SUNFISH Parts 1 and 2: 3-year efficacy and safety of risdiplam in Types 2 and 3 SMA

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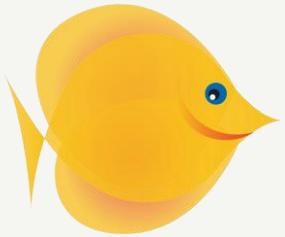

Disclosures

- JWD reports grants from: AMO Pharmaceuticals, aTyr, AveXis, Biogen, Bristol Meyers Squibb, Cytokinetics, Ionis Pharmaceuticals, Roche Pharmaceuticals, Sanofi-Genzyme and Sarepta Therapeutics; he has served as a consultant for: AMO Pharmaceuticals, AveXis, Biogen, Cytokinetics, Ionis Pharmaceuticals, Roche Pharmaceuticals, Pfizer, Sarepta Therapeutics and Santhera Pharmaceuticals; he has patents licensed to Athena Diagnostics for genetic testing of myotonic dystrophy Type 2 (US patent 7442782) and spinocerebellar ataxia type 5 (US patent 7527931)
- ND is a PI of SMA studies for F. Hoffmann-La Roche, Novartis, Biogen and AveXis. He has received consultancy fees from F. Hoffmann-La Roche, Biogen and AveXis
- ESM is a master trainer for SMA studies and receives consultancy fees from AveXis, Biogen, F. Hoffmann-La Roche and Scholar Rock
- AN is a PI of SMA studies for F. Hoffmann-La Roche, Biogen and Scholar Rock; he has received consultancy fees from F. Hoffmann-La Roche, Biogen, Scholar Rock and AveXis
- MO is a PI of SMA studies for F. Hoffmann-La Roche and Biogen
- KS has attended advisory boards for Biogen, Novartis Pharma and Roche/Chugai; she is a consultant for AveXis and has received research funding from AveXis/Novartis, Biogen and Roche/Chugai for research consultation for execution of clinical trial projects and from Ionis Pharmaceuticals for execution of clinical trial projects
- CV is a PI of SMA studies for F. Hoffmann-La Roche; she has attended SAB of Roche, Biogen and AveXis and received consultancy fees from F. Hoffmann-La Roche
- GB has received speaker and consultancy honoraria from AveXis, Inc., Roche, PTC and Sarepta Therapeutics
- OBT is a PI of studies for F. Hoffmann-La Roche, AveXis, Santhera, Italfarmaco, Ultragenyx and Metfora; she is a DSMB member for Inventiva and Minoryx Therapeutics
- NG is a PI of SMA studies for F. Hoffmann-La Roche; she has received consultancy fees from F. Hoffmann-La Roche, Biogen and AveXis
- JK has received honoraria for clinical research and/or consultancy activities from Biogen, Novartis Gene Therapies, Roche and Scholar Rock
- AKP is a PI of SMA studies for F. Hoffmann-La Roche; she has attended advisory boards of Biogen, PTC Therapeutics and AveXis, received speaker honoraria from Biogen and PTC Therapeutics and grant support from Biogen
- LS is a PI of SMA studies for F. Hoffmann-La Roche Ltd, Biogen, and AveXis; he has attended SAB 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 in the patent 20190029605 (Method for estimating physical activity of the upper limb) from which he has not perceived any financial interest
- JB, MG, KG, CM, RSS and WYY are employees of, and hold shares in, F. Hoffmann-La Roche Ltd
- EM receives fees from AveXis, Biogen and F. Hoffmann-La Roche

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Introduction

- 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[2–5]
- Risdiplam (EVRYSDI®) has been approved for the treatment of patients with SMA aged 2 months and older by the FDA[6]
- SUNFISH (NCT02908685) is a two-part clinical trial of risdiplam in a broad patient population with Types 2 and 3 SMA (aged 2–25 years)[7]
  - Part 1 was a dose-finding study, which determined the dose for Part 2
  - Part 2 is the confirmatory study assessing the efficacy of risdiplam at the dose selected in Part 1
- The primary outcome of Part 2 was met, showing a statistically significant difference in the change from baseline in MFM32 total score at Month 12 in patients treated with risdiplam (n=120) versus placebo (n=60)[8]
- Here we present efficacy and safety data from patients who have received long-term risdiplam treatment for 3 years (36 months)

FDA, US Food and Drug Administration; MFM32, 32-item Motor Function Measure; SMA, spinal muscular atrophy; SMN, survival of motor neuron.

1. Mercuri E, et al. Lancet Neurol. 2012; 11:443–452; 2. Ratni H, et al. J Med Chem. 2018; 61:6501–6517; 3. Poirier A, et al. Pharmacol Res Perspect. 2018; 6:e00447; 4. Chiriboga CA, et al. Data presented at WMS 2021; 5. Day JW, et al. Data presented at WMS 2020; 6. EVRYSDI® FDA prescribing information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213535s000lbl.pdf (Accessed March 2022); 7. ClinicalTrials.gov. NCT02908685 (Accessed March 2022); 8. Mercuri E, et al. Lancet Neurol. 2021; 21:42–52.

