Risdiplam: pharmacokinetic, pharmacodynamic, safety and efficacy exposure response analyses

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Disclosures

- HK, YC, PG, MG and RSS are current employees of, and hold shares in, F. Hoffmann-La Roche Ltd

The SUNFISH, FIREFISH and JEWELFISH studies were sponsored by F. Hoffmann La Roche Ltd, Basel, Switzerland. Writing and editorial assistance was provided by Emily Turner of Nucleus Global, in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3)

In collaboration with SMA FOUNDATION and PTC THERAPEUTICS

Introduction

- Risdiplam is a centrally and peripherally distributed, oral *SMN2* pre-mRNA splicing modifier that increases levels of functional SMN protein[1,2]
- Risdiplam (EVRYSDI®) has been approved for the treatment of patients with SMA in more than 80 countries worldwide[3]*
- The following risdiplam clinical studies were included in the presented analyses:
  - FIREFISH (NCT02913482):[4] patients with Type 1 SMA aged 1–7 months at treatment initiation
  - SUNFISH (NCT02908685):[5] patients with Type 2/3 SMA aged 2–25 years
  - JEWELFISH (NCT03032172):[6] non-treatment-naïve patients with SMA aged 6 months–60 years†

*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.[7,8] †The majority of patients enrolled in JEWELFISH were non-treatment naïve; however, three patients who were previously enrolled in the MOONFISH trial were treatment naïve as they received placebo treatment and were never switched to RG7800 treatment.

EC, European Commission; FDA, US Food and Drug Administration; SMA, spinal muscular atrophy; 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; 3. F. Hoffmann-La Roche. May 2022 press release: https://www.roche.com/media/releases/med-cor-2022-05-31 (Accessed June 2022); 4. ClinicalTrials.gov. NCT02913482 (Accessed June 2022); 5. ClinicalTrials.gov. NCT02908685 (Accessed June 2022); 6. ClinicalTrials.gov. NCT03032172 (Accessed June 2022); 7. EVRYSDI® prescribing information: https://www.gene.com/download/pdf/evrysdi_prescribing.pdf (Accessed June 2022); 8.EVRYSDI® summary of product characteristics: https://www.ema.europa.eu/en/documents/product-information/evrysdi-epar-productinformation_en.pdf (Accessed June 2022).

Methods

- Risdiplam plasma concentrations were measured in all patients; PK parameters were estimated by population PK modeling
- The PD markers, SMN protein and mRNA, were measured in blood
- A broad patient population, with a body weight up to 109 kg and aged 2 months–61 years, was included in the clinical studies
- Exposure–response analyses were conducted to assess whether patients on the lower or higher end of the exposure range would have different efficacy or safety outcomes

PD, pharmacodynamic; PK, pharmacokinetic; SMN, survival of motor neuron.

Demographics

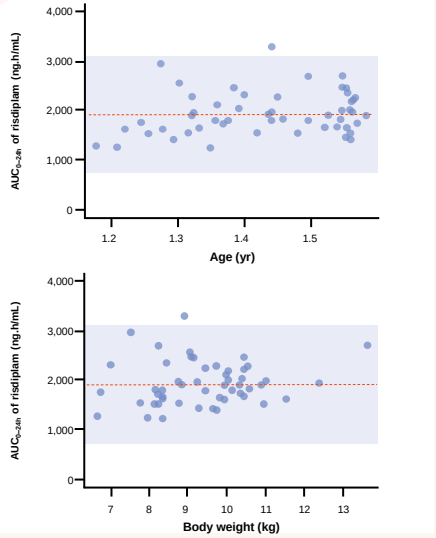
		FIREFISH (n=62)	SUNFISH (n=231)	JEWELFISH (n=173)
Age (years)				
	Mean	0.45	10.7	17.7
	Median (min–max)	0.5 (0.18–0.58)	9.8 (2.2–25.4)	15.0 (1.1–61)
Body weight (kg)				
	Mean	6.8	32.2	41.3
	Median (min–max)	6.6 (4.1–10.6)	27.5 (9.8–109)	39.0 (9.2–109)
Gender, n (%)				
	Male	25 (40)	113 (49)	95 (55)
	Female	37 (60)	118 (51)	78 (45)
SMA type, n (%)				
	1	62 (100)	0	15 (9)
	2	0	165 (71)	107 (62)
	3	0	66 (29)	51 (29)
Race, n (%)				
	White	35 (56)	167 (72)	142 (82)
	African American	0	2 (1)	1 (1)
	Asian	18 (29)	36 (16)	9 (5)
	Other	9 (15)	26 (11)	21 (12)

