SUNFISH Part 2: Efficacy and safety of risdiplam (RG7916) in patients with Type 2 or non-ambulant Type 3 spinal muscular atrophy (SMA)

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*Presenter

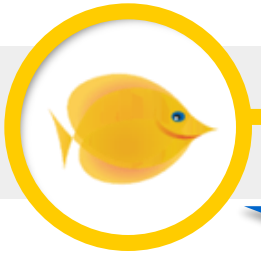
Introduction

- Risdiplam is a centrally and peripherally distributed oral *SMN2* pre-mRNA splicing modifier that increases the levels of functional SMN protein[1,2]
- The SUNFISH study (Part 2) is a positive placebo-controlled trial of risdiplam in a broad patient population with Type 2 and non-ambulant Type 3 SMA (2–25 years old)
- This group is representative of non-ambulant patients typically seen in clinics – including teenagers, adults and patients with reduced motor function – an under-represented group of patients in clinical trials

mRNA, messenger ribonucleic acid; 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.

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



Part 2[1]

12 Months | 12 Months

Risdiplam:placebo 2:1 → Risdiplam → Extension

N=180

Age 2–25 years

Type 2/non-ambulant Type 3 SMA*

Ability to sit independently[†] Scoliosis and surgery for scoliosis or hip fixation accepted[‡]

Primary endpoint:

- change from baseline in total MFM32 score at Month 12

Key secondary endpoints:

- percentage of participants who achieve stabilization (≥0) or improvement (≥3) in MFM32 total score at Month 12
- change from baseline in RULM total score at Month 12
- change from baseline in HFMSE total score at Month 12
- change from baseline in SMAIS total score at Month 12
- safety

*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 one year preceding screening or planned within the next 18 months.
HFMSE; Hammersmith Functional Motor Score – Expanded; MFM32, 32-item Motor Function Measure; RULM, Revised Upper Limb Module; SMAIS; SMA Independence Scale. 1. Clinicaltrials.gov. NCT02908685 (Accessed Jan 2020).

Overall baseline demographics are balanced between risdiplam and placebo 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 group, years, n (%)			
2–5	37 (30.8)	18 (30.0)	55 (30.6)
6–11	39 (32.5)	18 (30.0)	57 (31.7)
12–17	30 (25.0)	16 (26.7)	46 (25.6)
18–25	14 (11.7)	8 (13.3)	22 (12.2)
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)	50 (83.3)	157 (87.2)
4	10 (8.3)	8 (13.3)	18 (10)
Unknown	0	1 (1.7)	1 (0.6)