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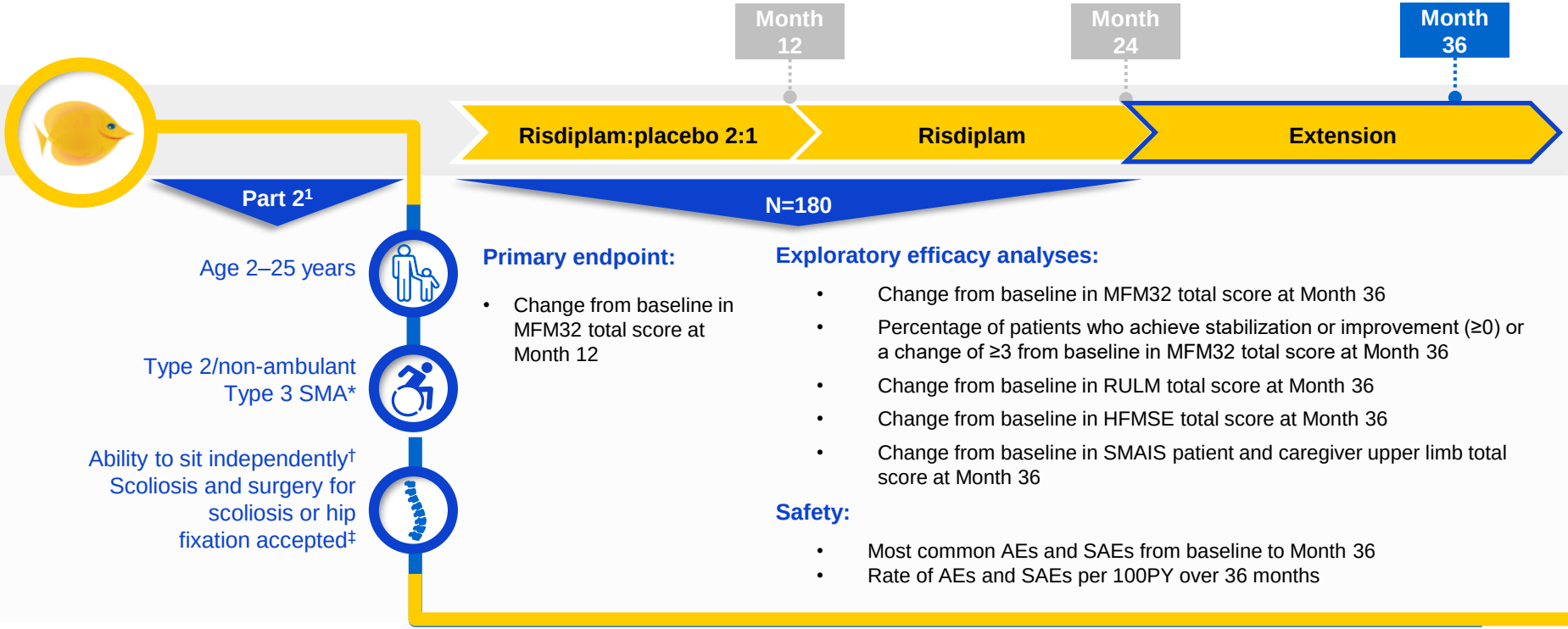
A randomized, placebo-controlled, double-blind study with broad inclusion criteria and a large dataset



*Non-ambulant is defined as not having the ability to walk unassisted for ≥10m. †RULM entry item A (Brooke score) ≥2; ability to sit independently (≥1 on item 9 of the MFM32). ‡Except in the 1 year preceding screening or planned within the next 18 months.
AE, adverse event; HFMSE, Hammersmith Functional Motor Score – Expanded; MFM32, 32-item Motor Function Measure; PY, patient years; RULM, Revised Upper Limb Module; SAE, serious AE; SMA, spinal muscular atrophy; SMAIS, SMA Independence Scale.
1. ClinicalTrials.gov. NCT02908685 (Accessed March 2022).

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Overall baseline demographics were balanced between risdiplam and placebo/risdiplam groups

	Risdiplam (n=120)	Placebo* (n=60)	Total (N=180)
Age at screening, years, median (range)	9 (2–25)	9 (2–24)	9 (2–25)
Age at onset of symptoms, months, mean (SD)	14.1 (8.4)	18.5 (21.1)	15.5 (14.1)
Gender, n (%)			
Female	61 (50.8)	30 (50.0)	91 (50.6)
Male	59 (49.2)	30 (50.0)	89 (49.4)
SMA type, n (%)			
2	84 (70.0)	44 (73.3)	128 (71.1)
3	36 (30.0)	16 (26.7)	52 (28.9)
SMN2 copy number, n (%)			
2	3 (2.5)	1 (1.7)	4 (2.2)
3	107 (89.2)	51 (85.0)	158 (87.8)
4	10 (8.3)	8 (13.3)	18 (10)
Scoliosis, n (%)			
Yes	76 (63.3)	44 (73.3)	120 (66.7)
>40° curvature	34 (28.3)	23 (38.3)	57 (31.7)
MFM32 total score, mean (SD)	45.48 (12.09)†	47.35 (10.12)‡	46.11 (11.46)§
RULM total score, mean (SD)	19.65 (7.22)‖	20.91 (6.41)¶	20.06 (6.97)**
HFMSE total score, mean (SD)	16.10 (12.46)	16.62 (12.09)	16.27 (12.30)

