Safety and efficacy of once-daily risdiplam in type 2 and non-ambulant type 3 spinal muscular atrophy (SUNFISH part 2): a phase 3, double-blind, randomised, placebo-controlled trial

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Summary

Background Risdiplam is an oral small molecule approved for the treatment of patients with spinal muscular atrophy, with approval for use in patients with type 2 and type 3 spinal muscular atrophy granted on the basis of unpublished data. The drug modifies pre-mRNA splicing of the *SMN2* gene to increase production of functional SMN. We aimed to investigate the safety and efficacy of risdiplam in patients with type 2 or non-ambulant type 3 spinal muscular atrophy.

Methods In this phase 3, randomised, double-blind, placebo-controlled study, patients aged 2–25 years with confirmed 5q autosomal recessive type 2 or type 3 spinal muscular atrophy were recruited from 42 hospitals in 14 countries across Europe, North America, South America, and Asia. Participants were eligible if they were non-ambulant, could sit independently, and had a score of at least 2 in entry item A of the Revised Upper Limb Module. Patients were stratified by age and randomly assigned (2:1) to receive either daily oral risdiplam, at a dose of 5·00 mg (for individuals weighing ≥20 kg) or 0·25 mg/kg (for individuals weighing <20 kg), or daily oral placebo (matched to risdiplam in colour and taste). Randomisation was conducted by permutated block randomisation with a computerised system run by an external party. Patients, investigators, and all individuals in direct contact with patients were masked to treatment assignment. The primary endpoint was the change from baseline in the 32-item Motor Function Measure total score at month 12. All individuals who were randomly assigned to risdiplam or placebo, and who did not meet the prespecified missing item criteria for exclusion, were included in the primary efficacy analysis. Individuals who received at least one dose of risdiplam or placebo were included in the safety analysis. SUNFISH is registered with ClinicalTrials.gov, NCT02908685. Recruitment is closed; the study is ongoing.

Findings Between Oct 9, 2017, and Sept 4, 2018, 180 patients were randomly assigned to receive risdiplam (n=120) or placebo (n=60). For analysis of the primary endpoint, 115 patients from the risdiplam group and 59 patients from the placebo group were included. At month 12, the least squares mean change from baseline in 32-item Motor Function Measure was 1·36 (95% CI 0·61 to 2·11) in the risdiplam group and –0·19 (–1·22 to 0·84) in the placebo group, with a treatment difference of 1·55 (0·30 to 2·81, p=0·016) in favour of risdiplam. 120 patients who received risdiplam and 60 who received placebo were included in safety analyses. Adverse events that were reported in at least 5% more patients who received risdiplam than those who received placebo were pyrexia (25 [21%] of 120 patients who received risdiplam *vs* ten [17%] of 60 patients who received placebo), diarrhoea (20 [17%] *vs* five [8%]), rash (20 [17%] *vs* one [2%]), mouth and aphthous ulcers (eight [7%] *vs* 0), urinary tract infection (eight [7%] *vs* 0), and arthralgias (six [5%] *vs* 0). The incidence of serious adverse events was similar between treatment groups (24 [20%] of 120 patients in the risdiplam group; 11 [18%] of 60 patients in the placebo group), with the exception of pneumonia (nine [8%] in the risdiplam group; one [2%] in the placebo group).

Interpretation Risdiplam resulted in a significant improvement in motor function compared with placebo in patients aged 2–25 years with type 2 or non-ambulant type 3 spinal muscular atrophy. Our exploratory subgroup analyses showed that motor function was generally improved in younger individuals and stabilised in older individuals, which requires confirmation in further studies. SUNFISH part 2 is ongoing and will provide additional evidence regarding the long-term safety and efficacy of risdiplam.

Funding F Hoffmann-La Roche.