- A total of 466 patients with SMA who received treatment with risdiplam were included in the PK analyses, with a body weight of 4–109 kg, and 2 months–61 years of age

PK, pharmacokinetic; SMA, spinal muscular atrophy.

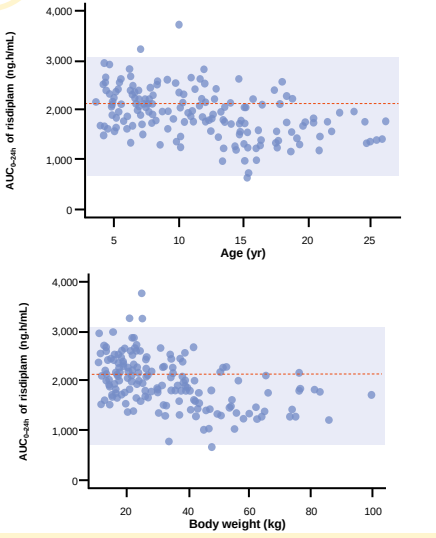
Risdiplam exposure was comparable across the very wide age and body weight range*

FIREFISH



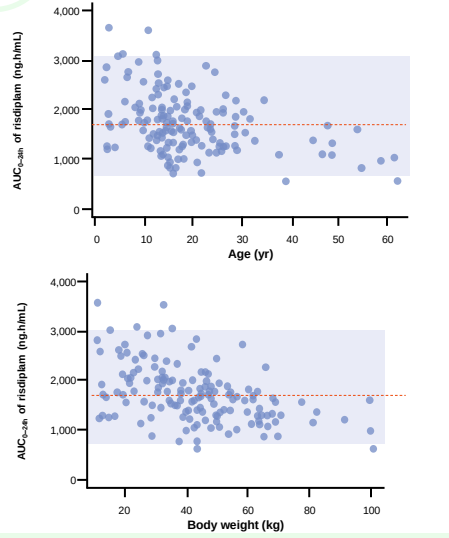
The mean $AUC_{0–24h}$ for patients with infantile-onset SMA† in FIREFISH was 1,930 ng.h/mL

SUNFISH



The mean $AUC_{0–24h}$ for patients with later-onset SMA‡ in SUNFISH was 2,070 ng.h/mL