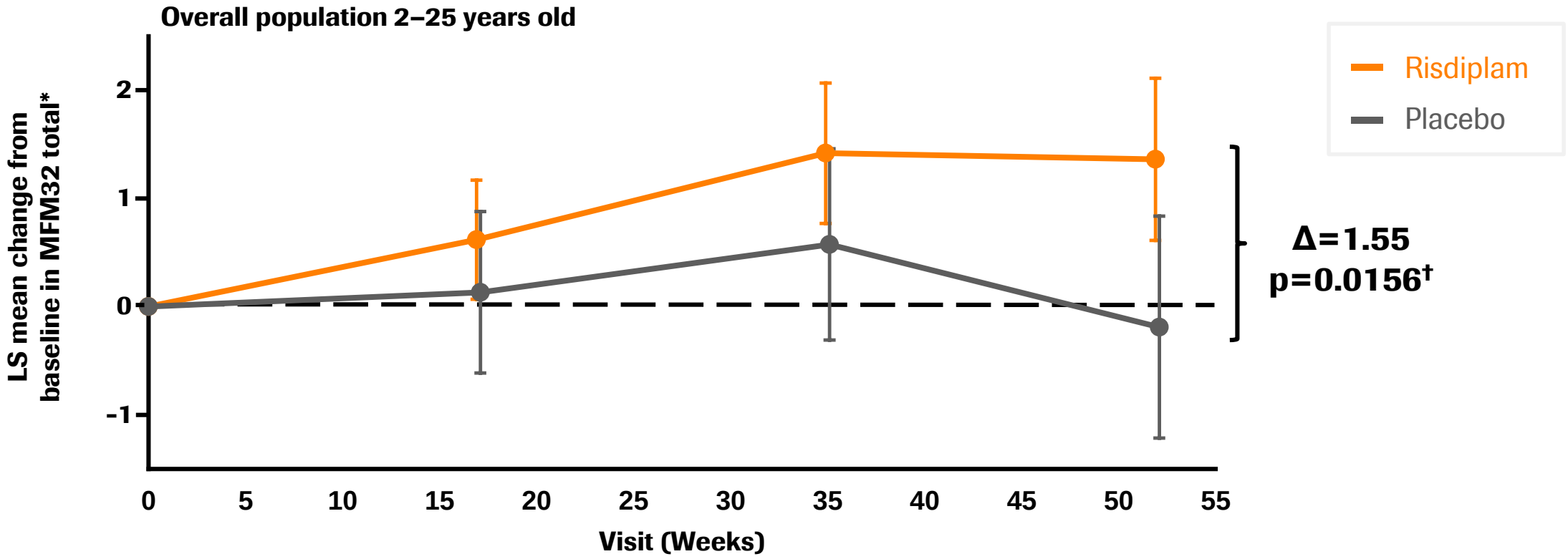
Data cut-off: 6th Sep 2019. Intent to treat population.
SMN, survival motor neuron

Overall baseline disease characteristics are balanced between risdiplam and placebo groups

	Risdiplam (n=120)	Placebo (n=60)	Total (N=180)
Age at onset of symptoms, months, mean (SD)	14.1 (8.4)	18.5 (21.1)	15.5 (14.1)
Scoliosis, n (%)			
Yes	76 (63.3)	44 (73.3)	120 (66.7)
>40 degrees curvature	34 (28.3)	23 (38.3)	57 (31.7)
Surgery for scoliosis before screening, n (%)*			
Yes	29 (24.2)	17 (28.3)	46 (25.6)
No	63 (52.5)	33 (55.0)	96 (53.3)
Not recorded	28 (23.3)	10 (16.7)	38 (21.1)
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)

*Surgery before screening is not a compulsory question and therefore some data are not available;
†n=115; ‡n=59; §n=174; ‖n=119; ¶n=58; **n=177.
Data cut-off: 6th Sep 2019. Intent to treat population.
HFMSE, Hammersmith Functional Motor Scale – Expanded; MFM32, 32-item Motor Function Measure; RULM, Revised Upper Limb Module; SD, standard deviation.