Introduction

Spinal muscular atrophy is an autosomal recessive neuromuscular disease caused by insufficient survival motor neuron protein (SMN) due to homozygous deletion of or loss-of-function mutations within the *SMN1* gene.[1,2] *SMN2* pre-mRNA transcript undergoes alternative

Research in context

Evidence before this study

We searched PubMed from database inception to May 3, 2016, for publications that featured the search term "spinal muscular atrophy". Results were filtered to include only articles that reported data from clinical trials, and thus we identified a total of 53 articles. 32 studies reported on non-disease-modifying and supportive therapies and two articles reported data from the same phase 1 trial investigating nusinersen, an intrathecally administered antisense oligonucleotide. Five articles reported data from observational studies, six reported data for specified symptoms, three reported on assessments in patients with spinal muscular atrophy, and two reported on candidates for biomarkers. The remaining three studies reported on carrier frequency and diagnostic screening. In 2016, at the time of the design of the SUNFISH study, there were no approved treatments for patients with spinal muscular atrophy.

Spinal muscular atrophy is caused by a deficiency of survival motor neuron protein (SMN). Evidence from mouse models showed that by increasing SMN expression in the CNS and in peripheral tissue, orally administered *SMN2* splicing modifiers, such as risdiplam, might provide additional benefit on treatment that increases SMN in the CNS alone. Proof of concept of this approach had already been established with a previous oral *SMN2* splicing modifier molecule (ie, RG7800 [also known as RO6885247]) in patients with spinal muscular atrophy. A single-ascending dose study in healthy volunteers in 2016 showed that risdiplam modified the splicing of *SMN2* mRNA in humans. Since the SUNFISH study began in 2016, three treatments have been approved for spinal muscular atrophy: nusinersen, onasemnogene abeparvovec, and risdiplam. Ten articles reported data from clinical trials investigating nusinersen, including one that reported data from infants with presymptomatic spinal muscular atrophy and four that reported data from patients with type 1 spinal muscular atrophy. Four articles reported data from patients with type 2 or type 3 spinal muscular atrophy; one was a randomised controlled trial. A final randomised controlled trial reported data for individuals with type 1 or type 2 spinal muscular atrophy who were not eligible for other nusinersen trials. Two manuscripts reported data from open-label studies of onasemnogene abeparvovec in patients with type 1 spinal muscular atrophy. Two articles have reported data from clinical trials of risdiplam: results from parts 1 and 2 of the open-label FIREFISH study (NCT02913482) have shown the efficacy and safety of risdiplam in infants with type 1 spinal muscular atrophy.

Added value of this study

In this study, we bring level 1 evidence that risdiplam treatment resulted in greater improvements in motor function than did placebo in individuals with type 2 or non-ambulant type 3 spinal muscular atrophy. The SUNFISH study is, to our knowledge, the first clinical trial to report efficacy of a treatment for spinal muscular atrophy across a broad age group, which included children, teenagers, and adults with a wide range of functional ability and comorbidities, such as scoliosis and contractures.

Implications of all the available evidence

Together with results from the FIREFISH trial, the results of SUNFISH part 2 provide evidence of the efficacy and safety of risdiplam in a broad range of patients with spinal muscular atrophy.

splicing to exclude exon 7, resulting in low expression of functional SMN, which is unable to compensate for the loss of *SMN1*.[3,4]

Spinal muscular atrophy is characterised by progressive motor neuron degeneration and muscle weakness[2] and encompasses a broad continuum of disease severity, which is clinically classified according to the maximum motor milestones reached.[2] For example, individuals with type 2 spinal muscular atrophy have symptom onset between 6 months and 18 months of age,[2] acquire an autonomous sitting position, and might stand with support but never walk independently.[2,5] Individuals with type 3 spinal muscular atrophy present with symptoms after 18 months of age and are able to walk independently, but many lose this ability over time.[2,5]

There are three approved treatments for spinal muscular atrophy: nusinersen, an intrathecally administered *SMN2*-targeting antisense oligonucleotide;[6,7] onasemnogene abeparvovec, an intravenously administered adenovirus-associated gene therapy;[8,9] and risdiplam, an orally administered small molecule. Risdiplam modifies *SMN2* pre-mRNA splicing to promote inclusion of exon 7 and increase production of functional SMN[10] and has been approved for the treatment of patients aged at least 2 months by the US Food and Drug Administration,[11] and for patients aged at least 2 months with type 1, type 2, or type 3 spinal muscular atrophy or 1–4 SMN2 gene copies in the EU by the European Medicines Agency.[12]

SUNFISH (NCT02908685) is a two-part randomised study assessing efficacy, safety, tolerability, pharmacokinetics, and pharmacodynamics of risdiplam in participants aged 2–25 years with type 2 or type 3 spinal muscular atrophy. Here, we report the results of SUNFISH part 2, the pivotal study that led to approval of risdiplam in patients with type 2 and type 3 spinal muscular atrophy.