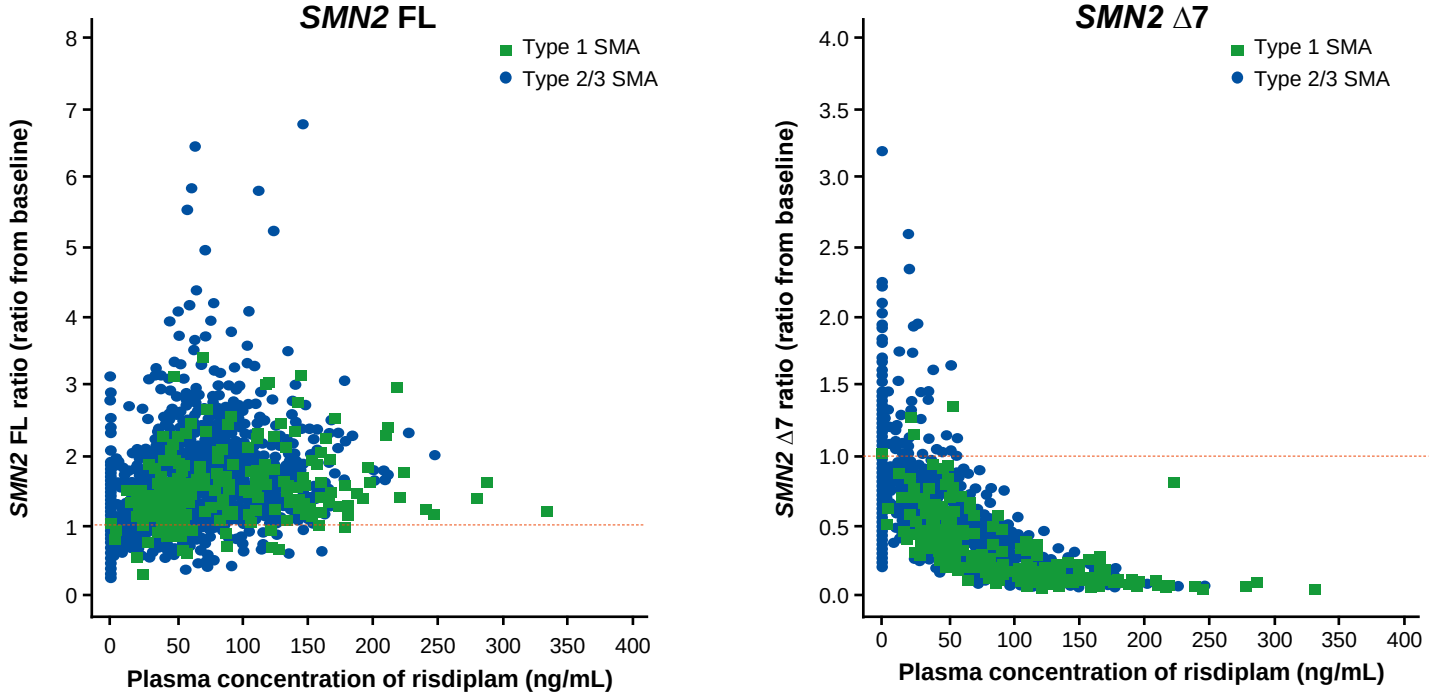
JEWELFISH



The mean $AUC_{0–24h}$ for non-treatment-naïve patients with SMA§ in JEWELFISH was 1,730 ng.h/mL

*After 12 months of treatment for FIREFISH and SUNFISH, and at the last available visit with PK blood sampling for JEWELFISH (in which many patients had not reached 12 months treatment). †Aged 2–7 months at enrollment. ‡Aged 2–25 years at enrollment. §Aged 6 months–60 years at enrollment.
$AUC_{0–24h}$, area under the plasma concentration–time curve over the 24h dosing interval; PK, pharmacokinetic; SMA, spinal muscular atrophy; yr, year.

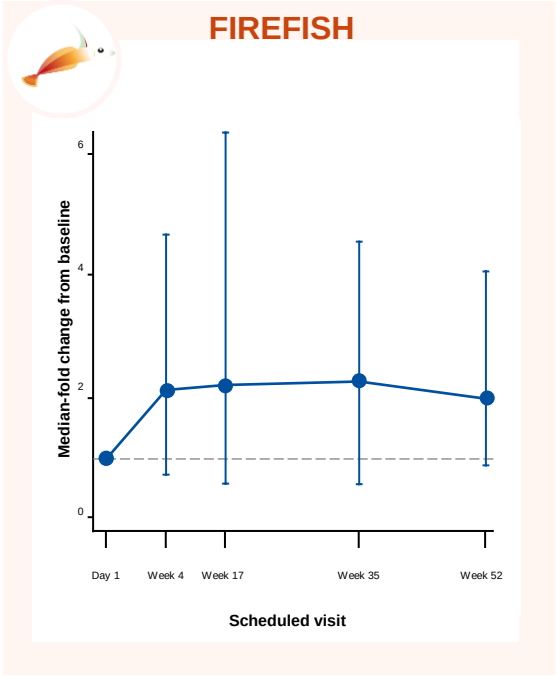
Risdiplam promoted near-complete splicing of *SMN2* pre-mRNA to FL mRNA*