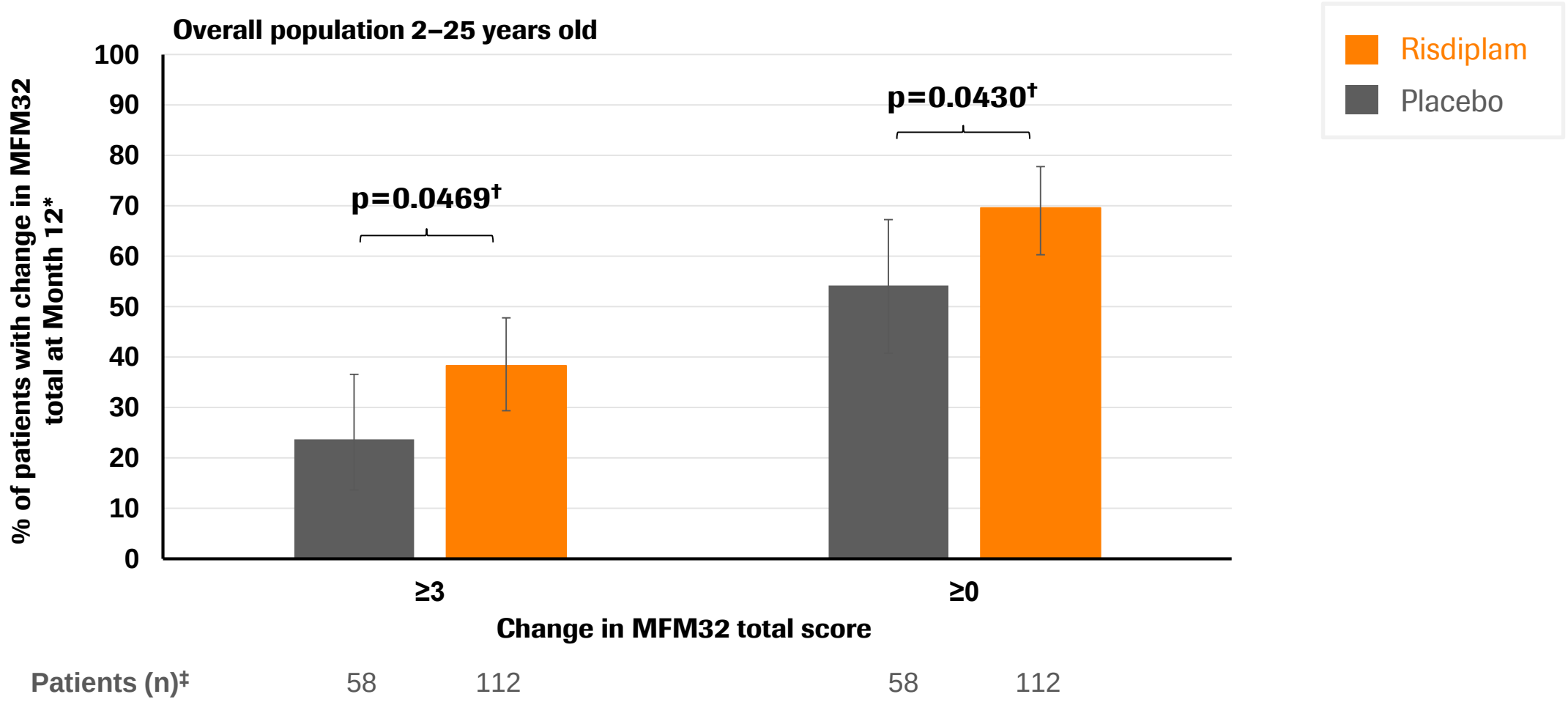
The primary endpoint, MFM32 total change from baseline, was significantly greater in patients receiving risdiplam relative to placebo



Risdiplam n)‡	115	112	113	112
Placebo (n)‡	59	57	58	58

*+/- 95% confidence interval. †Mixed Model Repeated Measure, unadjusted p-value at 5% significance level. ‡Number of patients with valid results = number of patients with an available total score (result) at respective time points.
Intent to treat patients. Data cut-off: 6th Sep 2019.
LS, least squares; MFM32, 32-item Motor Function Measure.

Significantly more patients treated with risdiplam improved or stabilized in MFM32 total versus placebo



