were lower in 2020 than previous years. BSID-III, Bayley Scales of Infant and Toddler Development, third edition; CI, confidence interval; MFM32, 32-item Motor Function Measure.

1. Gusset N et al. Neuromuscul Disord. 2021; 31:419–430.

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Conclusions

The JEWELFISH population is broad and heterogeneous, with a high degree of motor impairment at baseline, reflecting the real-world SMA population

AEs and SAEs were reflective of underlying disease

Risdiplam treatment has shown a sustained, >2-fold increase in median SMN protein levels versus baseline, irrespective of previous treatment

Low rates of discontinuation (5% [9/174]) were observed in the JEWELFISH study

Interim exploratory efficacy data showed that overall stabilization in motor function was observed in patients who began treatment with risdiplam following previous treatments

The JEWELFISH study is still ongoing. Primary analysis will be conducted at Month 24

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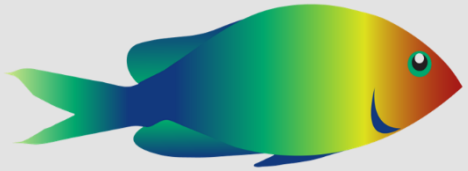
AE, adverse event; SAE; serious AE; SMN, survival of motor neuron.



RAINBOWFISH: A study of risdiplam in infants with presymptomatic spinal muscular atrophy (SMA)

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*Presenter

Introduction

- 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 efficacy of treatment[2]
  - A shorter disease duration results in better treatment outcomes
  - The timing of treatment initiation is therefore crucial
- Risdiplam is a centrally and peripherally distributed oral *SMN2* pre-mRNA splicing modifier that increases the levels of functional SMN protein[3,4]
  - Risdiplam (EVRYSDI™) has been approved for the treatment of patients with SMA, aged 2 months and older by the FDA[5] and the EMA[6*]
- Here we present data from the RAINBOWFISH study (NCT03779334),[7] which assesses efficacy and safety of risdiplam in infants with genetically diagnosed presymptomatic SMA

*Risdiplam is approved by the EMA for patients with SMA, aged 2 months and older with a clinical diagnosis of Type 1, Type 2 or Type 3 SMA or with one to four *SMN2* copies.
EMA, European Medicines Agency; FDA, US Food and Drug Administration; 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 (in press) DOI: https://doi.org/10.1002/cpt.2247; 3. Ratni H, et al. J Med Chem. 2018; 61:6501–6517; 4. Poirier A, et al. Pharmacol Res Perspect. 2018; 6:e00447; 5. EVRYSDI™ FDA prescribing information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213535s000lbl.pdf (Accessed May 2021); 6. EVRYSDI™ EMA product information: https://www.ema.europa.eu/en/documents/product-information/evrysdi-epar-product-information_en.pdf (Accessed May 2021);
7. ClinicalTrials.gov. NCT03779334 (Accessed May 2021).

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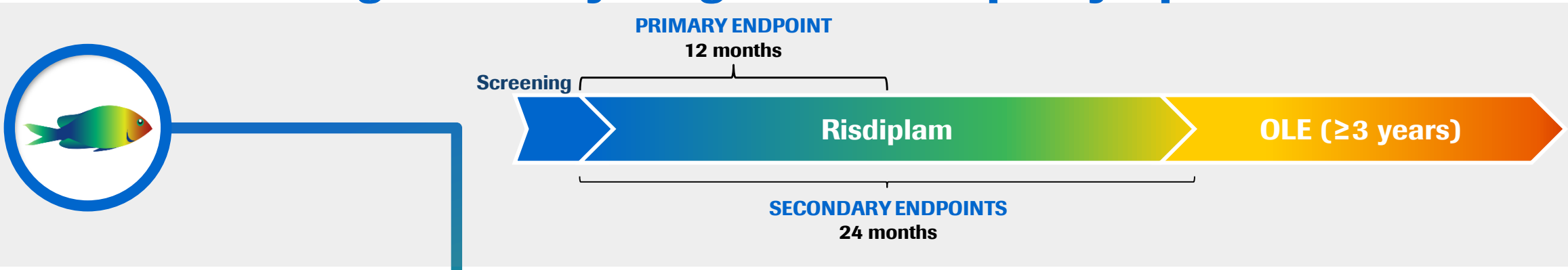
A multicenter, open-label, single-arm study of risdiplam in infants with genetically diagnosed and presymptomatic SMA



