Update from SUNFISH Part 1: Safety, tolerability and PK/PD from the dose-finding study, including exploratory efficacy data, in patients with type 2 or 3 spinal muscular atrophy (SMA) treated with risdiplam (RG7916)

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Disclosures

- EM receives fees from AveXis, Biogen and F. Hoffmann-La Roche
- GB was a PI in F. Hoffmann-La Roche and AveXis SMA trials, and received consultancy fees from PTC therapeutics, Sarepta and F. Hoffmann-La Roche
- JK reports grants from Ionis Pharmaceuticals, Biogen, F. Hoffmann-La Roche and Trophos, and has received consultant fees from Biogen, LabConsult, and F. Hoffmann-La Roche
- LS is a PI of SMA studies for Biogen, AveXis and F. Hoffmann-La Roche. He has attended SAB of Biogen and AveXis and received consultancy fees from Biogen
- NG and MCP have no disclosures to report
- 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
- MT, WY, JH and NC are employees of F. Hoffmann-La Roche
- HK, MG, YC, and KG are employees of, and hold shares in, F. Hoffmann-La Roche
- OK and CC are former employees F. Hoffmann-La Roche
- OK is an employee of, and holds shares in, Voyager Therapeutics
- CC is an employee of Therachon AG, and holds shares in F. Hoffmann-La Roche

Introduction

- Risdiplam (RG7916) is an orally administered, centrally and peripherally distributed *SMN2* pre-mRNA splicing modifier that increases the level of functional SMN protein
- Here we present data from Part 1 of the SUNFISH study[1] from patients who have been treated with risdiplam for a minimum of 12 months
- This is compared to 12 month data from Nat-His SMA,[2] a prospective natural history study of individuals with Type 2 and 3 SMA

SUNFISH[1]

Children and young adults with Type 2–3 SMA
2–25 years

SMA, spinal muscular atrophy; SMN, survival of motor neuron.
1. Clinicaltrials.gov: NCT02908685. Accessed May 2019; 2. Chabanon A, et al., 2018.

SUNFISH: Study overview

- SUNFISH (NCT02908685)[1] is a multicenter, two-part, randomized, placebo-controlled, double-blind study
  - Part 1: Dose finding – Identify a recommended dose of risdiplam for Part 2 and assess safety, tolerability, PK and PD of risdiplam
  - Dose selection for Part 2
    - Risdiplam:placebo (2:1) for a minimum of 12 weeks, followed by open-label extension at pivotal dose with the dose selected for Part 2
  - Part 2: Efficacy (MFM32) and safety (enrollment complete)
    - Risdiplam:placebo (2:1) for 12 months, followed by a further 12 months on active treatment and then an open-label extension

SUNFISH[1]
Type 2 or 3 SMA
2–25 years old

Inclusion/exclusion criteria		
Key inclusion criteria	**Part 1 (N=51)** • Type 2 or ambulatory and non-ambulatory Type 3 SMA. • Confirmed genetic diagnosis of SMA.*	**Part 2 (N=180)** • Type 2 or non-ambulatory Type 3 SMA. • Confirmed genetic diagnosis of SMA.*
Key exclusion criteria	• Previous participation in an *SMN2*-targeting study or gene therapy study. • Planned (within 18 months) or previous (<1 year prior) surgery for scoliosis or hip fixation.	

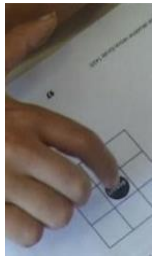
*5q-autosomal recessive SMA. MFM32, Motor Function Measure (32 items); PD, pharmacodynamics, PK, pharmacokinetics; SMA, spinal muscular atrophy; SMN, survival of motor neuron.
1. Clinicaltrials.gov: NCT02908685. Accessed May 2019.

Natural history as measured by MFM32 validated primary outcome measure in SMA

- Part 2 of SUNFISH uses the MFM32 assessment scale as a primary outcome measure
  - A natural history study carried out a year before SUNFISH used many of the same study sites and similar standard of care to generate data that allows for comparison with treatment interventions
- The MFM32 is a 32-item assessment classified into three domains on a 4-point scale (0–96, higher scores indicate motor function)
- The MFM32 has been validated for measuring motor function in patients with neuromuscular diseases, including SMA[1,2]

Domain 1: Standing, transfers and ambulation

Domain 2: Axial and proximal motor function



Domain 3: Distal motor function

MFM32, Motor Function Measure (32 items); SMA, spinal muscular atrophy.