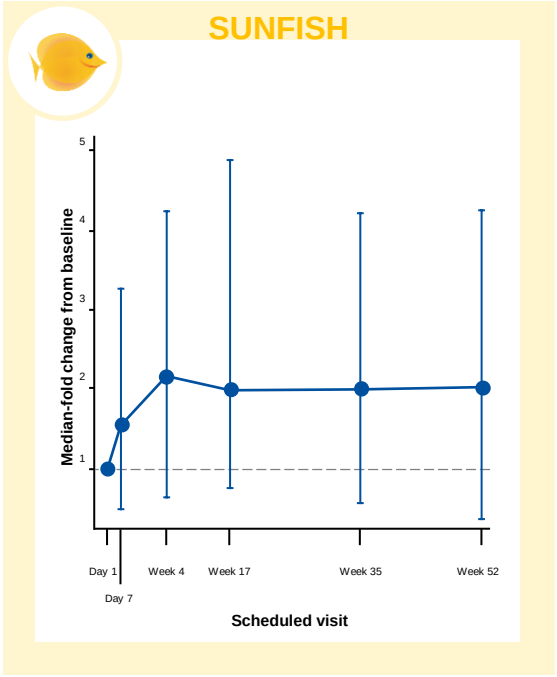


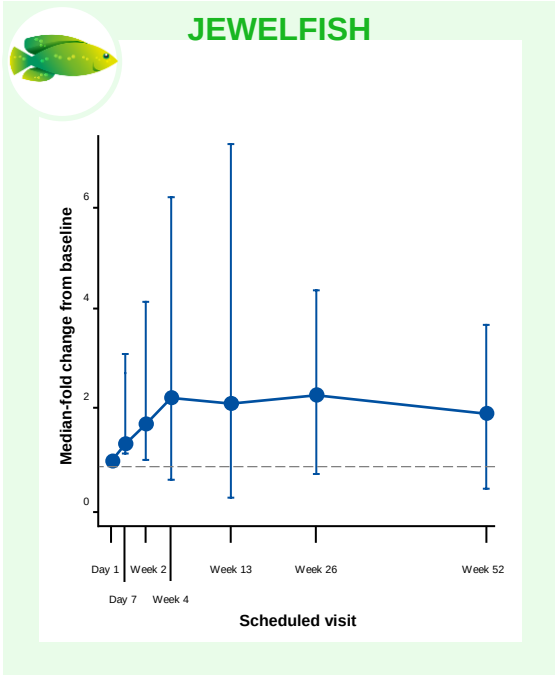
Risdiplam's mode of action was confirmed by an almost-complete shift from *SMN2* Δ7 mRNA to FL mRNA at the observed exposure range

*All data with mRNA and risdiplam concentration measurements available at the same time point were part of the PK/PD analysis, including the dose finding of FIREFISH and SUNFISH at lower dose levels.
FL, full length; PD, pharmacodynamic; PK, pharmacokinetic; SMA, spinal muscular atrophy; SMN, survival of motor neuron.

