SUNFISH Part 2: 24-month efficacy of risdiplam compared with external control comparators

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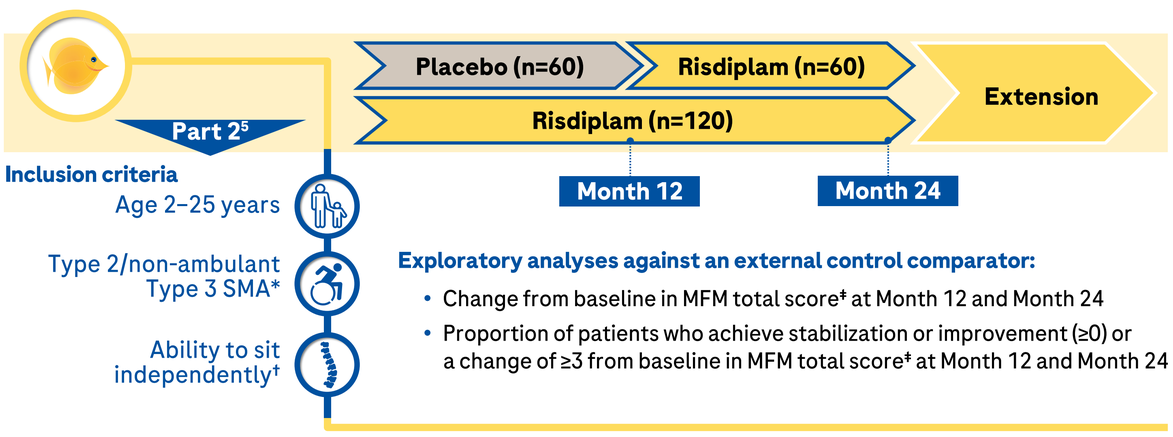
Background

- SMA is a severe, progressive, neuromuscular disease leading to loss of motor function and reduced life expectancy.[1]
- Risdiplam (EVRYSDI®) is a centrally and peripherally distributed, oral *SMN2* pre-mRNA splicing modifier that increases levels of functional SMN protein.[2,3]
  - Risdiplam has been approved for the treatment of patients with SMA aged 2 months and older by the FDA.[4]
- SUNFISH (NCT02908685)[5] is a two-part clinical trial of risdiplam in a broad patient population with Types 2 and 3 SMA (aged 2–25 years).
  - Part 1 was a dose-finding study, which determined the dose for Part 2.
  - Part 2 is the confirmatory study assessing the efficacy of daily, oral risdiplam at the dose selected in Part 1.
- SUNFISH Part 2 met its primary endpoint: 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).[6]
- Patients in the placebo arm of SUNFISH Part 2 were switched to receive risdiplam after 12 months in a blinded manner; there was no placebo group from Month 12 onwards with all patients receiving risdiplam.
- Here we present further analysis of SUNFISH Part 2 efficacy data after 24 months of risdiplam treatment compared with data from an external control comparator group.

Methods

MFM was chosen to compare motor function with an external comparator at Month 12 and Month 24

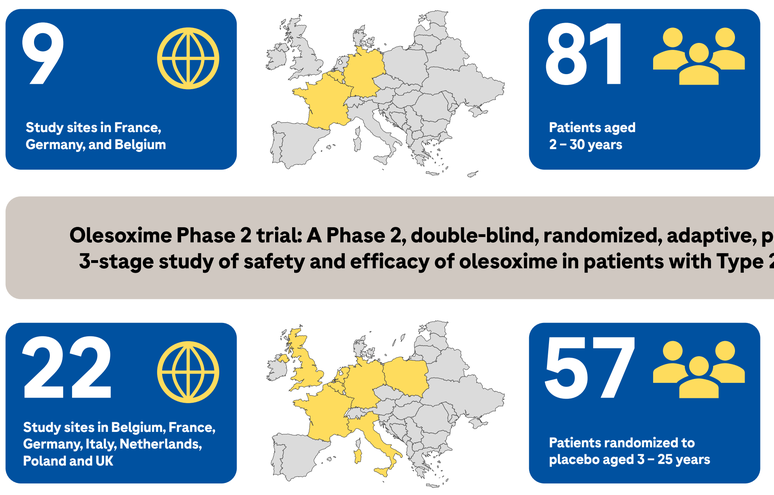


After Month 12 all patients in the study received risdiplam. *Non-ambulant is defined as not having the ability to walk unassisted for ≥10m. †Achieved a score of ≥1 on Item 9 of the MFM32 at baseline. ‡The MFM32 scale was used for participants aged ≥6 years and MFM20 scale was used for participants aged <6 years.