1. Bérard C, et al. Neuromuscul Disord. 2005; 15:463–470; 2. Vuillerot C, et al. Ann Phys Rehabil Med. 2013; 56:673–686. 3. Chabanon A, et al. PLoS One. 2018; 13:e0201004.

Images sourced from: Mesure de Fonction Motrice http://www.motor-function-measure.org/home.aspx.

Natural history cohort (NatHis): Prospective and longitudinal natural history study of patients with Type 2 and 3 SMA assessed with MFM32

9

study sites in France, Germany, and Belgium

81

patients aged 2 – 30 years

- 19 patients were non-sitters with Type 2 SMA
- 34 patients were sitters with Type 2 SMA
- 9 patients were non-ambulant with Type 3 SMA
- 19 patients were ambulant with Type 3 SMA

SMA, spinal muscular atrophy.

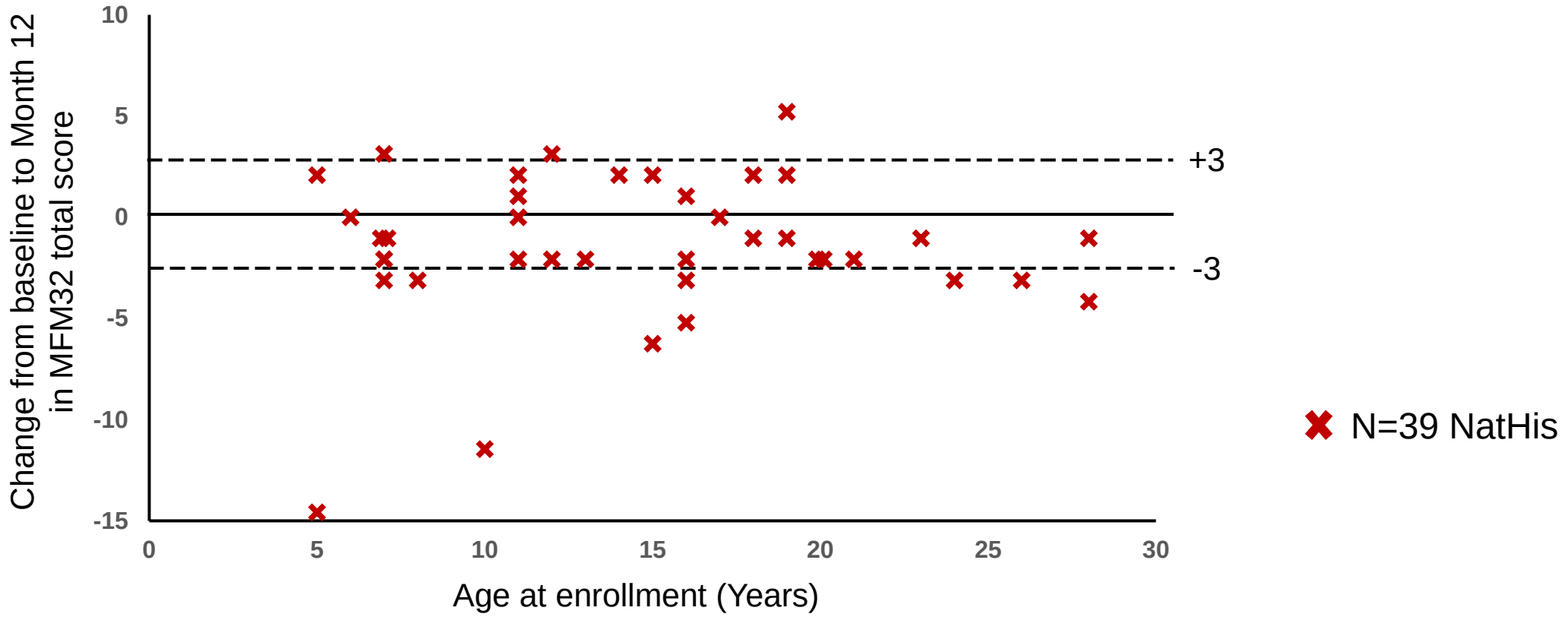
1. Chabanon A, et al. PLoS One. 2018; 13:e0201004; 2. Unpublished new analyses of NatHis Study data.