Methods

Study design

SUNFISH part 1 was an exploratory, dose-finding study conducted in 51 individuals with ambulant or non-ambulant type 2 or type 3 spinal muscular atrophy, which determined the dose for use in part 2.[13] Part 1 and

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See Online for appendix

part 2 had different patient cohorts. Here, we present the primary analyses from SUNFISH part 2 after 12 months of treatment.

SUNFISH part 2 was a multicentre, phase 3, double-blind, randomised, placebo-controlled trial. The study was conducted at 42 hospitals in Belgium, Brazil, Canada, China, Croatia, France, Italy, Japan, Poland, Russia, Serbia, Spain, Turkey, and the USA. This study was conducted in accordance with the principles of the Declaration of Helsinki, in full conformance with Good Clinical Practice guidelines, and in accordance with regulations and procedures outlined in the study protocol (appendix pp 30–182). The study was approved by the independent research ethics board at each participating site. Safety data were reviewed by an independent data monitoring committee on an ongoing basis.

Participants

Eligible individuals were aged 2–25 years with genetically confirmed 5q autosomal recessive spinal muscular atrophy. Individuals were non-ambulant (ie, unable to walk unassisted for ≥10 m), able to sit independently (ie, a score of ≥1 on item 9 of the 32-item Motor Function Measure [MFM32]; "with support of one or both upper limbs, maintains the seated position for 5 seconds"[14]), had a score of at least 2 in entry item A of the Revised Upper Limb Module (RULM; "can raise 1 or 2 hands to mouth, but cannot raise a 200 g weight to mouth"[15]), and had a negative pregnancy test and agreed to comply with measures to prevent pregnancy. There were no exclusion criteria related to the degree of scoliosis, contractures, feeding support, or non-invasive ventilation. Individuals were excluded from study entry if they had received treatment with an *SMN2*-targeting therapy or gene therapy. A full list of inclusion and exclusion criteria are in the appendix (pp 3–5).

Patients were recruited by the principal investigators (appendix pp 1–2) primarily from individual site databases and by referrals from other physicians or spinal muscular atrophy family support organisations. Written informed consent was provided by the patient or the patient's legally authorised representative before participation.

Randomisation and masking

Participants were randomly assigned to receive either risdiplam or placebo (in a 2:1 ratio) and stratified by age (aged 2–5 years, 6–11 years, 12–17 years, and 18–25 years) with permutated block randomisation (six patients per block and unknown to all individuals except for the sponsor statistician) by use of a computerised interactive (automated) response system, outsourced to an external party (ALMAC, Craigavon, UK). The randomisation list was maintained and concealed by the external party.

Employees of the sponsor who were involved in study management and data analysis were masked to treatment assignment until the primary analysis. Patients, investigators, and all individuals in direct contact with patients at each site (except for unblinded pharmacists handling study medication) were masked to treatment assignment until the final patient completed 24-month assessments. Masking was done by matching the placebo solution to that of risdiplam in colour and taste. A masking assessment was performed by the sponsor, initially via an in vitro taste assessment with an electronic tongue;[16] a taste assessment was also performed in healthy volunteers in the phase 1 study.[17]

Procedures

Risdiplam or placebo powders were dissolved in purified water to a concentration of 0·75mg/mL for risdiplam. Study medication was taken orally at home, once daily in the morning with the regular morning meal. On days with site visits (ie, during weeks 1, 2, 4, 8, 17, 26, 35, 43, and 52; appendix pp 24–26), study medication was administered at the clinical site. Risdiplam was administered at the dose determined in SUNFISH part 1 (ie, 5·00 mg daily for individuals weighing ≥20 kg or 0·25 mg/kg daily for individuals weighing <20 kg).