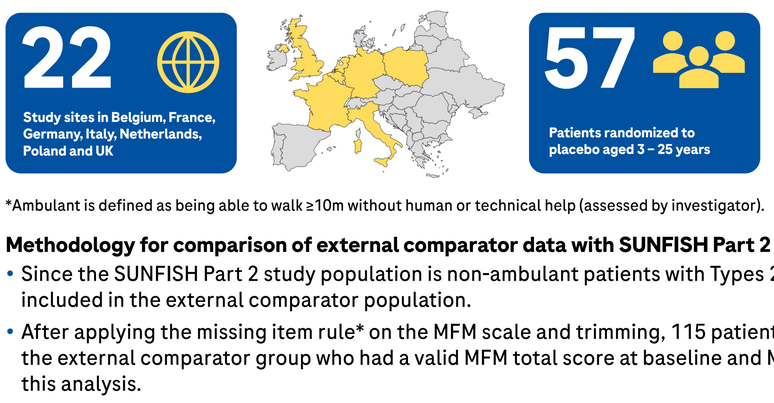
An external comparator group was used to give context to SUNFISH Part 2 results at Month 24

- Motor function data from the risdiplam arm of SUNFISH Part 2 were compared to an external comparator formed from:
  - A population of patients from the NatHis-SMA study (NCT02391831)[7,8]
  - The placebo arm from a Phase 2 trial of olesoxime (NCT01302600).[9,10]

NatHis-SMA: A prospective and longitudinal natural history study of patients with Types 2 and 3 SMA[7,8]



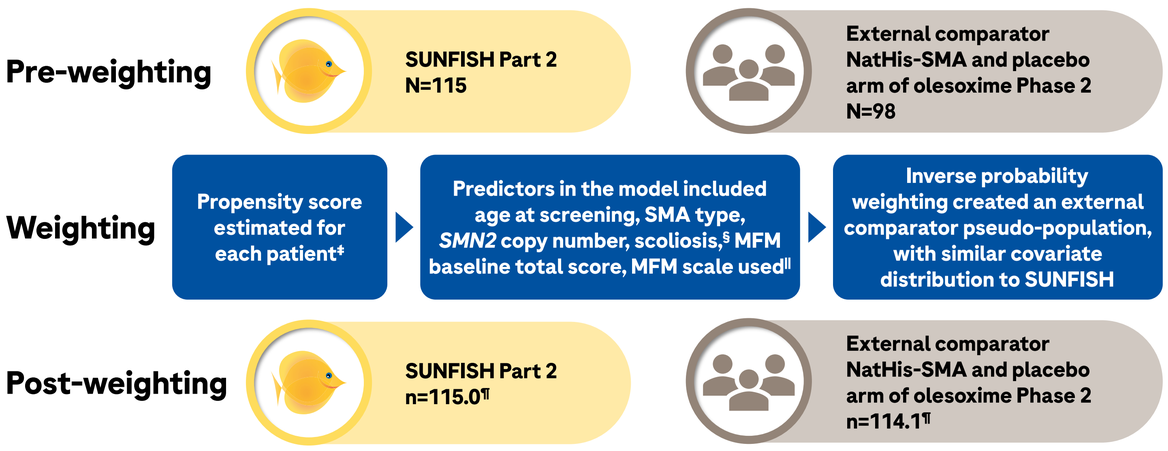
Olesoxime Phase 2 trial: A Phase 2, double-blind, randomized, adaptive, parallel-group, placebo-controlled 3-stage study of safety and efficacy of olesoxime in patients with Type 2 or non-ambulant Type 3 SMA[9,10]



*Ambulant is defined as being able to walk ≥10m without human or technical help (assessed by investigator).