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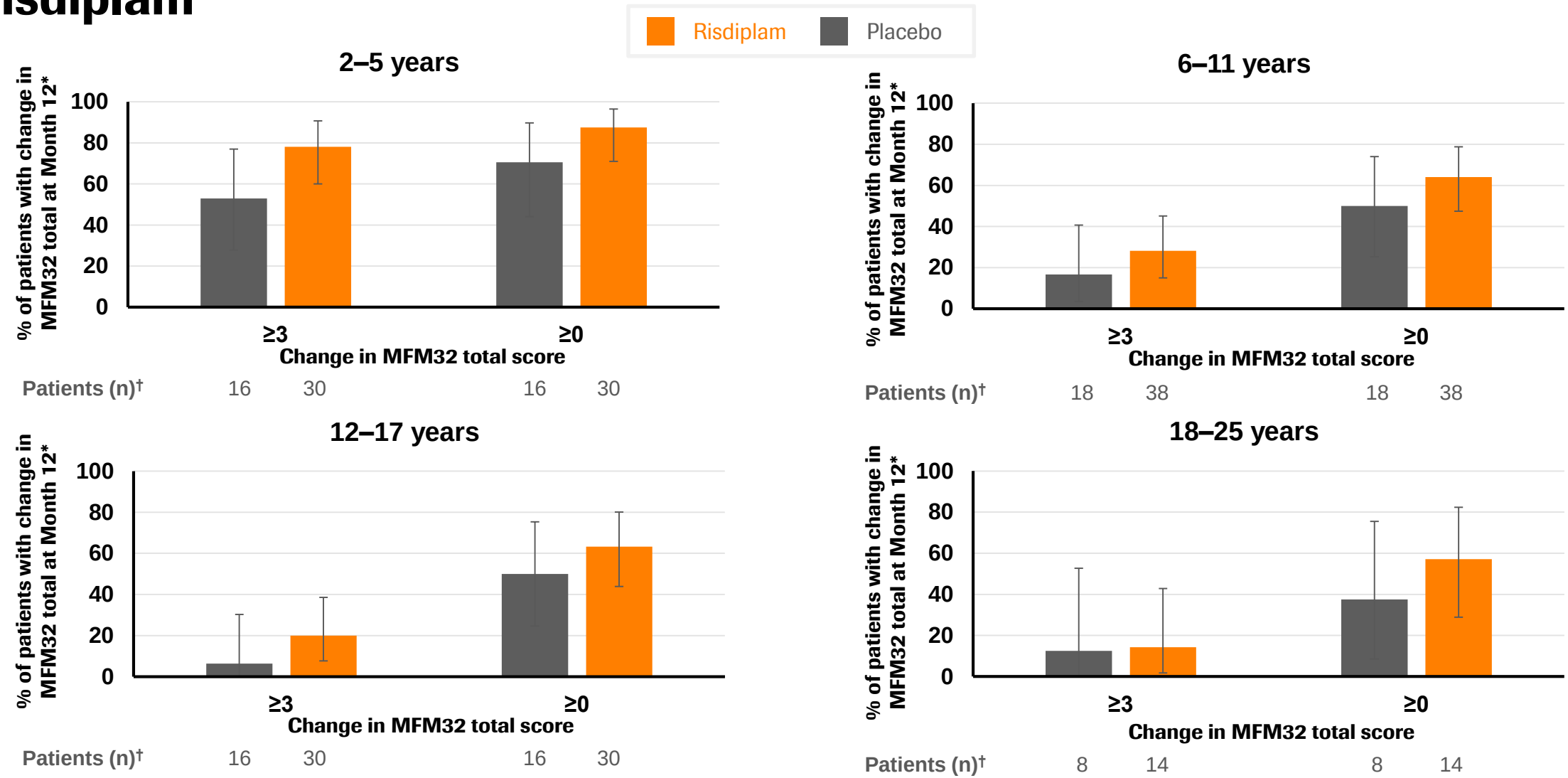