SUNFISH Part 1: Patient baseline characteristics

	SUNFISH Part 1 ITT population			Natural history[1,2]
Age range (years)	**2–11 (N=31)**	**12–25 (N=20)**	**All (2–25) (N=51)**	**All (2–30) (N=81)**
Age at screening, years, median (range)	5 (2–11)	14.5 (12–24)	7 (2–24)	7.1 (2.1–29.8)[2]
Gender, female/male, n (%)	14 (45.2) / 17 (54.8)	13 (65.0) / 7 (35.0)	27 (52.9) / 24 (47.1)	44 (54.3) / 37 (45.7)[1]
Type 2 SMA, n (%) Type 3 SMA, n (%)	23 (74) 8 (26)	14 (70) 6 (30)	37 (73) 14 (27)	53 (65)[1] 28 (35)[1]
Motor function at baseline Walkers, n (%) Sitters, n (%)* Non-sitters, n (%)*	 6 (19.4) 25 (80.6) 0	 1 (5.0) 8 (40) 11 (55.0)	 7 (13.7) 33 (64.7) 11 (21.6)	 19 (23.5)[1] Reported for Type 2 only[1] 19 (23.5)[1]
Scoliosis, n (%)	13 (42)	16 (80)	29 (57)	45 (55.6)[1]
Baseline MFM32 total score, mean (SD)	44.4 (11.9)	40.9 (18.2)	42.85 (15.0)	(n=46)[2] 52.0 (22.3)

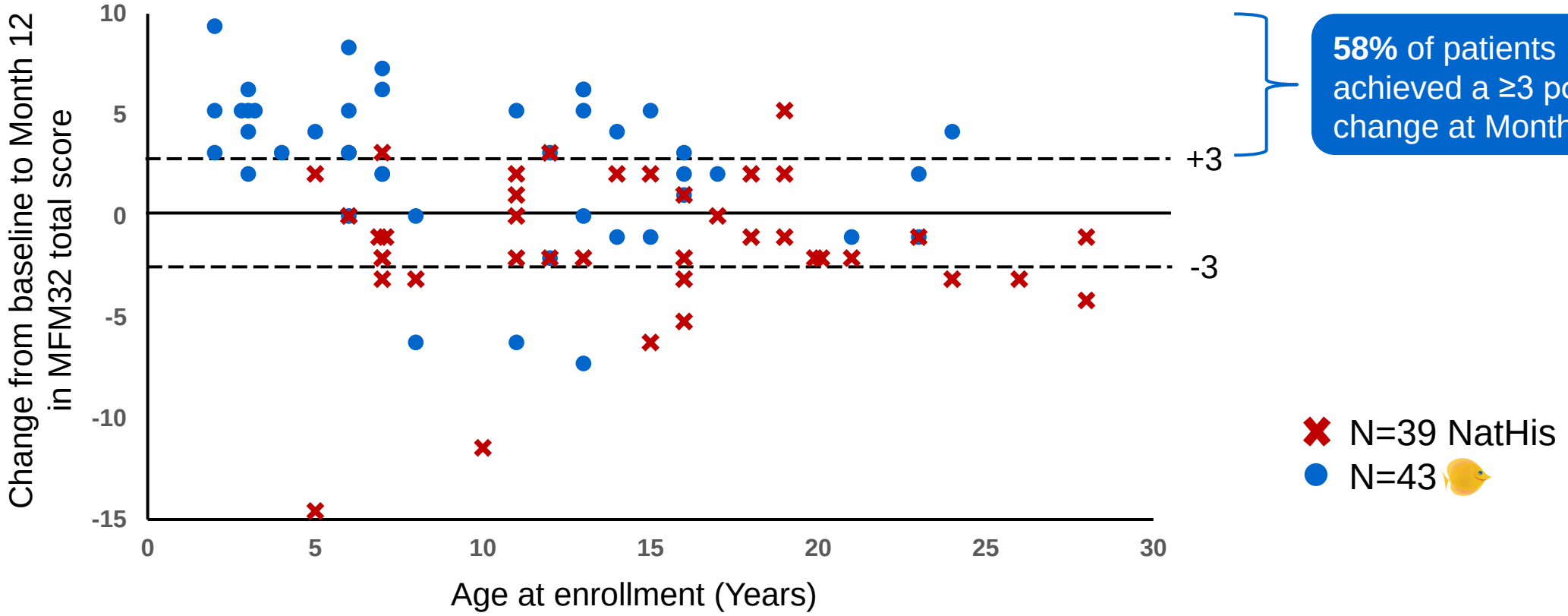
Data cut-off for SUNFISH: 9th Jan 2019.
*Non-sitters are defined as scoring 0 on item 9 of the MFM while sitters scored ≥1 on item 9 of the MFM but did not qualify as ambulant. †Excludes seven patients who performed the MFM20 assessment at baseline.
IQR, interquartile range; ITT, intent to treat; MFM20, Motor Function Measure (20 items); MFM32, Motor Function Measure (32 items); SMA, spinal muscular atrophy; SD, standard deviation.
1. Chabanon A, et al. PLoS One. 2018; 13:e0201004; 2. Unpublished new analyses of NatHis Study.