Methodology for comparison of external comparator data with SUNFISH Part 2

- Since the SUNFISH Part 2 study population is non-ambulant patients with Types 2 and 3 SMA, ambulant patients were not included in the external comparator population.
- After applying the missing item rule* on the MFM scale and trimming, 115 patients in SUNFISH Part 2 and 98 patients from the external comparator group who had a valid MFM total score at baseline and Month 12 or Month 24 were included in this analysis.
- To ensure robust analysis, patients from the external comparator dataset were selected based upon similarities to the SUNFISH Part 2 population (demographics, disease characteristics, MFM endpoint).
- After excluding patients with missing prognostic factors†, 98 patients in the external comparator arm with valid MFM data were selected for weighting. Patients in the external control group were weighted using Inverse Probability of Treatment Weighting based upon selected prognostic factors† at baseline.
  - Weights were summed to generate an external comparator population of 114.1.
  - All patients from SUNFISH Part 2 were each given a weight of 1.0 to give a population of 115.0.
- Change from baseline in MFM total score was analyzed using MMRM with time and prognostic factors† as covariates.
- Proportion of patients demonstrating improvement or stabilization were analyzed with logistic regression.



*Missing item rule – for the calculation of total domain scores, D1, D2 and D3, within each domain, total domains scores were only calculated if there were ≤15% of items missing. MFM total scores were only calculated where there is a calculated score for each domain (D1, D2 and D3). Missing MFM total scores were not imputed. Patients without a baseline MFM total score derived were not included in the analysis. †Prognostic factors – age, SMA type, *SMN2* copy number, scoliosis§, MFM total score, MFM scale used. ‡Using logistic regression incorporating potential predictors of treatment assignment (risdiplam versus no risdiplam) as independent variables. §Presence at screening (yes, no). ‖MFM20 or MFM32. ¶n=sum of weights.

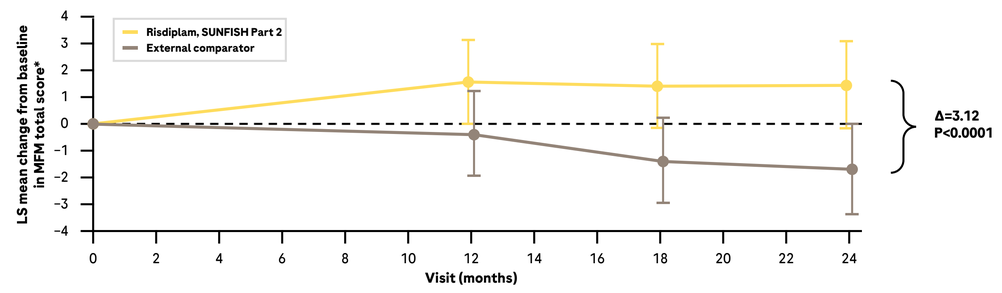
Results

Patient baseline characteristics

	SUNFISH Part 2 risdiplam arm, patients after weighting (n=115.0)*	External comparator (n=114.1)*
Age at enrollment, years, median (range)	10 (2–25)	8 (2–28)
Age group		
2–5	34.0 (30)	33.2 (29)
6–11	37.0 (32)	35.9 (31)
12–18	34.0 (30)	32.5 (29)
>18	10.0 (9)	12.5 (11)
Gender, n (%)		
Female	60.0 (52)	62 (54)
Male	55.0 (48)	52 (46)
SMA type, n (%)		
2	81.0 (70)	81.5 (71)
3	34.0 (30)	32.6 (29)
***SMN2* copy number, n (%)**		
2	3.0 (2.6)	2.6 (2.3)
3	103.0 (89.6)	102.2 (89.6)
4	9.0 (7.8)	9.2 (8.1)
Scoliosis, n (%)	75.0 (65)	74.8 (66)
MFM total score, mean (SD)†		
MFM20	(n=34.0) 51.1 (10.7)	(n=33.2) 49.1 (12.6)
MFM32	(n=81.0) 45.5 (12.7)	(n=80.9) 46.2 (13.0)

*n=sum of weights. †MFM (derived) total score means the MFM20 total score is used for all patients aged <6 years and the MFM32 total score is used for all patients aged ≥6 years. Both scales were transformed to 0–100%. SUNFISH Data cut-off: 30 Sep 2020.