*Patients in the placebo arm received placebo for 12 months followed by risdiplam treatment for 24 months. †n=115. ‡n=59. §n=174. ‖n=119. ¶n=58. **n=177.
Based on enrollment criteria, at least 56% of patients in SUNFISH Part 2 would have been ineligible for the CHERISH trial (CHERISH inclusion criteria included: aged 2–12 years, baseline HFMSE score ≥10; and exclusion criteria included: severe scoliosis [>40° curvature]). This percentage does not take into consideration patients with severe contractures (CHERISH exclusion criteria included any contracture that, according to the investigator, could interfere with HFMSE).[1] Intent-to-treat patients. Data cut-off: 30 Sep 2020.
HFMSE, Hammersmith Functional Motor Scale – Expanded; MFM32, 32-item Motor Function Measure; RULM, Revised Upper Limb Module; SD, standard deviation; SMA, spinal muscular atrophy; SMN, survival of motor neuron.

1. Mercuri E, et al. N Engl J Med. 2018; 378:625–635.

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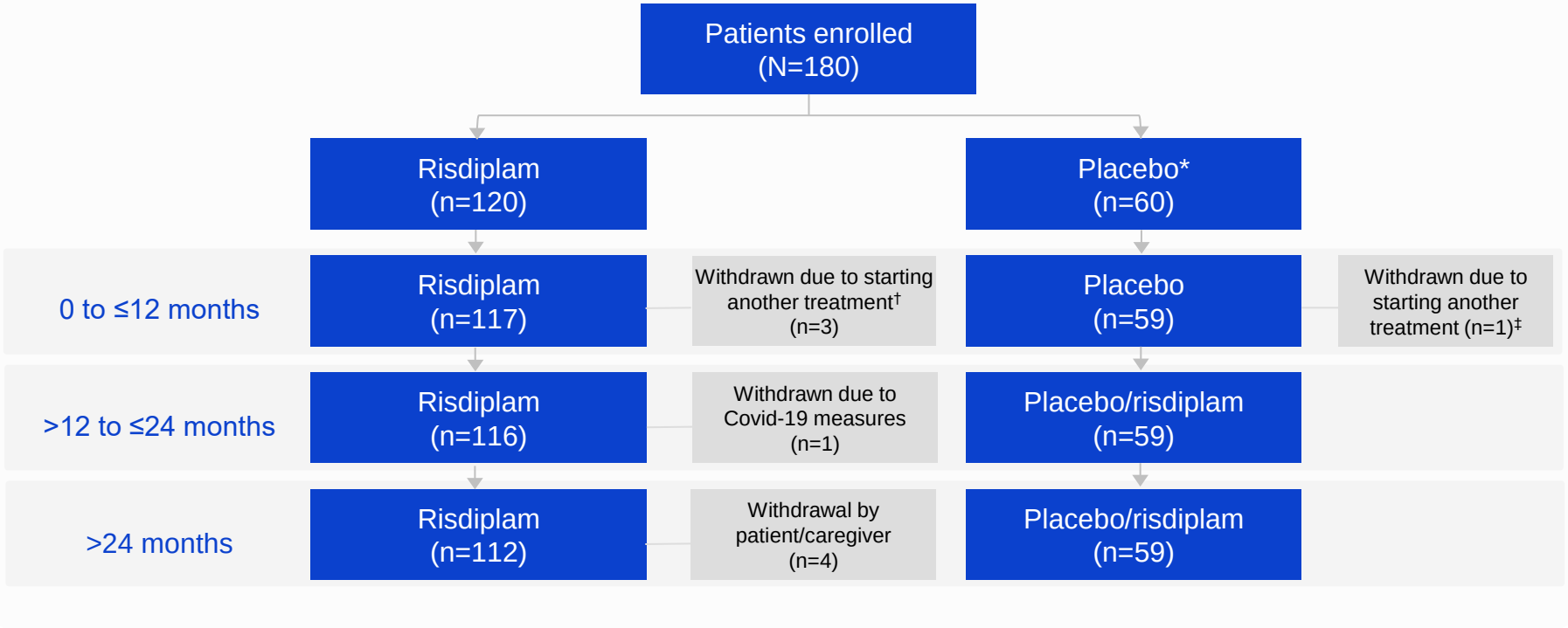
A total of 5% (9/180) of patients discontinued from SUNFISH Part 2 over 36 months



*Patients in the placebo arm received placebo for 12 months followed by risdiplam treatment for 24 months. †Two patients in the risdiplam arm switched to nusinersen (SPINRAZA®) treatment. ‡This patient withdrew from the study to start nusinersen treatment.
Data cut-off: 6 Sep 2021.

