Safety update: Risdiplam clinical trial program for spinal muscular atrophy (SMA)

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Background

- SMA is a severe, progressive neuromuscular disease leading to loss of motor function and reduced life expectancy.[1]
- Risdiplam is a centrally and peripherally distributed oral *SMN2* pre-mRNA splicing modifier that increases and sustains the levels of functional SMN protein.[2,3]
  - Risdiplam (EVRYSDI®) has been approved for the treatment of patients with SMA in more than 90 countries worldwide.[4]*
- Risdiplam is the first oral systemic treatment to have efficacy data in pediatric and adult patients to support its use in SMA, and has shown a favorable safety profile across a broad range of patients with SMA.[5–7]
- The pooled safety analyses aim to determine the longer-term safety profile of risdiplam in individuals with SMA who have participated in the risdiplam clinical trial program.

*Risdiplam has been approved for the treatment of patients with SMA of all ages by the FDA and for patients aged ≥2 months with a clinical diagnosis of Type 1, 2 or 3 SMA or with one to four copies of *SMN2* by the EC.[8,9]

Methods

- Safety data from FIREFISH Parts 1 and 2 (NCT02913482),[10] SUNFISH Parts 1 and 2 (NCT02908685),[11] and JEWELFISH (NCT03032172)[12] available at the CCODs (23 Nov 2021, 6 Sep 2021, and 31 Jan 2022, respectively) were pooled and analyzed in order to perform a comprehensive assessment of the safety profile of risdiplam in symptomatic patients, while safety data from RAINBOWFISH (NCT03779334)[13] at the CCOD (1 Jul 2021) were collected from presymptomatic patients and are presented separately.
- Safety assessments included AEs (non-serious and serious), laboratory assessments, vital signs, ECGs and ophthalmologic monitoring.
- AEs were reported from the first dose of risdiplam and continuously throughout the observation period for each patient, excluding AEs reported during the safety follow-up period.
  - To adjust for differing durations of risdiplam exposure across the clinical trials, AEs were also evaluated by exposure time (number of events per 100PY of exposure).

Results

Analysis population

- A total of 465 symptomatic and 18 presymptomatic patients with SMA who received treatment with risdiplam were included in the integrated safety analyses (Table 1).
- The overall exposure to risdiplam in symptomatic patients with SMA was 1,292.3PY.

Table 1. Baseline characteristics

	Symptomatic patients			Presymptomatic patients	
	Type 1 SMA	Types 2/3 SMA	All		
	FIREFISH Parts 1 and 2; JEWELFISH (n=77)	SUNFISH Parts 1 and 2; JEWELFISH (n=388)	FIREFISH Parts 1 and 2; SUNFISH Parts 1 and 2; JEWELFISH (N=465)	RAINBOWFISH (N=18)	
Median age at first dose, years (range)	0.56 (0.2–19.1)	12.63 (2.2–60.9)	10.82 (0.2–60.9)	**Median age at first dose, days (range)**	26.5 (16–40)
Median exposure to risdiplam, months (range)	36.11 (0.6–58.4)	30.95 (0.9–59.0)	34.50 (0.6–59.0)	8.72 (0.5–22.8)	
Sex, n (%)					
Male	33 (42.9)	200 (51.5)	233 (50.1)	8 (44.4)	
Female	44 (57.1)	188 (48.5)	232 (49.9)	10 (55.6)	
SMA type, n (%)				**Number of *SMN2* copies, n (%)**	
1	77 (100)	0	77 (16.6)	2	7 (38.9)
2	0	272 (70.1)	272 (58.5)	3	7 (38.9)
3	0	116 (29.9)	116 (24.9)	≥4	4 (22.2)
Race, n (%)					
Asian	18 (23.4)	45 (11.6)	63 (13.5)	2 (11.1)	
Black or African American	1 (1.3)	2 (0.5)	3 (0.6)	0	
White	46 (59.7)	297 (76.5)	343 (73.8)	15 (83.3)	
Multiple	0	2 (0.5)	2 (0.4)	0	
Unknown	12 (15.6)	42 (10.8)	54 (11.6)	1 (5.6)	
Ambulant*					
Yes	0	24 (6.2)	24 (5.2)	NA	
No	9 (11.7)	364 (93.8)	373 (80.2)		
Scoliosis*					
Yes	7 (9.1)	280 (72.2)	287 (61.7)	NA	
No	2 (2.6)	108 (27.8)	110 (23.7)		

CCODs: FIREFISH Parts 1 and 2 (23 Nov 2021), SUNFISH Parts 1 and 2 (6 Sep 2021), JEWELFISH (31 Jan 2022) and RAINBOWFISH (1 Jul 2021).
*Information about scoliosis and ambulatory status was only captured for SUNFISH and JEWELFISH patients.