Risdiplam treatment led to a ≥2-fold median increase in SMN protein within 4 weeks



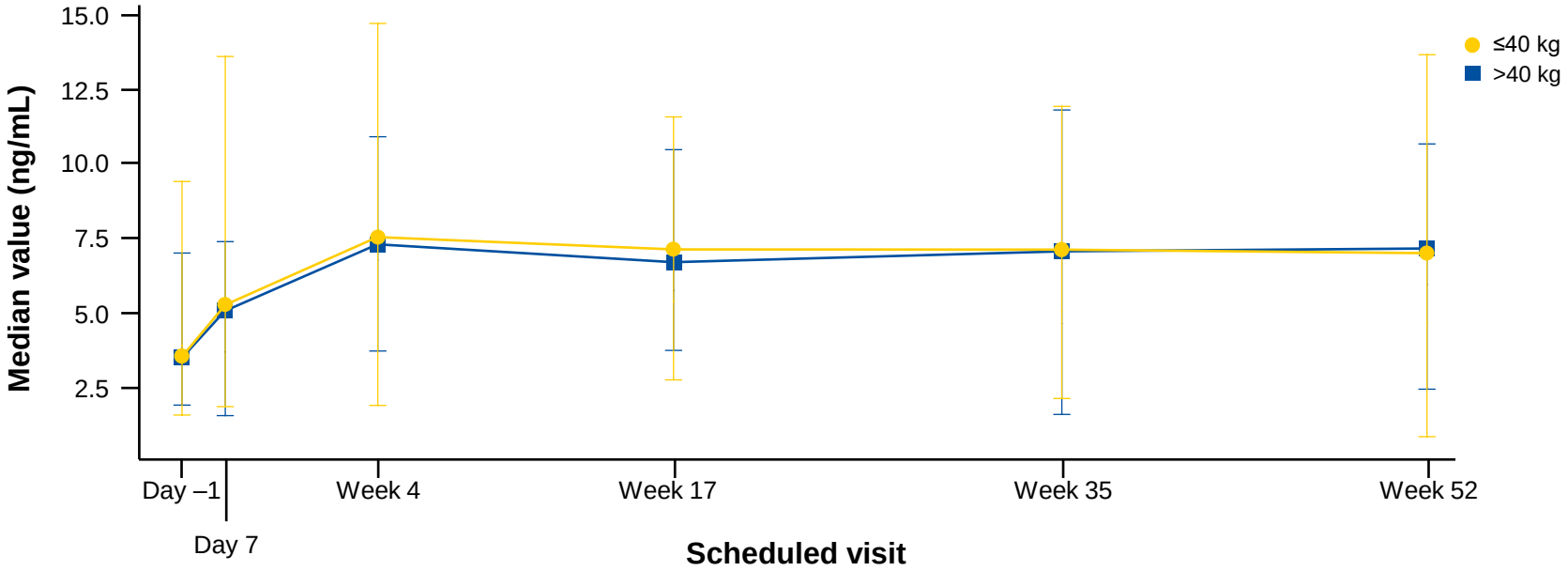




SMN protein levels were sustained throughout treatment

Error bars show minimum and maximum values. Blood mixed with lysis buffer 1:1.
SMN, survival of motor neuron.