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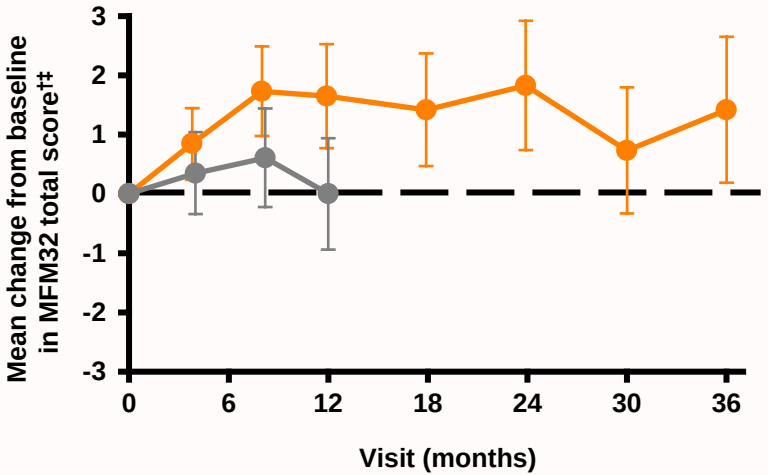
The increase in MFM32 total score from baseline was maintained between Months 12 and 36 in the risdiplam arm; an overall decline was seen in natural history

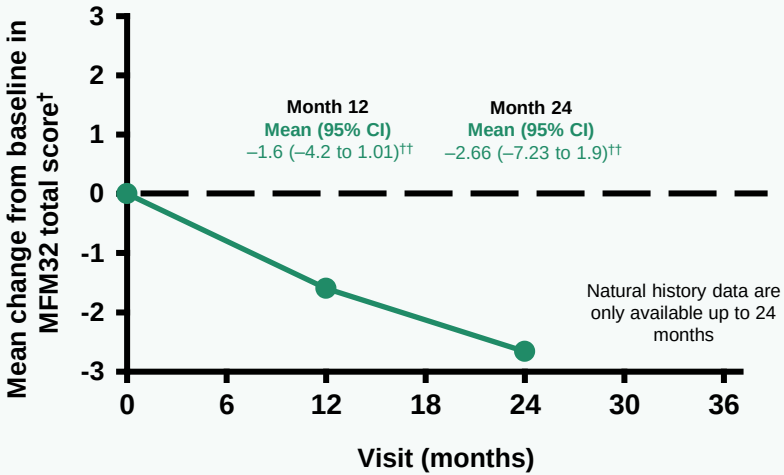
SUNFISH Part 2
Overall population 2–25 years old*



Risdiplam§ (Months 0–36) Placebo‖ (Months 0–12)

Risdiplam (n)¶	115	112	113	112	107	103	84	93
Placebo (n)¶	59	57	58	58				

NatHis-SMA[1]
Subgroup population 6–30 years old**



Sitters with Type 2 SMA and non-ambulant patients with Type 3 SMA

Patients (n)¶	20	15	9

*31% (55/180) of the SUNFISH intent-to-treat population were 2–5 years old at baseline. †+/- 95% CI. ‡Baseline is the last measurement prior to the first dose of risdiplam or placebo. §Data cut-off: 6 Sep 2021. ‖Data cut-off: 6 Sep 2019. Patients in the placebo arm received placebo for 12 months followed by risdiplam treatment for 24 months. Risdiplam period not shown in this graph. ¶Number of patients with valid results = number of patients with an available total score (result) at respective time points. Intent-to-treat patients.
**The NatHis-SMA study (NCT02391831) included nine study sites in Europe and 81 patients aged 2–30 years with Types 2 and 3 SMA. Patients aged 2–5 years old in the NatHis-SMA study were assessed using the MFM20 and were therefore not included in the data shown. ††The full 95% CIs have not been included in this graph as the y-axis has been shortened to allow an accurate comparison with SUNFISH results.
AIM, Association Institut de Myology; CI, confidence interval; MFM, Motor Function Measure; MFM20, 20-item MFM; MFM32, 32-item MFM; NatHis, natural history; SMA, spinal muscular atrophy.
1. Roche data on file; courtesy of AIM.