AEs

- The rate of AEs per 100PY was comparable across both symptomatic SMA pools; this was higher in presymptomatic patients (Table 2).
- The MedDRA standard organ classes with the highest number of AEs were infections and GI AEs.
- Most AEs related to study medication were mild and none resulted in patient withdrawal from treatment in symptomatic or presymptomatic patients.
- In presymptomatic patients, the five most common AEs per 100PY were vomiting (48.24), teething and pyrexia (41.35 each), nasal congestion (34.46), and diarrhea and viral infection (27.57 each) (see supplementary material).
- Differences in AE rates between the Type 1 and Types 2/3 SMA pools and presymptomtatic patients were mainly reflective of the differences in age (see supplementary material).

Table 2. Overview of AEs/SAEs and rates per 100PY

		Symptomatic patients			Presymptomatic patients
		Type 1 SMA	Types 2/3 SMA	All	
		FIREFISH Parts 1 and 2; JEWELFISH (n=77)	SUNFISH Parts 1 and 2; JEWELFISH (n=388)	FIREFISH Parts 1 and 2; SUNFISH Parts 1 and 2; JEWELFISH (N=465)	RAINBOWFISH (N=18)
Total PY at risk, n		220.8	1,071.5	1,292.3	14.5
Total number of patients with at least one AE, n (%)		77 (100)	375 (96.6)	452 (97.2)	14 (77.8)
Total number of AEs, n		869	4,110	4,979	81
Overall rate of AEs, per 100PY (95% CI)		393.59 (367.86–420.66)	383.56 (371.93–395.47)	385.28 (374.65–396.13)	558.21 (460.26–671.52)
Total number of deaths, n (%)		7 (9.1)*	0	7 (1.5)*	0
Number of fatal AEs, per 100PY (95% CI)		3.17 (1.27–6.53)	0	0.54 (0.22–1.12)	0
Total number of SAEs, n		145	190	335	0
Overall rate of SAEs, per 100PY (95% CI)		65.67 (55.42–77.28)	17.73 (15.30–20.44)	25.92 (23.22–28.85)	0
Total number of related AEs, n		38	179	217	2
Number of related AEs, per 100PY (95% CI)		17.21 (12.18–23.62)	16.71 (14.35–19.34)	16.79 (14.63–19.18)	13.78 (2.45–43.39)
Total number of patients with at least one, n (%)	SAE	57 (74.0)	95 (24.5)	152 (32.7)	0
	SAE leading to dose modification/ interruption	3 (3.9)	25 (6.4)	28 (6.0)	0
	AE leading to treatment withdrawal	1 (1.3)†	1 (0.3)‡	2 (0.4)	0
	AE leading to dose modification/ interruption	4 (5.2)	57 (14.7)	61 (13.1)	2 (11.1)
	Treatment-related AE	11 (14.3)	83 (21.4)	94 (20.2)	2 (11.1)
	Treatment-related AE leading to treat-ment withdrawal	0	0	0	0
	Grade 3–5 AE	46 (59.7)	92 (23.7)	138 (29.7)	2 (11.1)

*Six patients died during the FIREFISH study; one infant was withdrawn from risdiplam treatment and died 3.5 months after withdrawal. †Respiratory tract infection viral with fatal outcome. ‡Irritable bowel syndrome and panic attack were reported to lead to treatment withdrawal in one patient. Multiple occurrences of the same AE within an individual are counted only once except in the total number of AEs and SAEs rows (including AEs reported per 100PY), in which multiple occurrences of the same AE are counted separately. CCODs: FIREFISH Parts 1 and 2 (23 Nov 2021), SUNFISH Parts 1 and 2 (6 Sep 2021), JEWELFISH (31 Jan 2022) and RAINBOWFISH (1 Jul 2021).

SAEs

- In line with the severity of the underlying disease phenotype, the overall rate of SAEs was higher among the Type 1 SMA pool (65.67 per 100PY) compared with the Types 2/3 SMA pool (17.73 per 100PY) (Table 2).
  - In both pools, the most common SAE was pneumonia (reported in 29.9% of patients with Type 1 SMA and 5.7% of patients with Types 2/3 SMA; see supplementary material).
  - Three patients with Type 1 SMA (3.9%) had SAEs reported as related to risdiplam treatment (see supplementary material).
  - Three patients with Types 2/3 SMA (0.8%) had SAEs reported as related to risdiplam treatment (see supplementary material).
  - One patient with Type 1 SMA had an unrelated SAE that led to withdrawal from treatment (respiratory tract infection viral with fatal outcome).
- A total of seven patients died due to SMA-related respiratory complications unrelated to risdiplam (all had Type 1 SMA).
  - Six patients died during the FIREFISH study, while one infant was withdrawn from risdiplam treatment and died 3.5 months after withdrawal.
  - At the time of poster finalization, the total number of deaths was the same as reported at the previous data cut-off;[5] no additional deaths have been reported since.
- No SAEs were reported in presymptomatic patients.