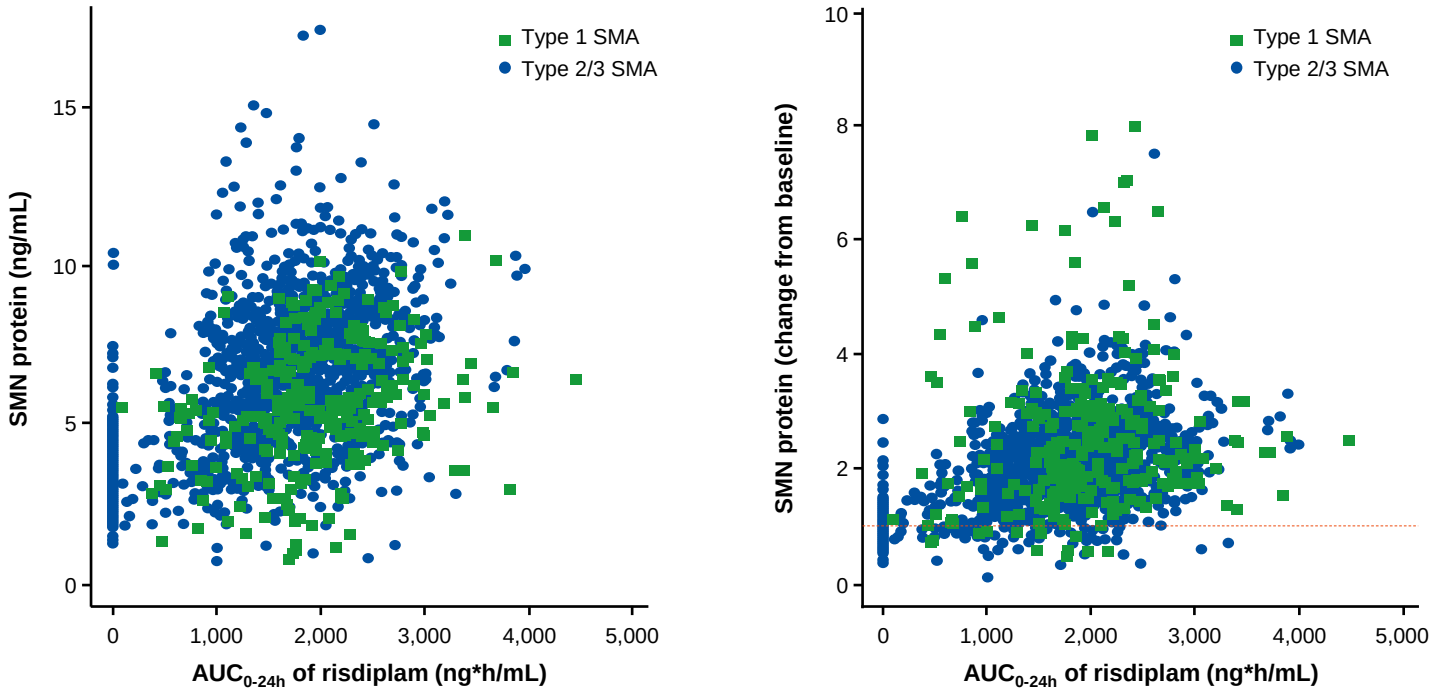
SMN protein in patients enrolled in SUNFISH Part 2 who are below or above 40 kg of body weight



The same increase in SMN protein was observed for lighter and heavier patients

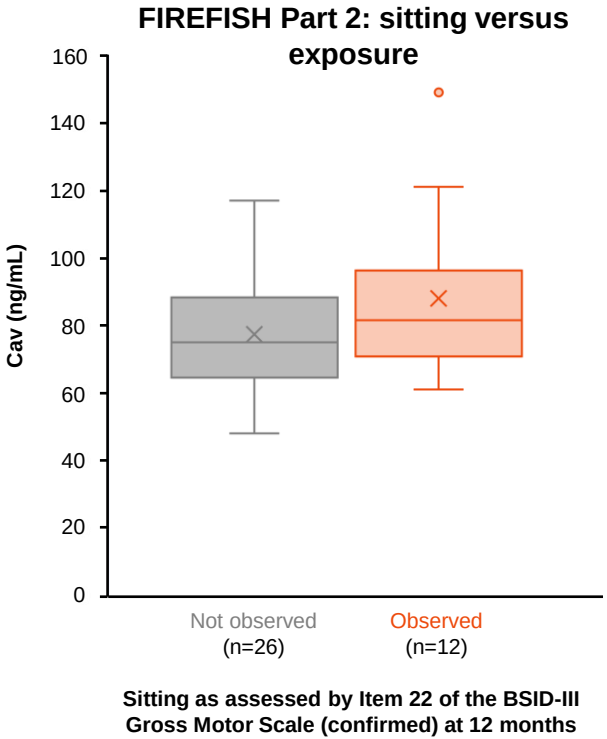
SMN, survival of motor neuron.