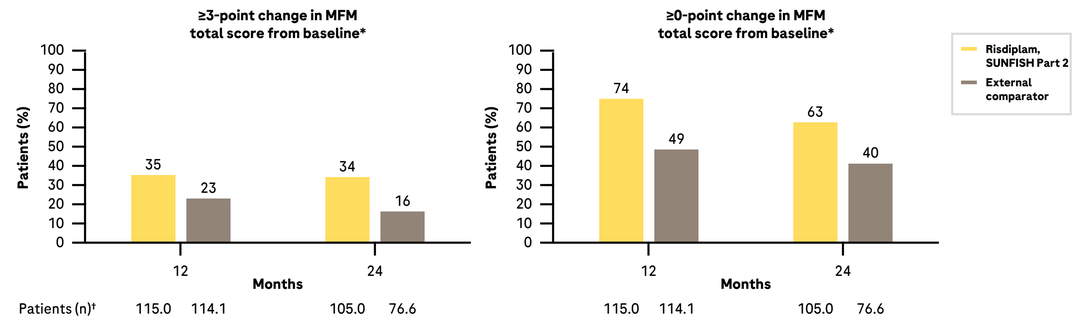
Increases in MFM total score at Month 12 were observed in patients treated with risdiplam. Increases were sustained over 24 months, in contrast to a progressive decline in the untreated external comparator



*±95% CI, weighted analysis of change from baseline, MMRM (Risdiplam, SUNFISH Part 2 n=115.0; external comparator n=114.1, n=sum of weights at baseline). Patients with baseline and at least one post-baseline timepoint at Month 12 or Month 24 with MFM32 total score were included in the analysis. MFM (derived) total score means the MFM20 total score is used for all patients aged <6 years and MFM32 total score is used for all patients aged ≥6 years. Both scales were transformed to 0–100%. SUNFISH Data cut-off: 30 Sep 2020.

- A comparison of SUNFISH Part 2 patients treated with risdiplam for 24 months with patients from the external comparator showed a mean difference in MFM total score of 3.12 (95% CI: 1.67–4.57, P<0.0001).
  - Weighted analysis at Month 12 showed a mean difference in MFM total score of 1.93 (95% CI: 0.71–3.15, P=0.002) between the risdiplam group and external comparator.
  - Weighted analysis at Month 12 was consistent with the primary endpoint analysis from SUNFISH Part 2 which reported a mean treatment difference of 1.55 (95% CI: 0.30–2.81, P=0.016) in MFM32 total score at Month 12 in favor of risdiplam compared with placebo.[6]
  - At Month 12 the mean change in MFM total score was −0.37 (95% CI: −1.96–1.22) in the external comparator group, compared with −0.19 (95% CI: −1.22–0.84) for the placebo group from SUNFISH Part 2.

Risdiplam administration over 24 months led to improvement or stabilization in motor function at 12 and 24 months



*Weighted analysis. For Month 12 results, patients with baseline and Month 12 results were included in the analysis. For Month 24 analysis, patients with baseline and Month 24 results are included in the analysis. Based on change from adjusted baseline. †n=sum of weights. SUNFISH data cut-off: 30 Sep 2020.

- The proportion of patients in SUNFISH Part 2 that demonstrated a marked improvement (a change of ≥3 points) or stabilization (a change of ≥0 points) in MFM total score at Month 24 was significantly larger than in the untreated external comparator (P=0.025 and P=0.002, respectively).

Conclusions

- Using an external comparator as a control group allowed the efficacy of risdiplam to be evaluated where there was no direct placebo comparison.
- Weighted analyses of MFM total score showed that risdiplam treatment in SUNFISH Part 2 led to an increase in mean score from baseline at Month 24, which was significantly different to the decrease observed in an untreated external comparator.
- After 24 months of treatment a statistically significant higher proportion of individuals treated with risdiplam showed improvement or stabilization (≥3- or ≥0-point change, respectively) in MFM total score compared with an untreated external comparator.
- External control comparison further supports the robustness of the conclusions from the 12-month placebo-controlled period and provides further confirmation of longer-term efficacy of risdiplam in a broad population of individuals with Type 2 and non-ambulant Type 3 SMA.

Abbreviations

CI, confidence interval; D, domain; FDA, Food and Drug Administration; MFM, Motor Function Measure; MFM20, 20-item MFM; MFM32, 32-item MFM; MMRM, mixed model for repeated measure; LS, least-squares; NatHis, natural history; SD, standard deviation; SMA, spinal muscular atrophy; SMN, survival of motor neuron.

Acknowledgments

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