Rate of AEs over time in symptomatic patients

- The overall rate of AEs decreased over time with continued risdiplam treatment, with the highest rate of AEs occurring during 0–≤6 months of treatment in both the Type 1 and Types 2/3 SMA pools (Figures 1a & b).
- No trend was seen in the rate of infection AEs per 100PY in 4-week periods across 6 months; conversely, the rate of GI AEs per 100PY declined by ≥3 fold between the first and fourth 4-week periods in both the Type 1 and Types 2/3 SMA pools (Figures 1c & d & supplementary material).
- The overall rate of SAEs per 100PY was 3.7-fold higher in patients with Type 1 SMA compared with patients with Types 2/3 SMA. The rate of SAEs declined by 1.6 fold between the first and third 6-month periods in the Type 1 SMA pool but remained stable in the Types 2/3 SMA pool (see supplementary material).
- The two most common AEs by preferred term within the MedDRA system organ classes with the highest number of AEs were URTI and nasopharyngitis (infections), and vomiting and diarrhea (GI).
  - Out of these, the most rapid decline was observed for diarrhea in the Types 2/3 SMA pool, where rates decreased markedly in the first 4 weeks of treatment (see supplementary material).

Figure 1a. Overall rates of AEs over time in symptomatic patients

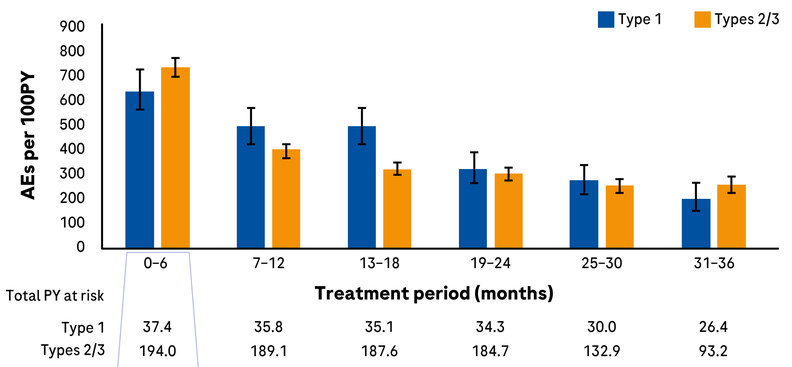


Figure 1b. First 6 months: overall rates of AEs over time in symptomatic patients*

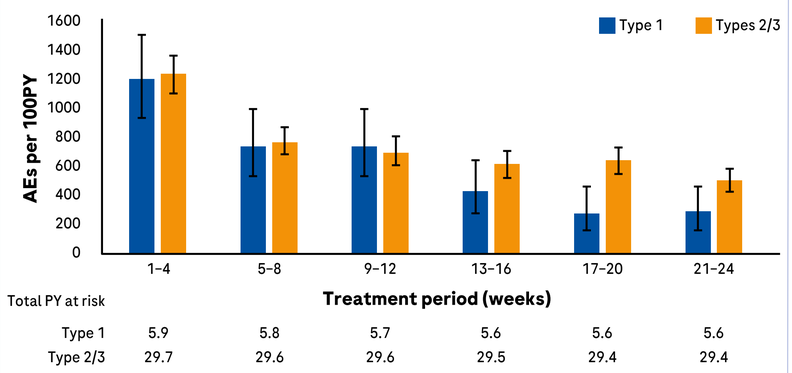


Figure 1c. Overall rates of GI AEs over time in symptomatic patients*

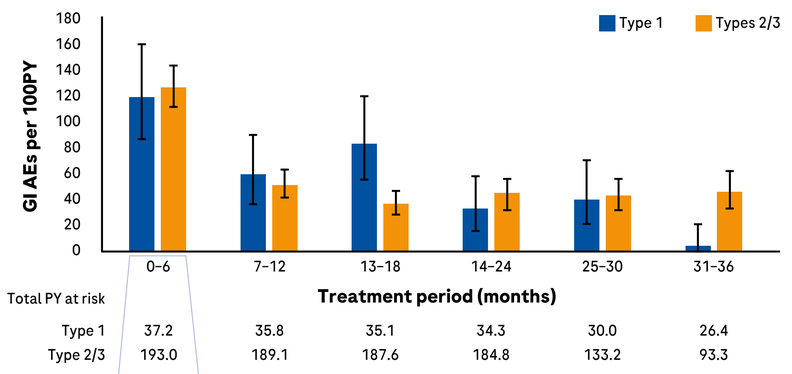
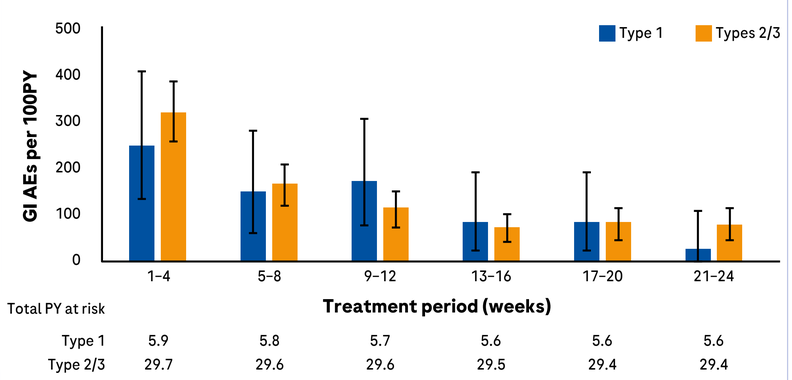