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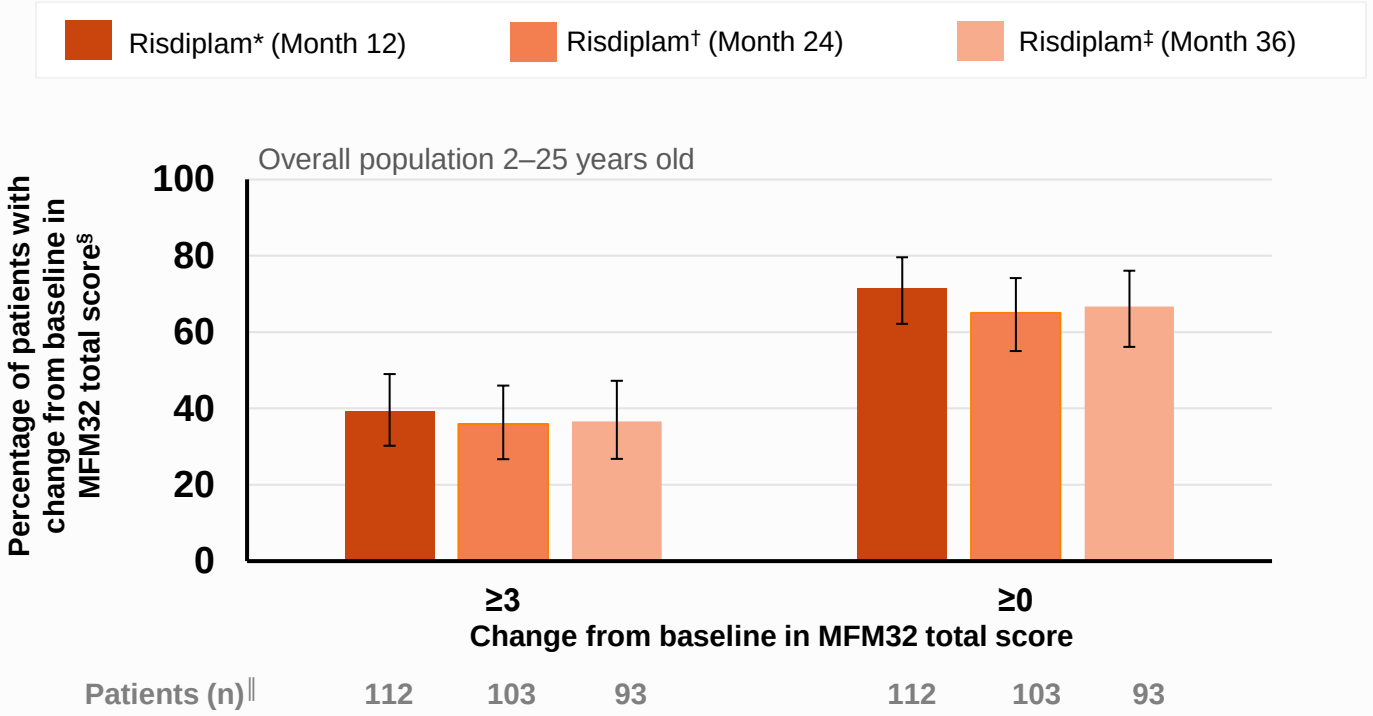
The percentage of patients improving or stabilizing in MFM32 total score from baseline was similar between Months 12 and 36



*Data cut-off: 6 Sep 2019. †Data cut-off: 30 Sep 2020. ‡Data cut-off: 6 Sep 2021. §+/- 95% CI. ‖Number of patients with valid results = number of patients with an available total score (result) at respective time points. Intent-to-treat patients.
The percentage of patients is calculated by using the number of valid total scores at corresponding visits as a denominator. A score of ≥3 shows a marked improvement and a score of ≥0 shows stabilization or improvement.
CI, confidence interval; MFM32, 32-item Motor Function Measure.

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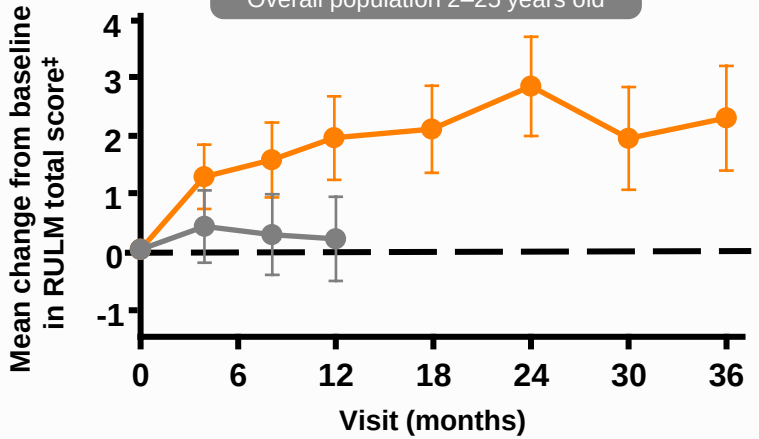
The increase in RULM and HFMSE total scores from baseline was sustained between Months 12 and 36 in the risdiplam arm

Without treatment, patients with Types 2 and 3 SMA show a decline in RULM and HFMSE scores over time[1,2]

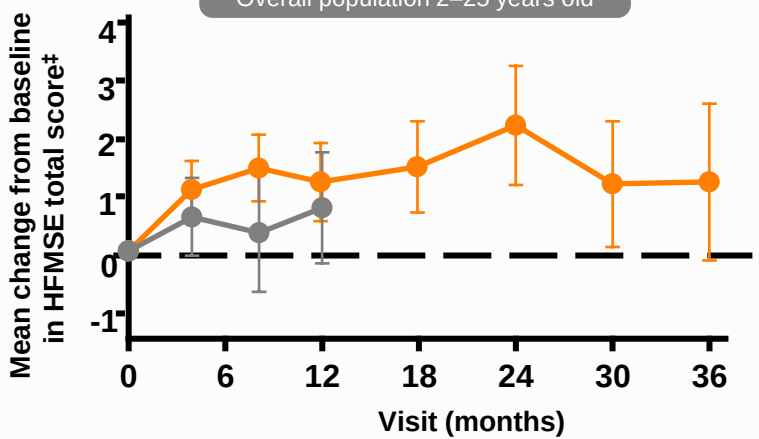
Risdiplam* (Months 0–36) **Placebo†** (Months 0–12)