The study had a screening period of up to 30 days, and a randomised, double-blind, 12-month placebo-controlled period, followed by a second 12-month open-label period where all individuals received risdiplam. After completion of the 24-month treatment period, individuals could continue in the open-label extension for 3 years.

This Article reports data from the 12-month double-blind period of the study. See the appendix (pp 24–26) for the full schedule of assessments.

Outcomes

The study had one primary endpoint and six key secondary endpoints, arranged into six families to enable hierarchical statistical analysis. The assessments for each of the endpoints were conducted in hierarchical order at the prespecificed trial visits. The primary endpoint (ie, family 1) was the change from baseline in MFM32 total score at month 12 in the risdiplam versus placebo group (ie, scores expressed as a percentage of the maximum score of 96; higher scores indicate better motor function than do lower scores) assessed at each site. MFM32 total score was chosen as the primary endpoint for SUNFISH as it is a validated assessment of motor function ability in patients with neuromuscular diseases.[14] Additional validation, including in individuals with non-ambulant types 2 and type 3 spinal muscular atrophy aged 2–25 years, has been conducted.[18] MFM32 comprises three domains—D1 (standing and transfers), D2 (axial and proximal function), and D3 (distal motor function)—and therefore has the ability to assess motor functions across a broad range of patients with spinal muscular atrophy at different stages of disease progression.

The six key secondary endpoints at month 12, listed in the hierarchical order used for statistical testing, were the proportion of patients who had marked improvement (ie, a change from baseline of ≥3 points) in MFM32 total

score (ie, family 2); the change from baseline in RULM total score (ie, family 3; scores ranging 0–37; higher scores indicate better motor function than do lower scores); change from baseline in the Hammersmith Functional Motor Scale—Expanded (HFMSE) total score (ie, scores ranging 0–66; higher scores indicate better motor function than do lower scores) and change from baseline in best percentage-predicted value in forced vital capacity (ie, both within family 4); change from baseline in upper limb total score on the Spinal Muscular Atrophy Independence Scale (SMAIS) as reported by caregivers (ie, family 5; scores ranging 0–44; higher scores indicate greater independence in completing daily activities than do lower scores); and the proportion of patients rated by clinician as "Improved" on the Clinical Global Impression of Change (CGI-C) scale (ie, family 6).

Other secondary endpoints were the proportions of individuals who had stabilisation or improvement (ie, a change from baseline of ≥0) on the MFM32, RULM, and HFMSE; the proportion of individuals whose MFM32 total score improved by at least 1 SEM (calculated at baseline); change from baseline in MFM32 individual domain scores of D1, D2, D3, D1 and D2 combined score, and D2 and D3 combined score (as per the MFM32 user manual, domain or combined total scores are expressed as a percentage of the sum of all items scores in each domain or combined domains relative to the maximum possible score); change from baseline in best percentage-predicted value in sniff nasal inspiratory pressure, best maximal inspiratory pressure, best maximal expiratory pressure, forced expiratory volume over 1 s, and peak cough flow; the proportion of individuals rated by clinicians as "No change" or "Improved" on the CGI-C scale; and change from baseline in upper limb total score on SMAIS as reported by the patient. A full list of study endpoints is in the appendix (pp 5–6).

Ophthalmological monitoring, including optical coherence tomography, was performed and safety was evaluated throughout the study, consisting of the monitoring and recording of adverse events, including serious adverse events, laboratory assessments, vital signs, and electrocardiograms (see appendix pp 24–26 for full schedule of assessments).

Statistical analysis

SUNFISH part 2 had a target sample size of 168 individuals to be randomly assigned (2:1) to receive risdiplam (n=112) or placebo (n=56). For the primary endpoint of mean change from baseline in MFM32 total score at month 12, this sample size provided at least 80% power at a two-sided 5% significance level for testing the null hypothesis that the true treatment difference was zero versus the alternative hypothesis, given that the true treatment difference was 3 and assuming that the common standard deviation would be 6, corresponding to a hypothesised effect size of 0·5. The minimal detectable treatment difference was approximately 2·03.