Figure 1d. First 6 months: overall rates of GI AEs over time in symptomatic patients*



*By MedDRA system organ class.[14]
CCODs: FIREFISH Parts 1 and 2 (23 Nov 2021), SUNFISH Parts 1 and 2 (6 Sep 2021) and JEWELFISH (31 Jan 2022). Error bars ±95% CI. Data for the follow-up and 6-month/4-week periods are limited from the RAINBOWFISH trial and so data from presymptomatic patients are not included.

Conclusions

- The overall exposure to risdiplam in symptomatic patients was 1,292.3PY.
- At the CCODs,* there were no treatment-related AEs leading to treatment withdrawal in any of the four risdiplam clinical trials (N=483).
- In both the Type 1 and Types 2/3 SMA symptomatic pools, the overall rate of AEs per 100PY decreased over time (36 months) with continued risdiplam treatment.
  - Reduction in AE rates may be indicative of therapeutic benefit of risdiplam treatment, with a marked deviation from the comorbidities associated with SMA.
- The rate of GI AEs decreased by ≥3 fold between the first and fourth 4-week periods in both the Type 1 and Types 2/3 SMA symptomatic pools.
- A rapid decline in the rate of GI AEs was seen during the first 4 weeks of treatment in symptomatic patients.
- The differences in the AE profile between Type 1 and Types 2/3 SMA pools appeared to be driven by illnesses and conditions that are common in the respective age groups.
- The rate of SAEs was overall 3.7-fold higher in patients with Type 1 SMA compared with patients with Types 2/3 SMA, which may be driven by the more severe phenotype of Type 1 SMA.
- The rate of SAEs declined in the Type 1 SMA pool but remained stable in the Types 2/3 pool.
- In presymptomatic patients, no SAEs were observed and the AE profile appears reflective of age.
- Seven deaths were reported overall, all in patients with Type 1 SMA who died of SMA-related respiratory complications unrelated to risdiplam.
- Data across all studies suggest that risdiplam has a favorable safety profile.
- The FIREFISH, SUNFISH, JEWELFISH (open-label extension) and RAINBOWFISH studies are currently ongoing; updated safety data will be published annually until patients have completed 5 years of treatment.

CCODs: FIREFISH Parts 1 and 2 (23 Nov 2021), SUNFISH Parts 1 and 2 (6 Sep 2021), JEWELFISH (31 Jan 2022) and RAINBOWFISH (1 Jul 2021).

Please scan using your QR reader application to access the graphs and data presented in this poster, and additional information. 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/3Kz7KH0.

Abbreviations

AE, adverse event; CCOD, clinical cut-off date; CI, confidence interval; EC, European Commission; ECG, electrocardiogram; FDA, US Food and Drug Administration; GI, gastrointestinal; MedDRA, Medical Dictionary for Regulatory Activities; NA, not available; PY, patient-years; SAE, serious AE; SMA, spinal muscular atrophy; SMN, survival of motor neuron; URTI, upper respiratory tract infection.

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SUPPLEMENTARY INFORMATION – the content below was not in the poster presented at MDA 2023 but is available via a QR code

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Supplementary material

Supplementary table 1. AEs reported per 100PY in symptomatic patients

AEs reported at a rate ≥10 per 100PY* by MedDRA preferred term[1]	Symptomatic patients		
	Type 1 SMA	Types 2/3 SMA	All
	FIREFISH Parts 1 and 2; JEWELFISH (n=77)	SUNFISH Parts 1 and 2; JEWELFISH (n=388)	FIREFISH Parts 1 and 2; SUNFISH Parts 1 and 2; JEWELFISH (N=465)
Headache	0	38.8	32.2
Pyrexia	57.1	18.9	25.5
URTI	43.5	19.8	23.8
Nasopharyngitis	15.0	15.2	15.2
Vomiting	13.1	12.9	12.9
Cough	6.8	11.2	10.5
Pneumonia	16.8	4.8	6.8

*In either SMA type. CCODs: FIREFISH Parts 1 and 2 (23 Nov 2021), SUNFISH Parts 1 and 2 (6 Sep 2021), JEWELFISH (31 Jan 2022) and RAINBOWFISH (1 Jul 2021).