RULM
Overall population 2–25 years old



Risdiplam (n)§	119	118	117	116	108	105	89	101
Placebo arm/ placebo (n)§	58	57	56	56				

HFMSE
Overall population 2–25 years old



Risdiplam (n)§	120	119	119	117	109	106	89	98
Placebo arm/ placebo (n)§	60	60	58	58				

*Data cut-off: 6 Sep 2021. †Data cut-off: 6 Sep 2019. Patients in the placebo arm received placebo for 12 months followed by risdiplam treatment for 24 months. Risdiplam period not shown in this graph. ‡+/- 95% CI. Baseline is the last measurement prior to the first dose of risdiplam or placebo. §Number of patients with valid results = number of patients with an available total score (result) at respective time points. Intent-to-treat patients.

CI, confidence interval; HFMSE, Hammersmith Functional Motor Scale – Expanded; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy.

1. Pera MC, et al. Muscle Nerve. 2019; 59:426–430; 2. Kaufmann P, et al. Neurology. 2012; 79:1889–1897.

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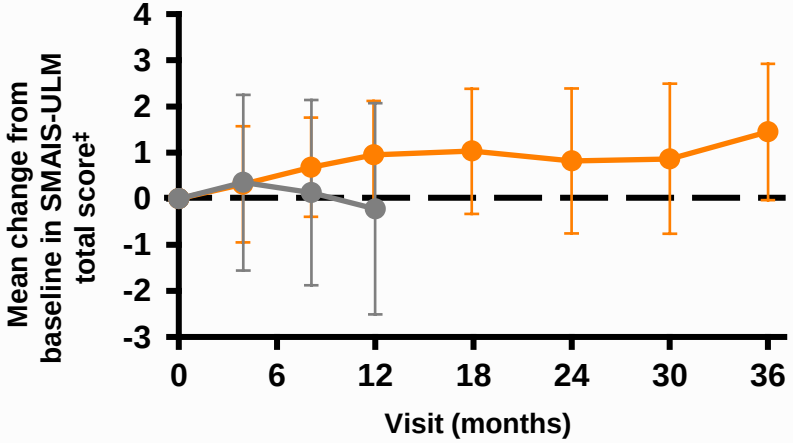
Patients and caregivers reported stabilization or continuous improvements in the SMAIS-ULM total score change from baseline with risdiplam treatment over 36 months

Additional information on the SMAIS and how it is scored can be found using the QR code at the end of this presentation

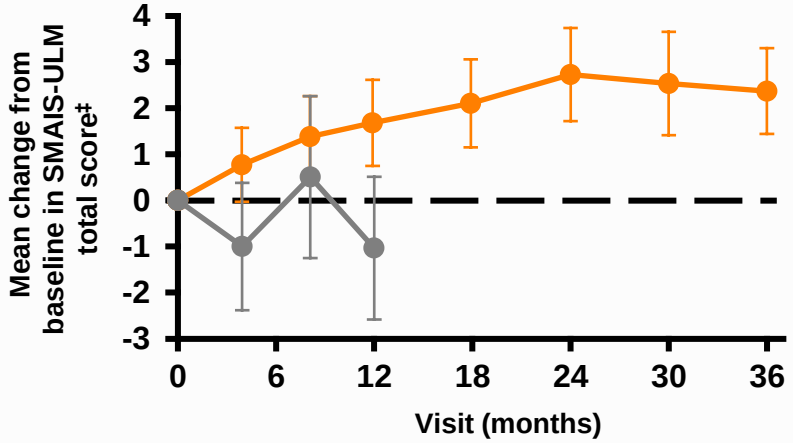
Risdiplam* (Months 0–36) **Placebo†** (Months 0–12)

Patient (≥12 years old)



Risdiplam (n)§	43	42	41	43	39	39	37	38
Placebo arm/ placebo (n)§	23	23	23	23				

Caregiver (for all patients)



Risdiplam (n)§	116	113	114	112	108	103	85	100
Placebo arm/ placebo (n)§	60	60	59	58				

*Data cut-off: 6 Sep 2021. †Data cut-off: 6 Sep 2019. Patients in the placebo arm received placebo for 12 months followed by risdiplam treatment for 24 months. Risdiplam period not shown in this graph. ‡+/- 95% CI. Baseline is the last measurement prior to the first dose of risdiplam or placebo. §Number of patients with valid results = number of patients with an available total score (result) at respective time points. Intent-to-treat patients.
CI, confidence interval; SMA, spinal muscular atrophy; SMAIS, SMA Independence Scale; SMAIS-ULM, SMAIS Upper Limb Measure.