Patients receiving risdiplam in SUNFISH Part 1 showed improvement compared with natural history, independent of age



MFM32, Motor Function Measure (32 items).

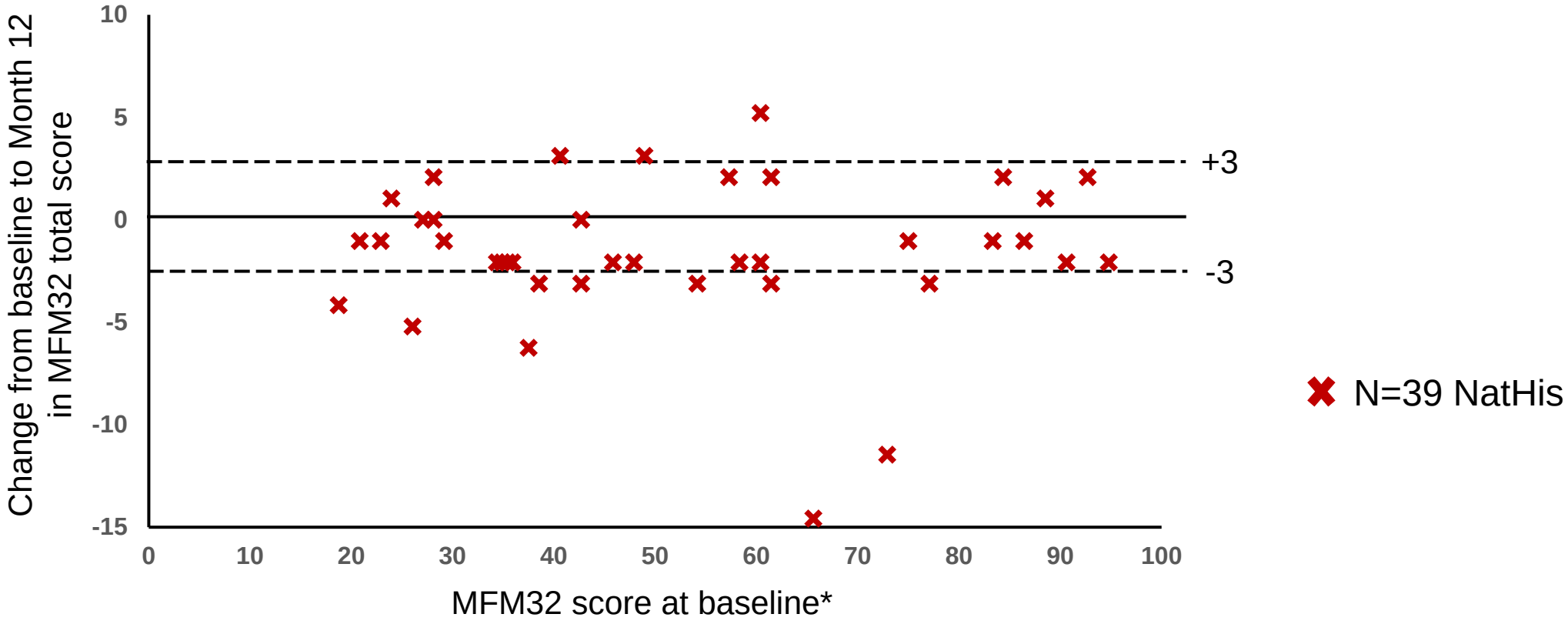
Patients receiving risdiplam in SUNFISH Part 1 showed improvement compared with natural history, independent of age