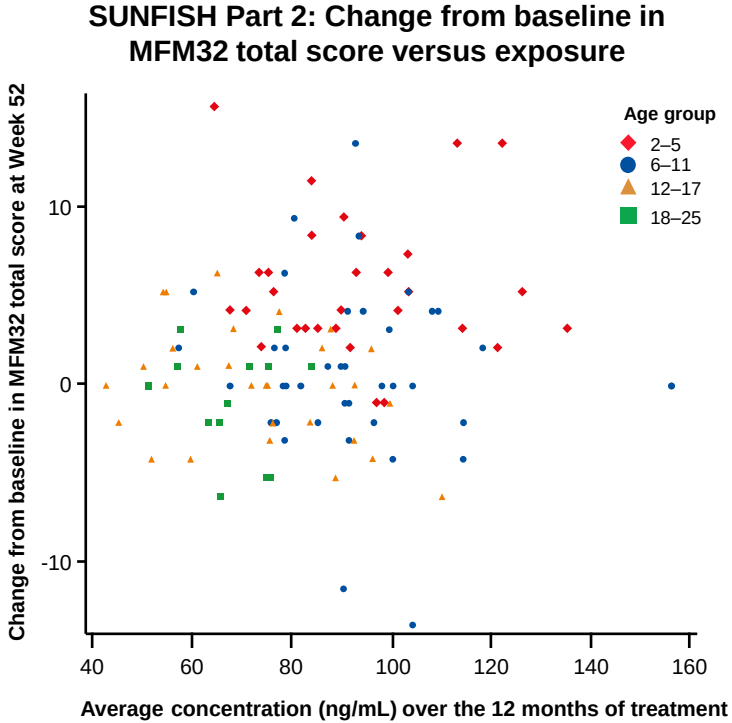
Comparable SMN protein increases were achieved across the observed exposure range and for all SMA types*



*All data at any timepoint where both PK and SMN protein level is available.
AUC_{0-24h}, area under the plasma concentration–time curve over the 24h dosing interval; PK, pharmacokinetic; SMA, spinal muscular atrophy; SMN, survival of motor neuron.

Exposure–response analyses showed no difference in outcomes within the observed exposure range* in FIREFISH Part 2 and SUNFISH Part 2 primary endpoints†