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~25†):

- development of clinically manifested SMA
- survival and permanent ventilation
- achievement of motor milestones as defined by the HINE-2 and BSID-III
- 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. †Target enrollment. Recruitment will close when either at least 25 patients, including a minimum of 5 patients who meet the criteria for the primary efficacy analysis are enrolled, OR when a total of 10 patients who meet the criteria for the primary efficacy analysis are enrolled.
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; SMN, survival of motor neuron.
ClinicalTrials.gov. NCT03779334 (Accessed May 2021).

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Baseline characteristics for 12 infants currently enrolled in RAINBOWFISH

Target enrollment ~25 infants
(recruitment will close when either at least 25 patients, including a minimum of 5 patients with two *SMN2* copies and a baseline CMAP amplitude of ≥1.5 mV are enrolled, OR when a total of 10 patients with two *SMN2* copies and a baseline CMAP amplitude of ≥1.5 mV are enrolled)

	Risdiplam (n=12)
Age at first dose, days, median (range)	28.5 (16–40)
SMN2 copy number, n (%)	
2	5 (42)
>2	7 (58)*
Gender, n (%)	
Female	8 (67)
Male	4 (33)
SMA identification method, n (%)	
Family history	4 (33)
Newborn screening	8 (67)

- Enrolled infants have been treated with risdiplam for a median of 7.4 months (range: 1.1–18.1 months)
  - Five infants have been treated for ≥12 months (preliminary efficacy data are available for these infants)
    - Includes two infants with two *SMN2* copies and three infants with >2 *SMN2* copies
  - Three infants have been treated for ≥6 to <12 months
  - Four infants have been treated for <6 months

*Includes five 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 one infant with ≥4 *SMN2* copies.
Data cut-off: 20 Feb 2021.
CMAP, compound muscle action potential; mV, millivolt; SMN, survival of motor neuron.