- The magnitude of improvement may be greater in younger patients (2–11 years)
- MFM32 results only are shown here for ease of comparison. Data from the NatHis study includes individuals ≥5 years only as younger patients were assessed with the MFM20 scale

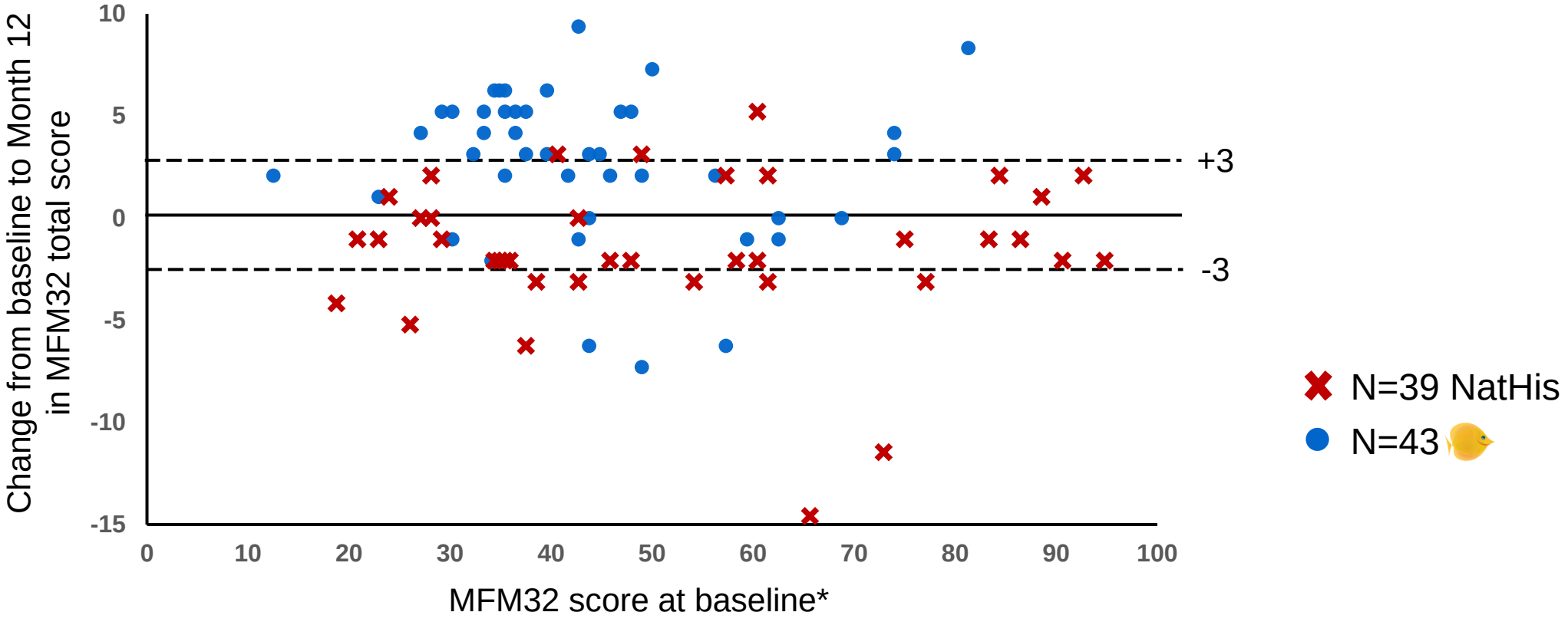
Excludes 7 patients who performed the MFM20 assessment at baseline and one patient who had dropped out of the study prior to the Month 12 visit. Data cut-off: 9th Jan 2019.
MFM32, Motor Function Measure (32 items); MFM20, Motor Function Measure (20 items).