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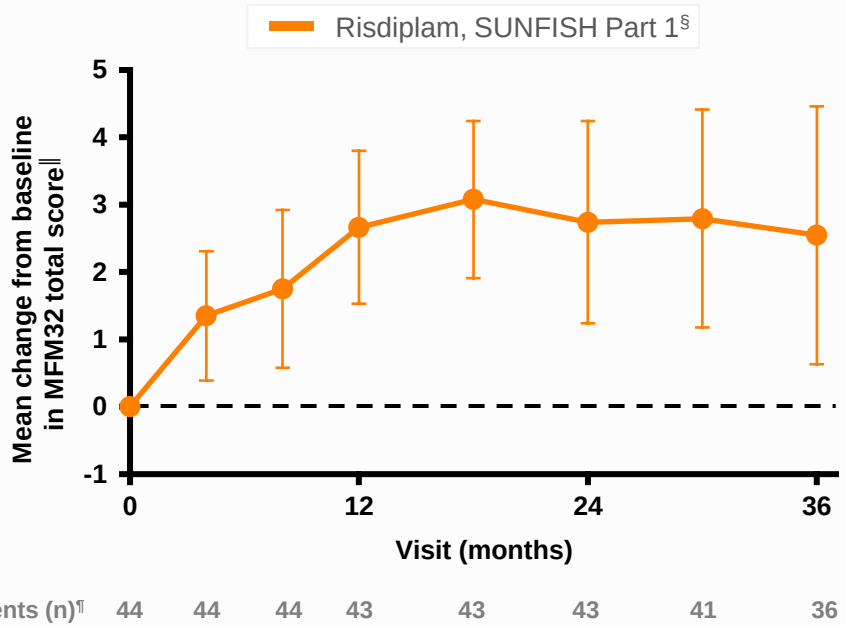
In SUNFISH Part 1, the increase in MFM32 total score change from baseline was maintained between Months 12 and 36 in patients treated with risdiplam

Baseline demographics*	SUNFISH Part 1 intent-to-treat population (N=51)
Age range (years)	**2–25**
Age at screening, years, median (range)	7 (2–24)
Gender, female/male, n (%)	27 (53)/24 (47)
Type 2 SMA, n (%) Type 3 SMA, n (%)	37 (73) 14 (27)
Motor function at baseline† Walkers, n (%) Sitters, n (%) Non-sitters, n (%)	 7 (14) 33 (65) 11 (21)
Scoliosis, n (%)	29 (57)
Baseline MFM32 total score, mean (SD)	(n=44)‡ 42.9 (15.0)



*Data cut-off: 28 June 2019. †Non-sitters are defined as scoring 0 on item 9 of the MFM32 while sitters scored ≥1 on item 9 of the MFM32 but did not qualify as ambulant. Ambulant patients are defined as walkers. ‡Excludes seven patients who performed the MFM20 assessment at baseline. §Data cut-off: 6 Sep 2021. ‖+/- 95% CI. ¶Number of patients with valid results = number of patients with an available total score (result) at respective time points. Intent-to-treat patients.
MFM, Motor Function Measure; MFM20, 20-item MFM; MFM32, 32-item MFM; SD, standard deviation; SMA, spinal muscular atrophy.

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SUNFISH Parts 1 and 2: The observed AE profile over 36 months was reflective of underlying disease

SUNFISH Part 1 (N=51)		Number of AEs per 100PY (95% CI)
Total PY at risk		214.5
AEs reported at a rate of ≥15 per 100PY	Headache	57.4 (47.7–68.4)
	Pyrexia	36.4 (28.8–45.4)
	Upper respiratory tract infection	28.9 (22.2–37.1)
	Cough	20.1 (14.5–27.0)
	Vomiting	18.2 (12.9–24.9)
	Dysmenorrhea	16.3 (11.4–22.7)
	Nasopharyngitis	15.9 (11.0–22.2)
SAEs reported at a rate of ≥0.9 per 100PY	Pneumonia	2.3 (0.8–5.4)
	Femur fracture	0.9 (0.1–3.4)
	Upper respiratory tract infection	0.9 (0.1–3.4)
	Vomiting	0.9 (0.1–3.4)

SUNFISH Part 2 (N=179)*		Number of AEs per 100PY (95% CI)
Total PY at risk		495.8
AEs reported at a rate of ≥11 per 100PY	Headache	46.4 (40.6–52.8)
	Upper respiratory tract infection	24.8 (20.6–29.6)
	Nasopharyngitis	22.4 (18.4–27.0)
	Vomiting	18.8 (15.1–23.0)
	Pyrexia	18.4 (14.8–22.5)
	Cough	11.7 (8.9–15.1)
	Diarrhea	11.3 (8.5–14.7)
SAEs reported at a rate of ≥0.8 per 100PY	Pneumonia	5.2 (3.4–7.7)
	Gastritis	1.0 (0.3–2.4)
	Pyrexia	0.8 (0.2–2.1)
	Upper respiratory tract infection	0.8 (0.2–2.1)

There have been no treatment-related AEs leading to withdrawal or treatment discontinuation

Ophthalmologic monitoring has not shown any evidence in humans of the retinal findings seen in preclinical monkey studies

Hematologic parameters have remained stable over time and no drug-induced skin findings have been observed