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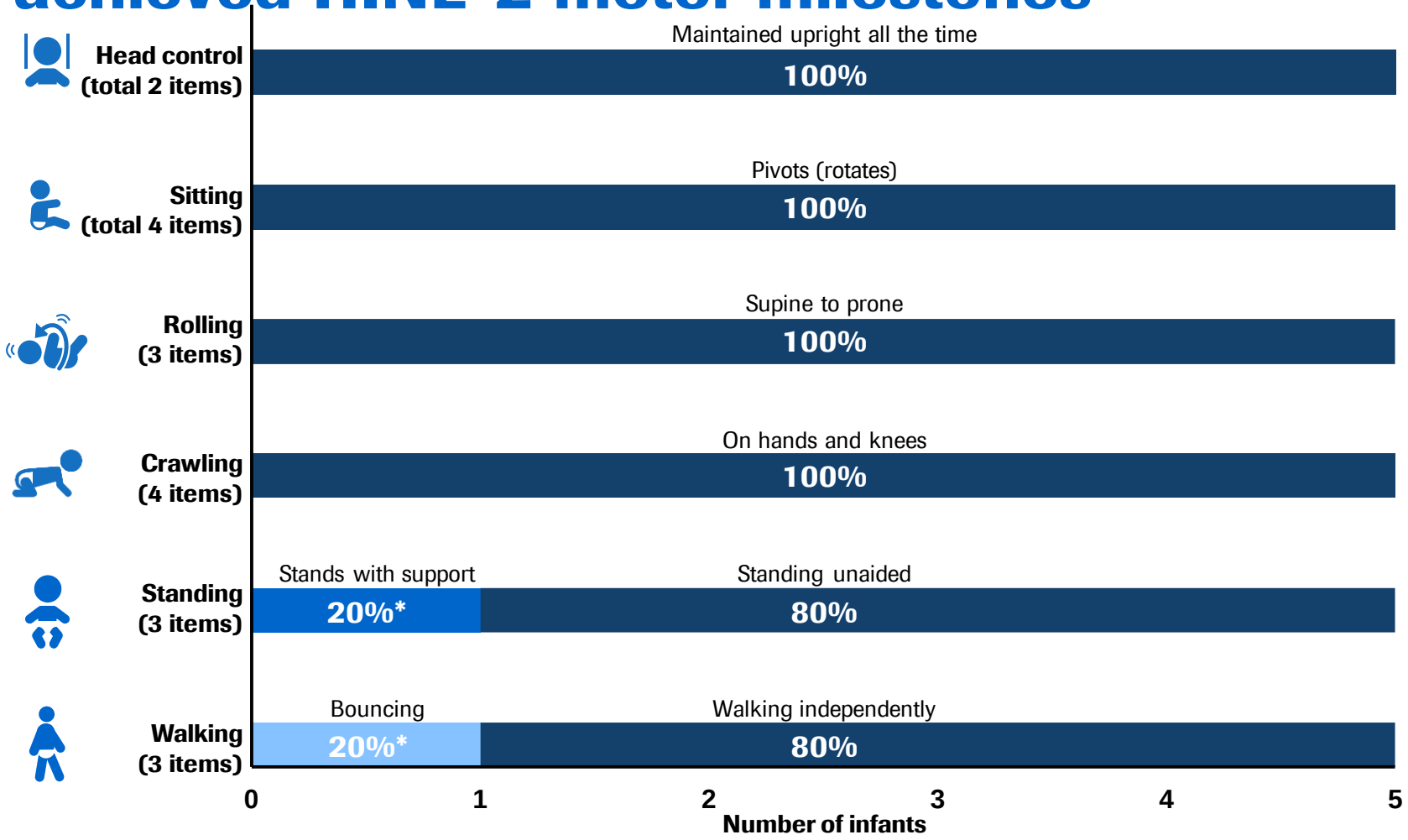
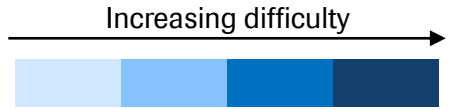
Infants treated with risdiplam for at least 12 months (n=5) achieved HINE-2 motor milestones





At the data cut-off:†

- 80% of infants (4/5) scored the maximum HINE-2 total score of 26
  - This included one infant with two *SMN2* copies
  - One infant with two *SMN2* copies had a HINE-2 total score of 23

Most of the infants treated for at least 12 months achieved motor milestones within the WHO windows for healthy children[1]

*This one infant was aged 15.47 months at their last visit before the data cut-off. The infant is still within the WHOMGRS 1st–99th percentile window to achieve the 'standing unaided' and 'walking independently' motor milestones of the HINE-2 within the normal age range based on the World Health Organization Motor Development Study.[1]
†Data cut-off: 20 Feb 2021. Infants were included in this analysis after they reached 12 months of treatment. Results for only the most difficult milestone achieved by each infant within each HINE-2 category at the last available visit before the data cut are shown. All infants achieved all motor milestones within the voluntary grasp, and the ability to kick categories (not shown).
HINE-2, Hammersmith Infant Neurological Examination, Section 2; SMN, survival of motor neuron; WHO, World Health Organization; WHOMGRS, WHO Multicentre Growth Reference Study Group.
1. WHOMGRS. Acta Paediatr Suppl. 2006; 450:86–95.