- Overall, the AEs reported at the highest rates per 100PY in symptomatic patients were headache (39.40), pyrexia (33.13), URTI (31.38), nasopharyngitis (21.58) and vomiting (18.20) (Supplementary table 1).
- Differences in AE rates between the Type 1 and Types 2/3 SMA pools were mainly reflective of the differences in age (Supplementary table 1).
- In presymptomatic patients, the most common AEs per 100PY were vomiting (48.24), teething and pyrexia (41.35 each), nasal congestion (34.46) and diarrhea (27.57) (Supplementary table 2).

Supplementary table 2. AEs reported per 100PY in presymptomatic patients

AEs reported at a rate ≥10 per 100PY by MedDRA preferred term[1]	Presymptomatic patients
	RAINBOWFISH (N=18)
Vomiting	48.24
Teething	41.35
Pyrexia	41.35
Nasal congestion	34.46
Diarrhea	27.57
Viral infection	27.57
Constipation	20.67
Cough	20.67
Eczema	20.67
Papule	20.67
Abdominal pain	13.78
Conjunctivitis	13.78
Gastroenteritis	13.78
Nasopharyngitis	13.78
Rhinitis	13.78
Accidental overdose	13.78
Rhinorrhea	13.78

CCOD: RAINBOWFISH (1 Jul 2021).

AEs reported as related to risidplam treatment

- The most common related AEs in symptomatic patients were hematuria (11 patients), diarrhea (10 patients), nausea (eight patients), URTI (eight patients) and rash (seven patients) (Supplementary table 3).
- All AEs that were reported as related to risdiplam in symptomatic patients resolved, with the exception of 50 AEs in 35 patients with Types 2/3* SMA and six AEs in six patients with Type 1 SMA.†
- AEs related to risdiplam in presymptomatic patients were infrequent, and included diarrhea (n=1) and skin discoloration (n=1).

*Hematuria (n=8), aphthous ulcer, APTT prolonged,‡ skin exfoliation (n=3 each), dry skin, erythema, weight increased (n=2 each), cyanosis, livedo reticularis, eye nevus, skin discoloration, papule, rash, urticaria, retinal dystrophy, mosquito bite reaction,‡ elevated ALT in blood chemistry,‡ gastroesophageal reflux disease, nausea, headache, palmar erythema, rectal hemorrhage, right hydronephrosis,‡ polliakiuria,‡ anemia, lipase increased, oral mucosal erythema, arthralgia, leukopenia,‡ fatty liver disease,‡ small nodules in the right lung,‡ ALP increased,‡ coagulation dysfunction,‡ gamma-glutamyltransferase increased (n=1 each). †Hematuria (n=3), lymphocyte count increased, fall, cardiomyopathy (n=1 each). ‡Reported term. MedDRA preferred term[14] coding not complete at CCOD.