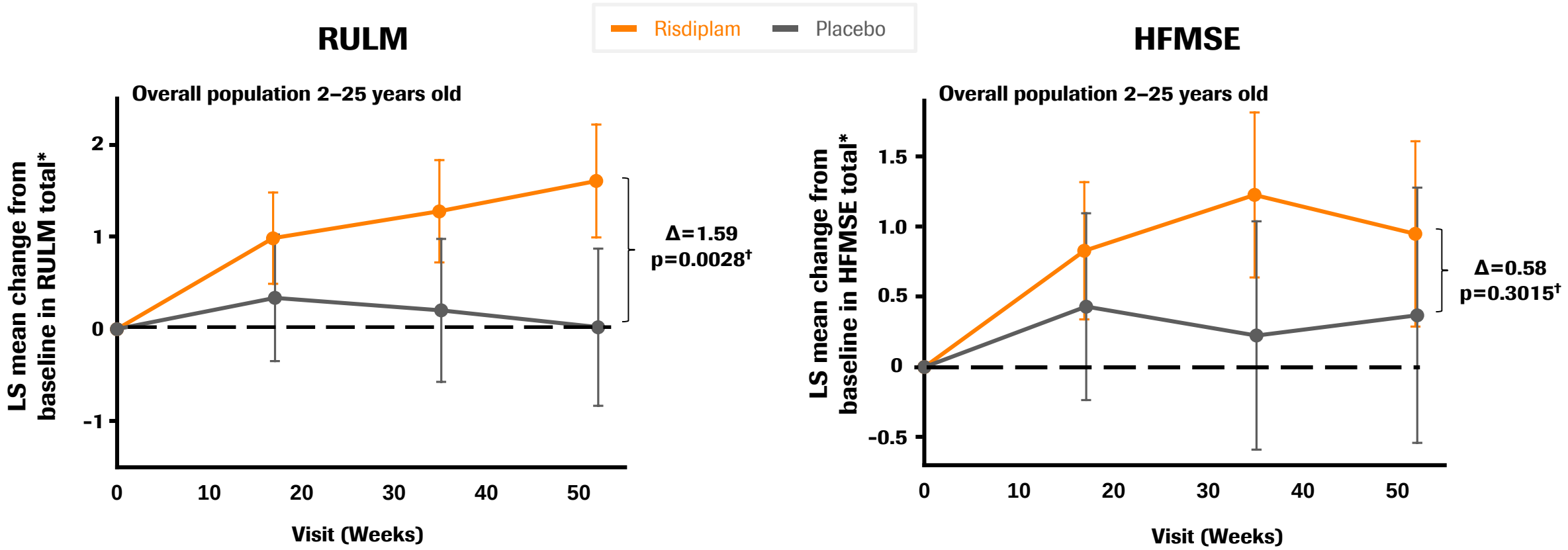
Intent to treat patients. Data cut-off: 6th Sep 2019.
MFM32, 32-item Motor Function Measure.

