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, SMU pro-MSN splicing modifier that increases levels of functional SMN protein.

Risdiplam has been approved for the treatment of patients with SMA aged 2 months and older by the FDA.2

- 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)
  - Part 1 was a dose-finding study, which determined the dose for Part 2.
  - Part 2 (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 change from baseline in MFM32 total score at Month 12 in patients treated with risdiplam (+12.0) versus placebo (+0.0),2
- 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 comparator group.

Methods

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

- For MFM, there is no direct placebo comparison.
- 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<0.0007) between the risdiplam group and external comparator.
- Weighted analysis at Month 12 showed a mean difference in MFM total score of 1.92 (95% CI: 0.17-3.65, P=0.02), which was consistent with the primary endpoint analysis from SUNFISH Part 2 which reported a mean treatment difference of 1.55 (95% CI: 0.26-2.81, P=0.017) in MFM32 total score at Month 12 in favor of risdiplam compared with placebo.

- At Month 12, the MFM total mean score was 105.0 (95% CI: 71-157.6) in the external comparator group and 109.7 (95% CI: 100.5-119.0) in the placebo group.

- In the placebo arm of SUNFISH Part 2, patients after weighting

- 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 compared with an untreated external comparator (≥3 points, 21.0% (95% CI: 11.7-31.0); ≥0 points, 66.0% (95% CI: 54.7-76.2)) was significantly larger than in the untreated external comparator (P=0.002 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.
- The proportion of patients in SUNFISH Part 2 that demonstrated a marked improvement in MFM total score from baseline at Month 24 was significantly higher compared with the placebo group (P=0.002).
- After 24 months of treatment, patients in the placebo arm of SUNFISH Part 2 showed a statistically significant improvement compared with the placebo group, confirming the efficacy of risdiplam in the treatment of SMA Type 2 and 3.

References