Supplementary table 3. AEs reported as related to risdiplam

AEs by MedDRA preferred term, n* (%)[1]	Symptomatic patients			Presymptomatic patients
	Type 1 SMA	Types 2/3 SMA	All	
	FIREFISH Parts 1 and 2; JEWELFISH (n=77)	SUNFISH Parts 1 and 2; JEWELFISH (n=388)	FIREFISH Parts 1 and 2; SUNFISH Parts 1 and 2; JEWELFISH (N=465)	RAINBOWFISH (N=18)
Hematuria	3 (3.9)	8 (2.1)	11 (2.4)	0
Diarrhea	1 (1.3)	9 (2.3)	10 (2.2)	1 (5.6)
Nausea	1 (1.3)	7 (1.8)	8 (1.7)	0
URTI	1 (1.3)	7 (1.8)	8 (1.7)	0
Rash	0	7 (1.8)	7 (1.5)	0
Aphthous ulcer	0	5 (1.3)	5 (1.1)	0
Headache	0	5 (1.3)	5 (1.1)	0
Abdominal pain	0	4 (1.0)	4 (0.9)	0
Dry skin	0	4 (1.0)	4 (0.9)	0
Lipase increased	0	4 (1.0)	4 (0.9)	0
Rash maculo-papular	2 (2.6)	2 (0.5)	4 (0.9)	0
Skin discoloration	2 (2.6)	2 (0.5)	4 (0.9)	1 (5.6)
Skin exfoliation	0	3 (0.8)	3 (0.6)	0
Neutropenia	2 (2.6)	1 (0.3)	3 (0.6)	0
Urinary tract infection	2 (2.6)	1 (0.3)	3 (0.6)	0
Pneumonia	2 (2.6)	1 (0.3)	3 (0.6)	0
Constipation	2 (2.6)	0	2 (0.4)	0
Aspartate aminotransferase increased	1 (1.3)	2 (0.5)	3 (0.6)	0
Pyrexia	1 (1.3)	2 (0.5)	3 (0.6)	0
Mouth ulceration	0	2 (0.5)	2 (0.4)	0
Dizziness	0	2 (0.5)	2 (0.4)	0
Tachycardia	0	2 (0.5)	2 (0.4)	0
ALT increased	0	2 (0.5)	2 (0.4)	0
Weight increased	0	2 (0.5)	2 (0.4)	0
Erythema	0	2 (0.5)	2 (0.4)	0
Amylase increased	0	2 (0.5)	2 (0.4)	0
Anemia	0	2 (0.5)	2 (0.4)	0
Eczema	1 (1.3)	1 (0.3)	2 (0.4)	0
Cough	1 (1.3)	1 (0.3)	2 (0.4)	0
Abdominal discomfort	0	1 (0.3)	1 (0.2)	0
Vomiting	0	1 (0.3)	1 (0.2)	0
Feces soft	1 (1.3)	0	1 (0.2)	0
Oral mucosal erythema	0	1 (0.3)	1 (0.2)	0
Blister	0	1 (0.3)	1 (0.2)	0
Hyperhidrosis	0	1 (0.3)	1 (0.2)	0
Hyperkeratosis	0	1 (0.3)	1 (0.2)	0
Livedo reticularis	0	1 (0.3)	1 (0.2)	0
Macule	1 (1.3)	0	1 (0.2)	0
Palmar erythema	0	1 (0.3)	1 (0.2)	0
Photosensitivity reaction	0	1 (0.3)	1 (0.2)	0
Pruritus	0	1 (0.3)	1 (0.2)	0
Urticaria	0	1 (0.3)	1 (0.2)	0
Blood triglycerides increased	0	1 (0.3)	1 (0.2)	0
Hepatic enzyme increased	0	1 (0.3)	1 (0.2)	0
International normalized ratio increased	0	1 (0.3)	1 (0.2)	0
Neutrophil count decreased	1 (1.3)	0	1 (0.2)	0
Platelet count decreased	1 (1.3)	0	1 (0.2)	0
Platelet count increased	0	1 (0.3)	1 (0.2)	0
Lymphocyte count increased	1 (1.3)	0	1 (0.2)	0
Prothrombin time prolonged	0	1 (0.3)	1 (0.2)	0
Gastroenteritis	0	1 (0.3)	1 (0.2)	0
Sinusitis	0	1 (0.3)	1 (0.2)	0
Eosinophilia	1 (1.3)	0	1 (0.2)	0
Palpitations	0	1 (0.3)	1 (0.2)	0
Supraventricular tachycardia	0	1 (0.3)	1 (0.2)	0
Fatigue	0	1 (0.3)	1 (0.2)	0
Granuloma	0	1 (0.3)	1 (0.2)	0
Edema peripheral	0	1 (0.3)	1 (0.2)	0
Decreased appetite	0	1 (0.3)	1 (0.2)	0
Amenorrhea	0	1 (0.3)	1 (0.2)	0
Pulmonary hypertension	1 (1.3)	0	1 (0.2)	0
Vertigo	0	1 (0.3)	1 (0.2)	0
Sunburn	0	1 (0.3)	1 (0.2)	0
Apathy	0	1 (0.3)	1 (0.2)	0
Eye nevus	0	1 (0.3)	1 (0.2)	0
Cyanosis	0	1 (0.3)	1 (0.2)	0
Arthralgia	0	1 (0.3)	1 (0.2)	0
Retinal dystrophy	0	1 (0.3)	1 (0.2)	0
Fall	1 (1.3)	0	1 (0.2)	0
Asthma	0	1 (0.3)	1 (0.2)	0
Respiratory failure	1 (1.3)	0	1 (0.2)	0
Hypoglycemia	0	1 (0.3)	1 (0.2)	0
Malnutrition	1 (1.3)	0	1 (0.2)	0
Metabolic acidosis	0	1 (0.3)	1 (0.2)	0
Cardiomyopathy	1 (1.3)	0	1 (0.2)	0
Bladder pain	0	1 (0.3)	1 (0.2)	0
Renal pain	0	1 (0.3)	1 (0.2)	0
Conjunctivitis	1 (1.3)	0	1 (0.2)	0
Furuncle	1 (1.3)	0	1 (0.2)	0
Pharyngitis	1 (1.3)	0	1 (0.2)	0
Respiratory tract infection	0	1 (0.3)	1 (0.2)	0
Rhinitis	0	1 (0.3)	1 (0.2)	0
Gamma-glutamyltransferase increased	0	1 (0.3)	1 (0.2)	0
Papule	0	1 (0.3)	1 (0.2)	0
Gastroesophageal reflux disease	0	1 (0.3)	1 (0.2)	0
Rectal hemorrhage	0	1 (0.3)	1 (0.2)	0
Upper GI hemorrhage	1 (1.3)	0	1 (0.2)	0