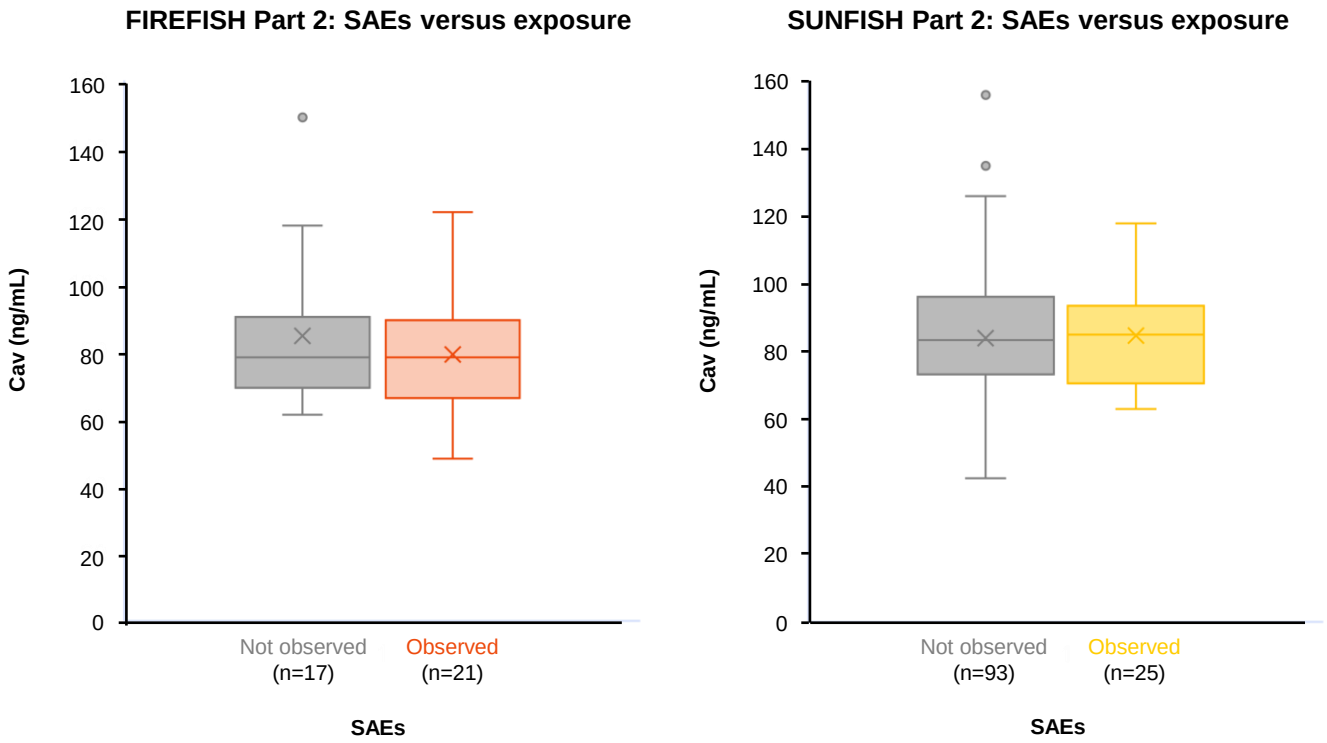




Similar findings were observed for other assessed efficacy endpoints over the 12 months of treatment

*The pivotal dosing regimen was used. †Sitting independently (as assessed by Item 22 of the BSID-III Gross Motor Scale) and MFM32, respectively, at 12 months.
BSID-III, Bayley Scales of Infant and Toddler Development, third edition; Cav, average concentration over the observation period; MFM32, 32-item Motor Function Measure.

Exposure–safety analyses showed no difference in exposure between patients with and without SAEs in FIREFISH Part 2 and SUNFISH Part 2



Cav, average concentration over the observation period; SAE, serious adverse event.

Conclusions

The dosing regimen for risdiplam for patients ≥2 months of age* was selected based on PK and PD data obtained in FIREFISH and SUNFISH Part 1, with the aim of obtaining a median 2-fold increase in SMN protein and reaching the target exposure of mean $AUC_{0–24h}$ of 2,000 ng.h/mL across the wide range of patient characteristics:

- **0.2 mg/kg for infants aged 2 months–2 years**
- **0.25 mg/kg for children aged >2 years with a body weight ≤20 kg**
- **5 mg for patients with a body weight >20 kg**

The selected dosing regimen provides comparable exposure across the very wide age and body weight range in the SMA population and achieves the desired median 2-fold increase in SMN protein in blood

Exposure–response analyses showed that there was no difference in efficacy or safety outcomes within the observed exposure range at the pivotal dosing regimen

*Risdiplam has also been approved by the FDA for the treatment of SMA in patients <2 months of age at a dose of 0.15 mg/kg.[1]
$AUC_{0–24h}$, area under the plasma concentration–time curve over the 24h dosing interval; FDA, US Food and Drug Administration; PD, pharmacodynamic; PK, pharmacokinetic; SMA, spinal muscular atrophy; SMN, survival of motor neuron.

1. EVRYSDI® prescribing information: https://www.gene.com/download/pdf/ evrysdi_prescribing.pdf (Accessed June 2022).

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Acknowledgments

We thank the individuals with SMA and their families, as well as the investigators and trial staff involved in the FIREFISH, SUNFISH, and JEWELFISH studies

We would also like to thank our collaborators at PTC Therapeutics and the SMA Foundation, and Tammy McIver from Roche Products Ltd for their contributions to these studies