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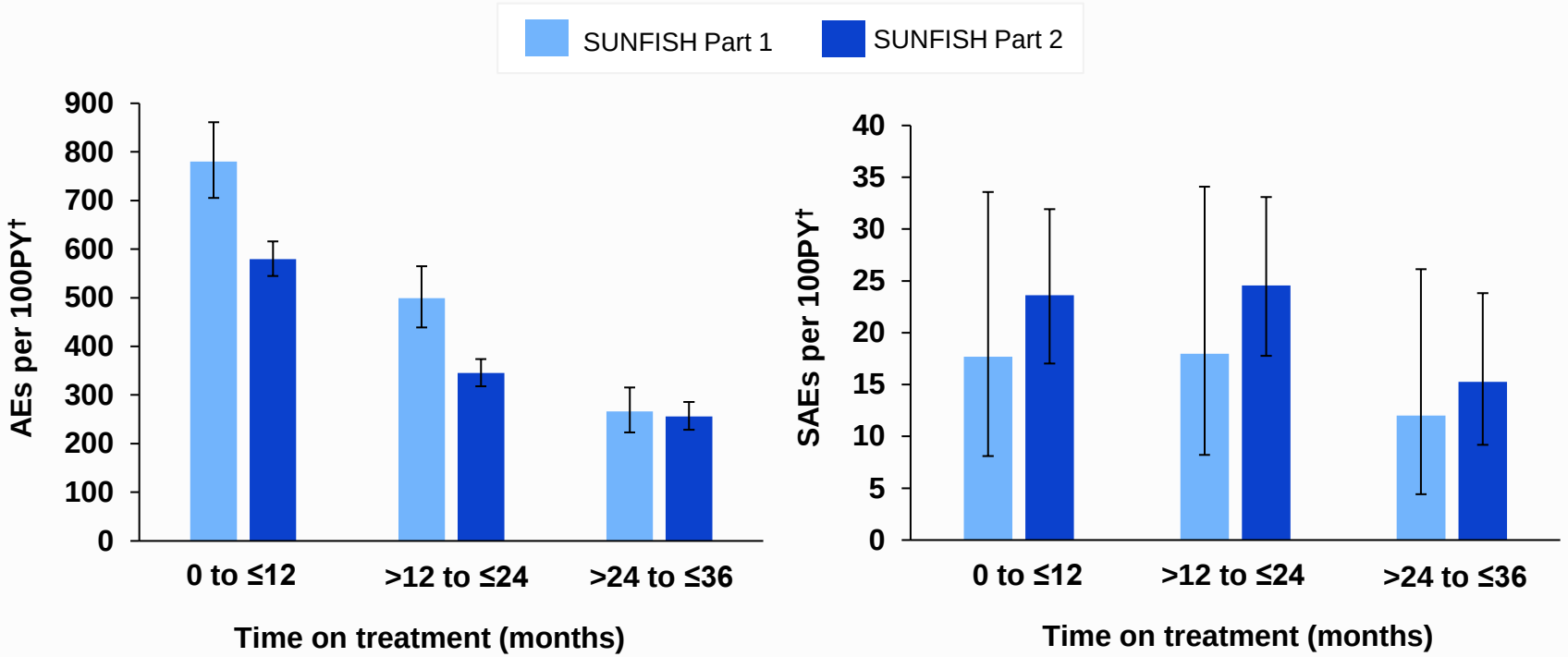
*Includes 120 patients in the risdiplam arm who have been treated with risdiplam for 36 months and 59 patients from the placebo arm who were switched to the risdiplam arm after 12 months and have been treated with risdiplam for 24 months. One patient randomized to placebo was withdrawn prior to receiving any risdiplam dose.
Data cut-off: 6 Sep 2021.
AE, adverse event; CI, confidence interval; PY, patient years; SAE, serious AE.

SUNFISH Parts 1 and 2: The overall rate of AEs per 100PY decreased over 36 months*



*Includes 51 patients from Part 1 and 179 patients from the risdiplam and placebo/risdiplam arms in Part 2 (one patient randomized to placebo was withdrawn prior to receiving any risdiplam dose). †+/- 95% CI.
AE, adverse event; CI, confidence interval; PY, patient years; SAE, serious AE.
Data cut-off: 6 Sep 2021.

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Conclusions

The increase in motor function observed during the first year was sustained in the third year after long-term treatment with risdiplam (as measured by changes in MFM32, HFMSE and RULM)

Continuous improvement or stabilization in the level of help needed for activities of daily living was reported using the SMAIS-ULM

In SUNFISH Parts 1 and 2, AEs and SAEs were reflective of underlying disease. No treatment-related AEs led to withdrawal from the study

In SUNFISH Parts 1 and 2, the overall rate of AEs decreased over 36 months. A trend towards lower SAE rates was observed in the third year of treatment

The gains observed with risdiplam treatment at Month 12 were maintained at Month 36

These results are an important milestone confirming longer-term efficacy and safety of risdiplam in a broad, heterogeneous population of individuals with Type 2 and non-ambulant Type 3 SMA

AE, adverse event; HFMSE, Hammersmith Functional Motor Scale – Expanded; MFM32, 32-item Motor Function Measure; RULM, Revised Upper Limb Module; SAE, serious AE; SMA, spinal muscular atrophy; SMAIS, SMA Independence Scale.
Please scan using your QR reader application to access the graphs and data presented in this presentation.
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