*Total number of patients with at least one reported AE. CCODs: FIREFISH Parts 1 and 2 (23 Nov 2021), SUNFISH Parts 1 and 2 (6 Sep 2021), JEWELFISH (31 Jan 2022) and RAINBOWFISH (1 Jul 2021).

SUPPLEMENTARY INFORMATION – the content below was not in the poster presented at MDA 2023 but is available via a QR code

Safety update: Risdiplam clinical trial program for spinal muscular atrophy (SMA)

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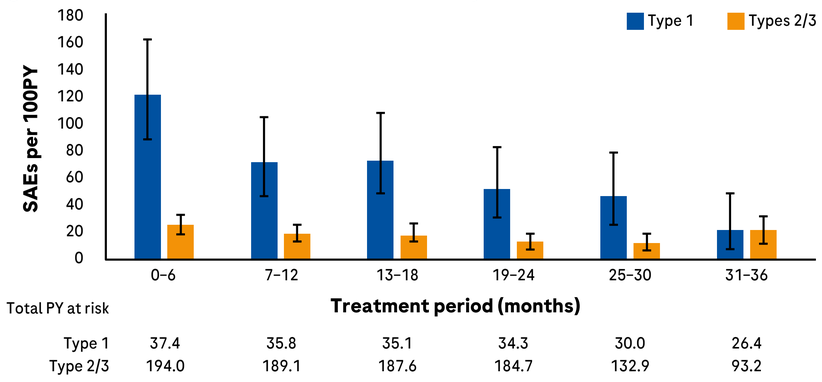
Supplementary material

Supplementary table 4. SAEs in symptomatic patients

SAEs reported in ≥3* patients by MedDRA preferred term, n (%)[1]	Symptomatic patients		
	Type 1 SMA	Types 2/3 SMA	All
	FIREFISH Parts 1 and 2; JEWELFISH (n=77)	SUNFISH Parts 1 and 2; JEWELFISH (n=388)	FIREFISH Parts 1 and 2; SUNFISH Parts 1 and 2; JEWELFISH (N=465)
Pneumonia	23 (29.9)	22 (5.7)	45 (9.7)
URTI	3 (3.9)	6 (1.5)	9 (1.9)
Respiratory distress	7 (9.1)	1 (0.3)	8 (1.7)
Pneumonia viral	7 (9.1)	0	7 (1.5)
Respiratory failure	5 (6.5)	3 (0.8)	8 (1.7)
Dehydration	4 (5.2)	3 (0.8)	7 (1.5)
Hypoglycemia	4 (5.2)	1 (0.3)	5 (1.1)
Influenza	2 (2.6)	3 (0.8)	5 (1.1)
Lower respiratory tract infection	3 (3.9)	2 (0.5)	5 (1.1)
Respiratory tract infection	3 (3.9)	2 (0.5)	5 (1.1)
Gastroenteritis	2 (2.6)	2 (0.5)	4 (0.9)
Bronchitis	2 (2.6)	1 (0.3)	3 (0.6)
Acute respiratory failure	4 (5.2)	1 (0.3)	5 (1.1)
Vomiting	1 (1.3)	3 (0.8)	4 (0.9)
Femur fracture	0	3 (0.8)	3 (0.6)
Back pain	0	3 (0.8)	3 (0.6)
Pyrexia	0	3 (0.8)	3 (0.6)
Aspiration	2 (2.6)	1 (0.3)	3 (0.6)
Atelectasis	2 (2.6)	1 (0.3)	3 (0.6)
Constipation	2 (2.6)	1 (0.3)	3 (0.6)
Decreased appetite	1 (1.3)	2 (0.5)	3 (0.6)

*In the all-patient population in either SMA type. There were no SAEs reported in the presymptomatic population. CCODs: FIREFISH Parts 1 and 2 (23 Nov 2021), SUNFISH Parts 1 and 2 (6 Sep 2021) and JEWELFISH (31 Jan 2022).