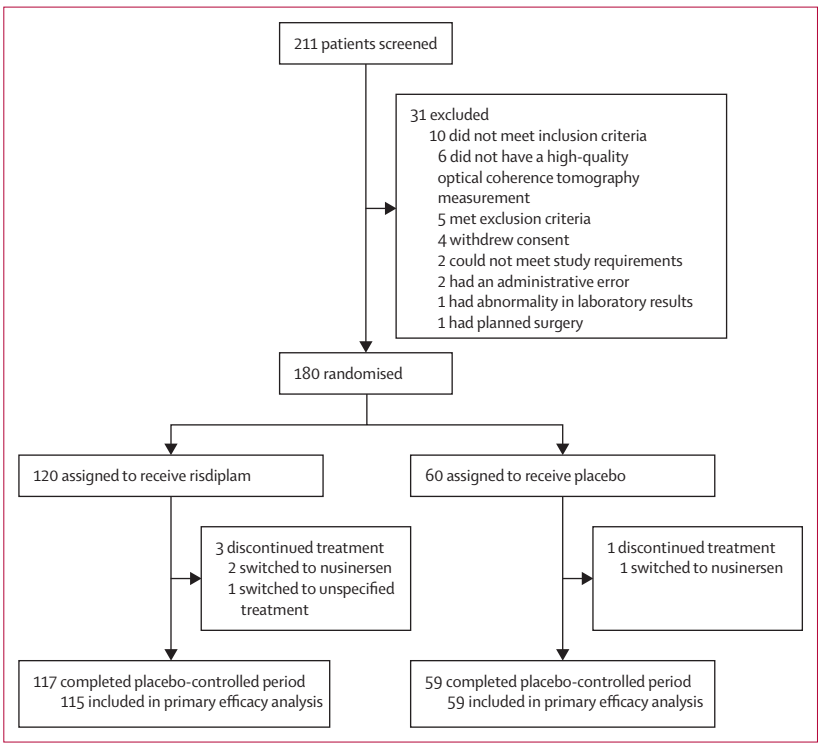

Figure 1: **Trial profile**
For efficacy analyses for each endpoint, individuals who fulfilled the corresponding missing item rules were excluded as predefined in the statistical analysis plan (appendix pp 183–291). Efficacy data at all timepoints up to month 12 (or, for those who withdrew early from the study, efficacy data at all timepoints when they were still receiving the randomised treatment) were included in the analyses. All individuals who received at least one dose of risdiplam or placebo were included in the safety analysis (n=120 in the risdiplam group, n=60 in the placebo group).

Analyses were conducted after the final individual completed 12 months of treatment. To control the overall type I error rate due to multiple testing of risdiplam versus placebo for the primary and key secondary efficacy endpoints, a hierarchical gatekeeping approach was applied to the seven null hypotheses, grouped into six families. Hypotheses were tested hierarchically, and the truncated Hochberg procedure was used in the family with multiple hypotheses (appendix pp 6–7). Data are presented in the prespecified hierarchical order.

For efficacy analyses, all individuals who were randomly assigned to a group were included; for each endpoint, individuals who fulfilled the corresponding missing item rules were excluded, as predefined in the statistical analysis plan (appendix pp 183–291). For example, in MFM32 analyses, including the primary endpoint, total scores were calculated only where there was a calculated score in all domains. Individual domain scores were calculated only if there were less than 15% of data missing. The efficacy estimand is based on a hypothetical treatment strategy, assuming that no prohibited medications intended for treatment of spinal muscular atrophy were available and patients continued on randomised treatment until the primary analysis timepoint. Efficacy data at all timepoints up to month 12 or, for those