Patients receiving risdiplam in SUNFISH Part 1 showed improvement compared with natural history, independent of disease severity



*Total score at adjusted baseline.
MFM32, Motor Function Measure (32 items).

Patients receiving risdiplam in SUNFISH Part 1 showed improvement compared with natural history, independent of disease severity



*Total score at adjusted baseline.
Excludes 7 patients who performed the MFM20 assessment at baseline and one patient who had dropped out of the study prior to the Month 12 visit. Data cut-off: 9th Jan 2019.
MFM32, Motor Function Measure (32 items); MFM20, Motor Function Measure (20 items).

SUNFISH Part 1 exploratory efficacy: Risdiplam administration led to improvements in motor function

12 months from baseline	SUNFISH Part 1			Natural history
Age range (years)	2–11 (N=24)*	12–25 (N=19)†	All (2–25) (N=43)‡	All (5–30)[1] (N=39)§
Total MFM32 change from baseline, mean (SD)	3.47 (3.77)	1.64 (3.43)	2.66 (3.70)	-1.44 (3.68)
≥3 point change at Month 12, n (95% CI)	**17 (71%) (49–87%)**	**8 (42%) (20–67%)**	**25 (58%) (42%–73%)**	**3 (7.6%) (2%–21%)**

*Excludes seven patients who performed the MFM20 assessment at baseline. †Excludes one patient who had dropped out of the study prior to the Month 12 visit. ‡Excludes seven patients who performed the MFM20 assessment at baseline and one patient who had dropped out of the study prior to the Month 12 visit. §Excludes 32 patients who performed the MFM20 assessment. MFM32 was used for patients older than 6 years, and the MFM20 for children between 2 and 5 years. For patients between 4 and 6 years, the physiotherapist selected either the MFM20 or MFM32 based on the child's abilities, and was instructed to administer the same scale throughout the study.
Based on change from adjusted baseline. SUNFISH data cut-off: 9th Jan 2019.
CI, confidence interval; MFM32, Motor Function Measure (32 items); SD, standard deviation; SMA, spinal muscular atrophy.
1. Unpublished new analyses of NatHis Study data.

SUNFISH Part 1: There have been no deaths or drug-related safety findings leading to withdrawal

		Total patients (N=51)*
Patients with at least one AE, n (%)		48 (94)
Patients with at least one SAE, n (%)		9 (18)
Most common AEs, n (number of patients)	Pyrexia, n (number of patients [%])	21 (41)
	Cough, n (number of patients [%])	17 (33)
	Vomiting, n (number of patients [%])	15 (29)
	Upper respiratory tract infection, n (number of patients [%])	13 (25)
	Oropharyngeal pain, n (number of patients [%])	11 (22)
	Nasopharyngitis, n (number of patients [%])	10 (20)

- 48 patients (94.1%) had at least one AE and 9 patients (17.6%) had at least one SAE
- The most common SAE was pneumonia, reported by 2 patients (4%)
- There have been no drug-related ophthalmological findings to date

*All exposure to risdiplam treatment period. Data cut-off: 9th Jan 2019.
AE, adverse event; SAE, serious adverse event.

Conclusions from SUNFISH Part 1

- All patients in SUNFISH have been treated for at least 12 months
  - Part 1 of SUNFISH has helped determine the dose for Part 2 of the study
- Risdiplam has been well tolerated at all doses and there have been no drug-related safety findings leading to withdrawal of any patient
- There have been no drug-related ophthalmological findings to date
- Exploratory MFM results showed an improvement over 12 months with risdiplam treatment compared with natural history in a broad age range of patients with broad functional status at baseline
- Part 1 and Part 2 of SUNFISH are ongoing globally

MFM, motor function measure; PK/PD, pharmacokinetics/pharmacodynamics; SMN, survival of motor neuron.
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