Improvement or stabilization in MFM32 total in all age groups with risdiplam



*+/- 95% confidence interval. †Number of patients with valid results = number of patients with an available total score (result) at respective time points.
Exploratory analysis. Intent to treat patients. Data cut-off: 6th Sep 2019.
MFM32, 32-item Motor Function Measure.

RULM total change from baseline was significantly greater in patients receiving risdiplam relative to placebo



Risdiplam (n)‡	119	118	116	112
Placebo (n)‡	58	57	56	56

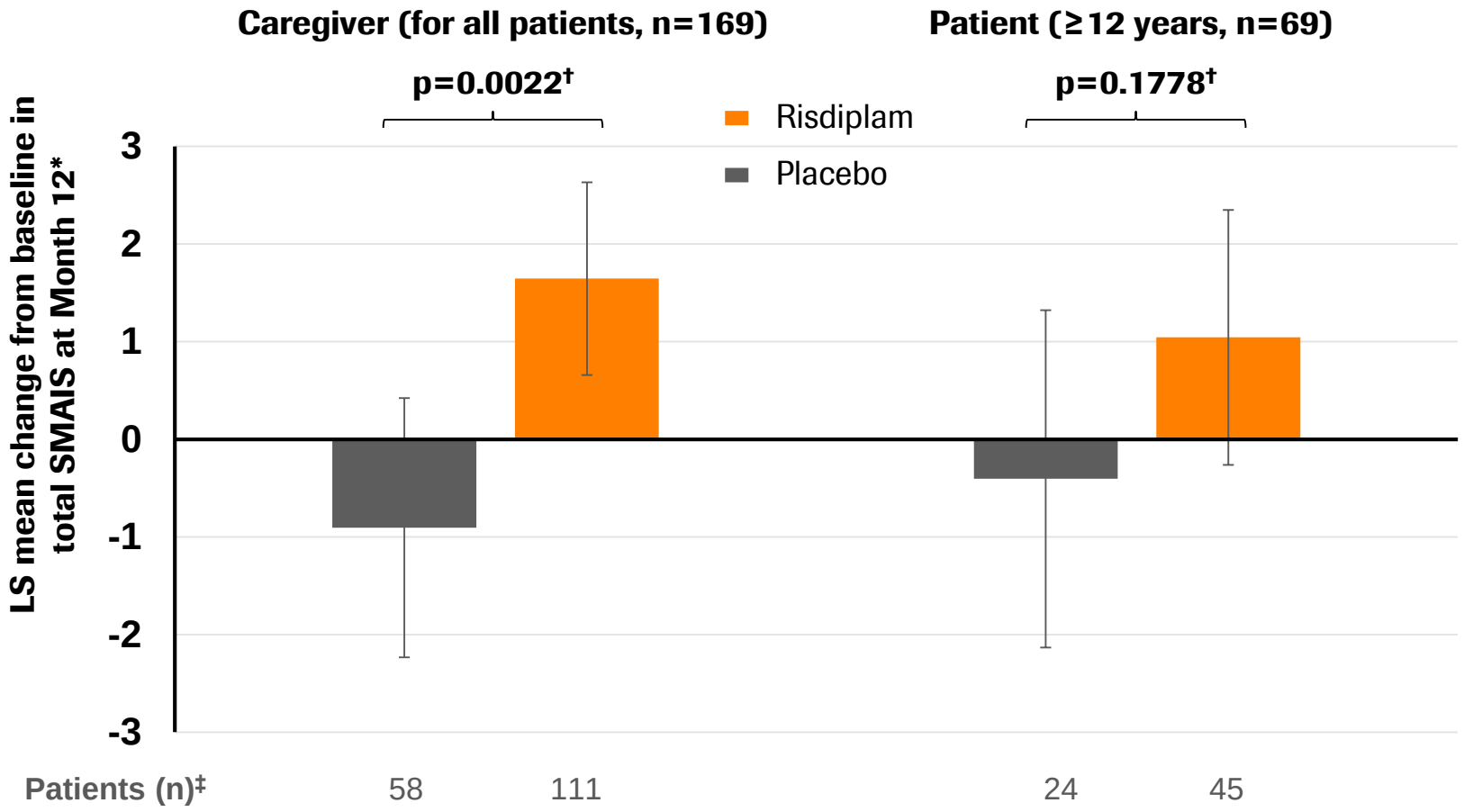
Risdiplam (n)‡	120	119	118	113
Placebo (n)‡	60	60	58	58

*+/- 95% confidence interval. †Mixed Model Repeated Measure, unadjusted p-value at 5% significance level. ‡Number of patients with valid results = number of patients with an available total score (result) at respective timepoints.
Intent to treat patients. Data cut-off: 6th Sep 2019.
HFMSE, Expanded Hammersmith Functional Motor Scale – Expanded; LS, least squares; RULM, Revised Upper Limb Module.

Caregivers and patients (≥12 years) reported improvements in independence after treatment with risdiplam

The SMAIS includes 22 items assessing the level of independence when completing activities of daily living:

- eating a meal using hands, fork or spoon
- brushing teeth
- writing/using a pen



*+/- 95% confidence interval. †Mixed Model Repeated Measure, unadjusted p-value at 5% significance level. ‡Number of patients with valid results = number of patients with an available total score (result) at respective time points.
Intent to treat patients. Data cut-off: 6th Sep 2019.
LS, least squares; SMAIS, SMA Independence Scale.