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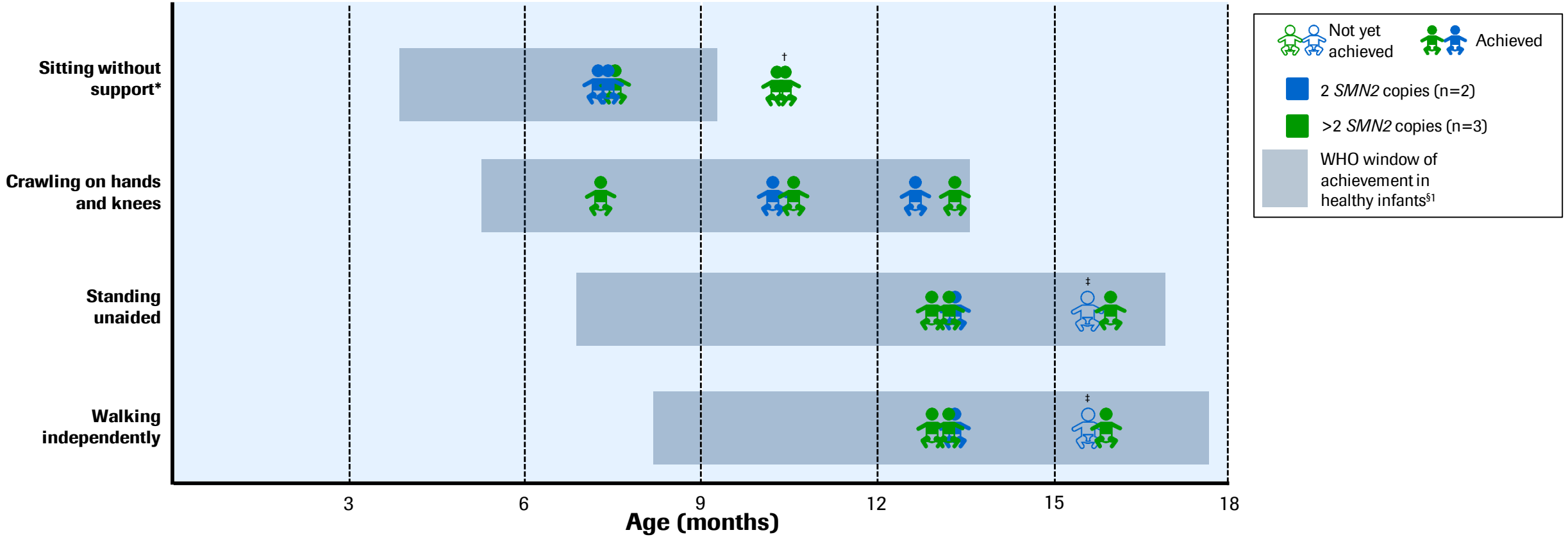
Most of the infants treated for at least 12 months achieved motor milestones within the WHO windows for healthy children



*All infants first acquired 'pivots', the most difficult sitting motor milestone according to the HINE-2 at the same visit as the 'sitting without support' milestone. †This infant missed the Day 196 visit due to Covid restrictions and so missed an opportunity to potentially achieve the sitting without support milestone within the window. ‡One infant was aged 15.47 months at the last patient visit prior to the data cut-off and did not achieve the motor milestones of 'walking alone' and 'standing unaided' at their last visit. §Shaded areas represent the 1st–99th percentile window for achievement of motor milestones based on the World Health Organization Motor Development Study.[1]

Infants were included in this analysis after they reached 12 months of treatment. All infants achieved all motor milestones in the head control, voluntary grasp, rolling and the ability to kick categories of the HINE-2 (not shown). The age that infants first achieved the most difficult milestone within each HINE-2 category up to the data cut-off are shown.

Data cut-off: 20 Feb 2021.

HINE-2, Hammersmith Infant Neurological Examination, Section 2; SMN, survival of motor neuron; WHO, World Health Organisation; WHOMGRS, WHO Multicentre Growth Reference Study Group.