Supplementary figure 1. Overall rates of SAEs over time in symptomatic patients

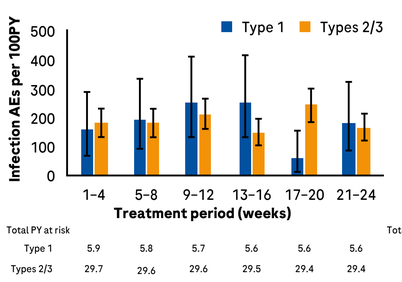


CCODs: FIREFISH Parts 1 and 2 (23 Nov 2021), SUNFISH Parts 1 and 2 (6 Sep 2021) and JEWELFISH (31 Jan 2022). Error bars ±95% CI.
By MedDRA system organ class.[1] *Data for the follow-up and 6-month/4-week periods are limited from the RAINBOWFISH trial and so data from presymptomatic patients are not included.

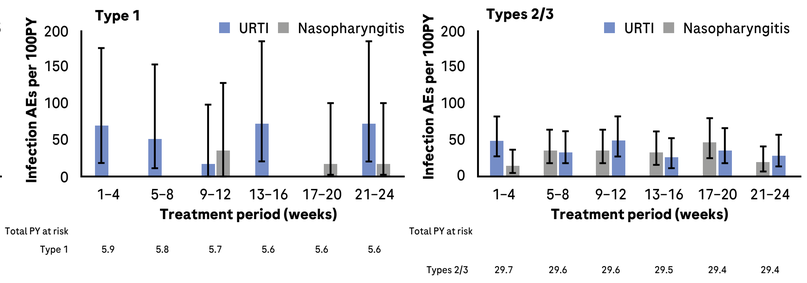
SAEs reported as related to risdiplam treatment

- **Type 1 SMA:** neutropenia in the context of pneumonia, which resolved after 3 and 7 days, respectively, and did not require changing the risdiplam dose; pneumonia, which resolved after 15 days and did not require changing the risdiplam dose, and a fall in the same patient, which is resolving; and pneumonia, which resolved after 25 days and did not require changing the risdiplam dose.
- **Types 2/3 SMA:** supraventricular tachycardia in the context of hypoxia, which resolved after 1 day and did not require changing the risdiplam dose; hypoglycemia, metabolic acidosis and GI hemorrhage in the same patient, which resolved after 3, 12 and 4 days, respectively, and led to dose interruption. URTI and acute gastritis occurred in this same patient, resolved after 6 and 24 days, respectively, and did not require changing the risdiplam dose; pneumonia and asthma in the same patient, which resolved after 13 and 11 days, respectively, and did not require changing the risdiplam dose.
- **Presymptomatic patients:** none.

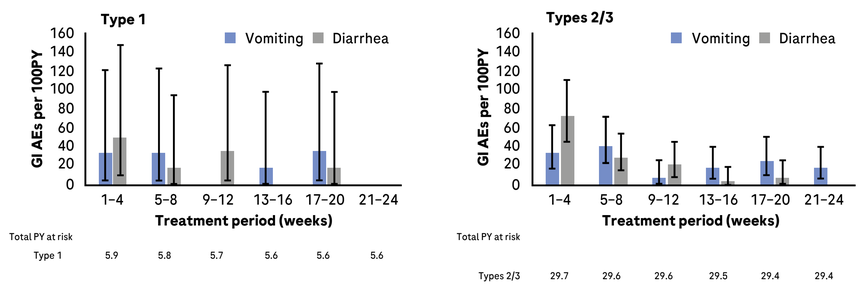
Supplementary figure 2a. Overall rates of infection AEs over time in symptomatic patients – first 6 months*



Supplementary figure 2b. Rates of most frequent infection AEs over time in symptomatic patients – first 6 months†



Supplementary figure 2c. Rates of most frequent GI AEs over time in symptomatic patients – first 6 months†



*By MedDRA system organ class.[1] †By MedDRA preferred term.[1]
CCODs: FIREFISH Parts 1 and 2 (23 Nov 2021), SUNFISH Parts 1 and 2 (6 Sep 2021) and JEWELFISH (31 Jan 2022). Error bars ±95% CI. The follow-up and 4-week periods are limited from the RAINBOWFISH trial and so data from presymptomatic patients are not included.

Ophthalmologic evaluations

- Ophthalmologic monitoring in clinical studies has not shown evidence of the retinal findings seen in preclinical monkey studies.

Clinical laboratory evaluations

- Review of all available laboratory results, vital signs and ECGs did not show any clinically significant adverse findings.

Abbreviations

AE, adverse event; ALT, alanine transaminase; ALP, alkaline phosphatase; APTT, activated partial thromboplastin clotting time; CCOD, clinical cut-off date; CI, confidence interval; ECG, electrocardiogram; GI, gastrointestinal; MedDRA, Medical Dictionary for Regulatory Activities; PY, patient-years; SAE, serious AE; SMA, spinal muscular atrophy; URTI, upper respiratory tract infection.

Reference

1. MedDRA: https://www.meddra.org/news-and-events/news/english-meddra-v221-now-available-download (Accessed March 2023).