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

		Risdiplam (n=120)	Placebo (n=60)
Patients with at least one AE, n (%)		111 (92.5)	55 (91.7)
Total number of AEs		789	354
Total number of deaths		0	0
Total number of patients with at least one, n (%)	AE with fatal outcome	0	0
	SAE	24 (20.0)	11 (18.3)
	SAE leading to withdrawal from treatment	0	0
	SAE leading to dose modification/interruption	4 (3.3)	2 (3.3)
	Treatment-related SAE	0	0
	AE leading to withdrawal from treatment	0	0
	AE leading to dose modification/interruption	8 (6.7)	2 (3.3)
	Treatment-related AE	16 (13.3)	6 (10.0)
	Related AE leading to withdrawal from treatment	0	0
	Related AE leading to dose modification/interruption	0	0
	Grade 3–4 AE	21 (17.5)	8 (13.3)

- There was a trend towards more Grade 3 to 4 AEs in patients on risdiplam; however, these AEs generally resolved without changes to study medication

Data cut-off: 6th September 2019.
AE, adverse event; SAE, serious AE.

AEs and SAEs were balanced and reflective of underlying disease

		Risdiplam (n=120)	Placebo (n=60)
Most common AEs, n (number of patients [%])	Upper respiratory tract infection	38 (31.7)	18 (30.0)
	Nasopharyngitis	31 (25.8)	15 (25.0)
	Pyrexia	25 (20.8)	10 (16.7)
	Headache	24 (20.0)	10 (16.7)
	Diarrhoea	20 (16.7)	5 (8.3)
	Vomiting	17 (14.2)	14 (23.3)
	Cough	17 (14.2)	12 (20.0)
Most common SAEs, n (number of patients [%])	Pneumonia	9 (7.5)	1 (1.7)
	Gastroenteritis	2 (1.7)	2 (3.3)
	Bacteremia	2 (1.7)	0 (0)
	Influenza	2 (1.7)	0 (0)
	Pyrexia	2 (1.7)	0 (0)

- Safety laboratory results, vital signs and ECG data were comparable across both arms
- Preclinical safety findings were not observed in any patient*

*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.
Data cut-off: 6th September 2019.
AE, adverse event; ECG, electrocardiogram; SAE, serious AE.

Conclusions from SUNFISH Part 2

MFM32 and RULM scores showed risdiplam significantly improved motor function after 12 months versus placebo

Risdiplam improved independence in activities of daily living using the novel SMAIS measure

No treatment-related safety findings have led to withdrawal in SUNFISH Part 2

Risdiplam is the first treatment to have positive pivotal placebo-controlled data in a broad population of children, teenagers and adults – preserving and potentially enabling motor function independence for patients with Type 2 and non-ambulant Type 3 SMA

MFM-32, 32-item Motor Function Measure; RULM, Revised Upper Limb Module.

Acknowledgments

Many thanks to all the patients who participate in these studies and their families, healthcare professionals and the support of patient groups throughout the world

Multiple motor function endpoints included in SUNFISH Part 2

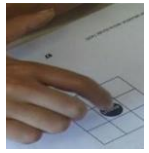
MFM32: selected as **primary endpoint** due to its expected sensitivity for a broad SMA population

- Validated, reliable, and easy-to-conduct test to measure motor function in SMA.
- 32 items classified into 3 domains with a total score of 0–100; higher scores indicate greater motor function.

Domain 1:
standing, transfers and ambulation

Domain 2:
axial and proximal motor function

Domain 3:
distal motor function



RULM (Revised Upper Limb Module): **Secondary EP**

- Next most important endpoint in SUNFISH SAP (after MFM32) due to its focus on upper limb function – especially relevant for a non-ambulant population.
- 19 items scored in a total score of 0-37; higher scores indicate greater upper limb function.
- Items assessed include moving hands from lap to table, bringing a cup to the mouth, as well as items involving weighted objects.

HFMSE (Expanded Hammersmith Functional Motor Scale): **Secondary EP**

- Third ranked endpoint in SUNFISH SAP due to its anticipated lower sensitivity in weaker patients.
- 33 items resulting in a total score of 0 – 66; higher scores indicate greater motor function.
- Items assessed include sitting, rolling, crawling, standing, walking, squatting, jumping and going up and down stairs.

EP= End Point; SAP=statistical analysis plan