1. WHOMGRS. Acta Paediatr Suppl. 2006; 450:86–95.

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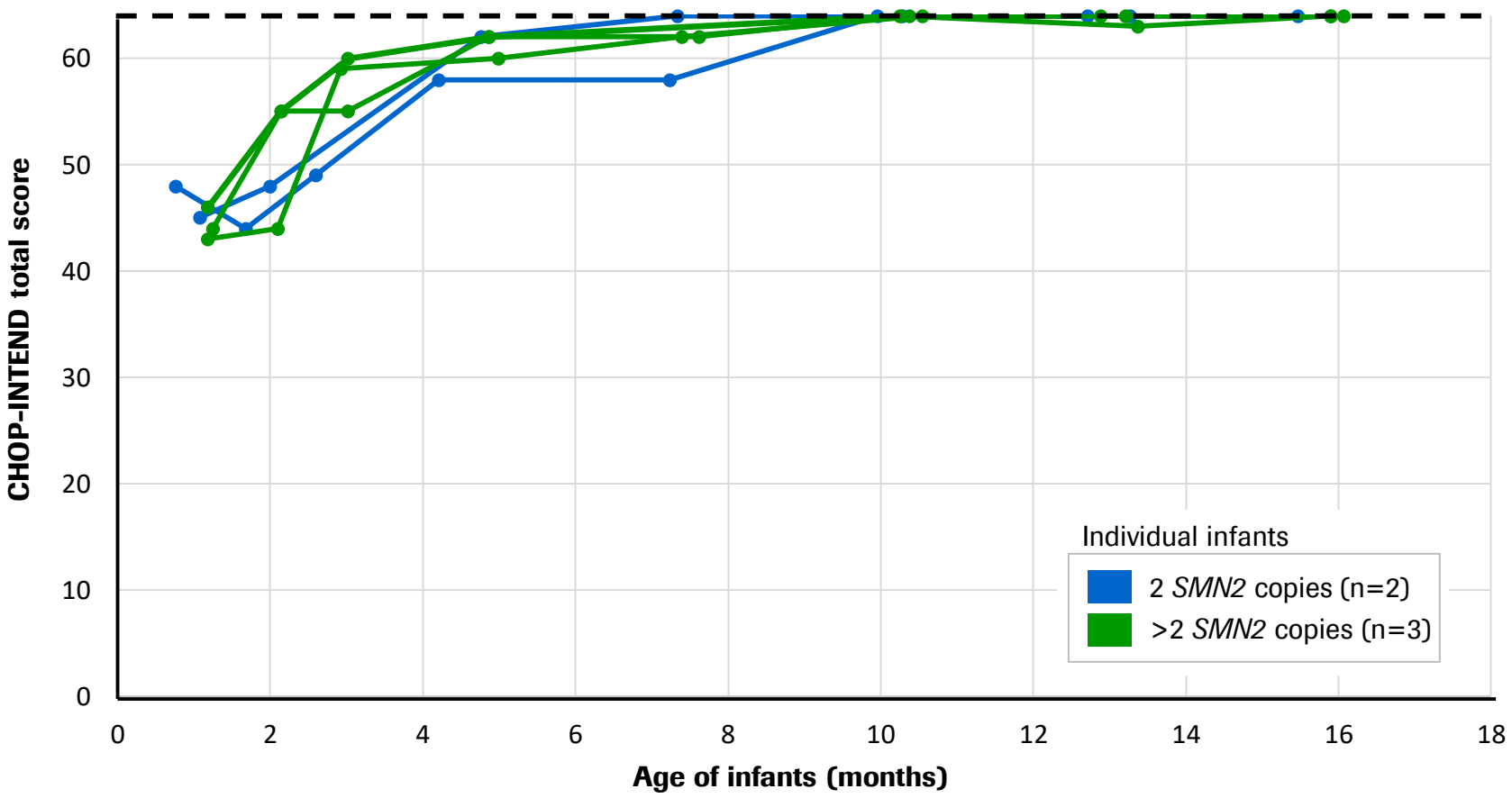
Infants treated with risdiplam for at least 12 months (n=5) reached near maximum CHOP-INTEND scores by 4–5 months of age



Maximum score = 64

At 4 months of treatment:

- 4/5 infants (80%) scored ≥60
- 1/5 infants (20%) scored 58

At 12 months of treatment:

- 5/5 infants (100%) scored ≥60
- 4/5 infants (80%) scored the maximum score of 64*
- 1/5 infants (20%) scored 63†

*Includes both infants that had two *SMN2* copies. †This infant scored 64 at the subsequent visit.
At the data-cut off, only five infants had received treatment with risdiplam for ≥12 months and were included in this analysis.
Data cut-off: 20 Feb 2021.
CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; SMN, survival of motor neuron.

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No treatment-related SAEs were reported in presymptomatic infants treated with risdiplam

		2 *SMN2* copies (n=5)	>2 *SMN2* copies (n=7)	Total risdiplam (n=12)
Infants with at least one AE, n (%)		4 (80)	6 (86)	10 (83)
Total number of AEs		15	31	46
Total number of deaths, n (%)		0	0	0
Number of infants with at least one, n (%)	SAE	0	1 (14)	1 (8)
	Treatment-related SAE	0	0	0
	Treatment-related AE	1 (20)	2 (29)	3 (25)
	AE leading to withdrawal from treatment	0	0	0
	AE leading to dose-modification/interruption	0	1 (14)	1 (8)
	Related AE leading to withdrawal from treatment	0	0	0
	Related AE leading to dose-modification/interruption	0	0	0

- One SAE of gastroenteritis norovirus was reported – this was considered unrelated to risdiplam
- Four related AEs were reported in three infants:
  - increased alanine aminotransferase and increased aspartate aminotransferase (both reported in one infant)
  - 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

*Data cut-off: 20 Feb 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 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=5)	>2 *SMN2* copies (n=7)	Total risdiplam (n=12)
Most common AEs, n (%) (reported in ≥2 infants)	Nasal congestion	1 (20)	3 (43)	4 (33)
	Cough	0	3 (43)	3 (25)
	Teething	1 (20)	2 (29)	3 (25)
	Vomiting	1 (20)	2 (29)	3 (25)
	Eczema	1 (20)	1 (14)	2 (17)
	Abdominal pain	2 (40)	0	2 (17)
	Diarrhea	0	2 (29)	2 (17)
	Gastroenteritis	1 (20)	1 (14)	2 (17)
	Papule	2 (40)	0	2 (17)
	Pyrexia	0	2 (29)	2 (17)

Preclinical safety findings were not observed in any infant 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. Includes AEs with onset from first dose of study drug up to the cut-off date.
Data cut-off: 20 Feb 2021.
AE, adverse event; SMN, survival of motor neuron.

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RAINBOWFISH summary

Roche

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

As of the data cut-off,* all 5 infants who had received risdiplam for ≥12 months reached the maximum score of 64 on the CHOP-INTEND

No treatment-related SAEs were reported in presymptomatic infants treated with risdiplam for up to 18.1 months

RAINBOWFISH is recruiting globally†

Recruitment will close when either at least 25 patients, including a minimum of 5 patients with two SMN2 copies and a baseline CMAP amplitude of ≥1.5 mV are enrolled, OR when a total of 10 patients with two SMN2 copies and a baseline CMAP amplitude of ≥1.5 mV are enrolled

RAINBOWFISH will help to determine the dose of risdiplam for infants <2 months of age

*Data cut-off: 20 Feb 2021. †RAINBOWFISH is currently recruiting in Australia, Belgium, Brazil, China, Italy, Poland, Russia, Saudi Arabia, Taiwan and the USA.
CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound muscle action potential; mV, millivolt; SAE, serious adverse event; WHO, World Health Organization.

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Summary of Roche data at CureSMA

JEWELFISH

- The first trial in a diverse SMA population aged from 1 to 60 years who received prior treatment, which has showed a consistent safety profile and >2-fold increase in SMN protein levels and stabilization in motor function

RAINBOWFISH

- Pre-symptomatic babies with SMA treated with Evrysdi for at least one year were able to sit, stand and walk in preliminary data achieving motor milestones within the WHO windows for healthy children

Q&A

Doing now what patients need next