	Risdiplam group (n=120)	Placebo group (n=60)
Median age at screening, years (IQR; range)	9 (5–14; 2–25)	9 (5–14; 2–24)
Mean age at onset of symptoms, months (SD)	14·1 (8·4)	18·5 (21·1)
Age group		
2–5 years	37 (31%)	18 (30%)
6–11 years	39 (33%)	18 (30%)
12–17 years	30 (25%)	16 (27%)
18–25 years	14 (12%)	8 (13%)
Sex		
Female	61 (51%)	30 (50%)
Male	59 (49%)	30 (50%)
Ethnicity		
Asian	23 (19%)	12 (20%)
Black	2 (2%)	0 (0%)
White	80 (67%)	41 (68%)
Multiple	1 (1%)	0 (0%)
Unknown	14 (12%)	7 (12%)
Spinal muscular atrophy type		
2	84 (70%)	44 (73%)
3	36 (30%)	16 (27%)
SMN2 copy number		
2	3 (3%)	1 (2%)
3	107 (89%)	50 (83%)
4	10 (8%)	8 (13%)
Unknown	0	1 (2%)
Scoliosis		
Yes	76 (63%)	44 (73%)
Cobb angle >40° curvature*	34 (28%)	23 (38%)
Surgery for scoliosis before screening*		
Yes	29 (24%)	17 (28%)
No	63 (53%)	33 (55%)
Not recorded	28 (23%)	10 (17%)
MFM32 total score, mean (SD)†	45·48 (12·09)‡	47·35 (10·12)‡
RULM total score, mean (SD)§	19·65 (7·22)¶	20·91 (6·41)¶
HFMSE total score, mean (SD)‖	16·10 (12·46)	16·62 (12·09)
Pulmonary care**		
Yes	40 (33%)	30 (50%)
Feeding status		
Gastrostomy tube	2 (2%)	0
Mixed (ie, fluid or puree) oral intake	1 (1%)	0
Modified food intake	1 (1%)	1 (2%)
Solid food	116 (97%)	59 (98%)

Data are n (%), unless otherwise stated. HFMSE=Hammersmith Functional Motor Scale—Expanded. MFM32=32-item Motor Function Measure. RULM=Revised Upper Limb Module. *The questions of whether surgery occurred before screening or what was the curvature of the scoliosis were not compulsory, and therefore some data are not available. †MFM32 absolute scores range from 0 to 96 (ie, 32 items, each with a maximum score of 3), with higher scores indicating better motor function than do lower scores; MFM32 total score is expressed as a percentage of the maximum score. ‡n=115 for the risdiplam group and n=59 for the placebo group. §RULM scores range from 0 to 37, with higher scores indicating better upper limb function than do lower scores. ¶n=119 for the risdiplam group and n=58 for the placebo group. ‖HFMSE scores range from 0 to 66, with higher scores indicating better motor function than do lower scores. **Includes the use of cough assist or bilevel positive airway pressure. No patient had a tracheostomy.

Table 1: **Baseline characteristics**

withdrawn early from the study, efficacy data at all timepoints when these patients were still receiving the randomised treatment, were included in the analyses. All individuals who received at least one dose of risdiplam or placebo were included in the safety population.

For the primary endpoint and key secondary continuous endpoints, mixed model repeated measure analyses were performed with SAS version 9.4. Risdiplam and placebo were compared by use of all data up to month 12. The handling of missing data is described in the statistical analysis plan (appendix pp 183–291). Estimated treatment differences in least squares mean change from baseline between risdiplam and placebo are presented with corresponding 95% CIs and unadjusted and adjusted (if available) p values. Adjusted p values were derived on the basis of all the p values from endpoints in hierarchical order up to the current endpoint. Unadjusted p values refer to the p value obtained without considering multiplicity adjustment such that each endpoint is tested at the 5% significance level. Logistic regression models were used for responder analyses. The proportion of responders are shown and are presented with corresponding odds ratios (ORs) and 95% CIs.

Prespecified exploratory subanalyses by age (ie, 2–5 years, 6–11 years, 12–17 years, and 18–25 years) and *SMN2* copy number (ie, two *vs* three *vs* four copies) were conducted on total score results from MFM32, RULM, and HFMSE with mixed model repeated measures analyses. The study was not powered to find the significance of differences between subgroups; subanalyses are presented to give further context. This study is registered with ClinicalTrials.gov, NCT02908685.

Role of the funding source

The funder of the study (F Hoffmann-La Roche) provided study drug, study management, medical monitoring, drug safety management and analysis, data management, and statistical analysis; and some of its employees contributed to study conception and design. The funder had no role in data collection, which was performed by the clinical staff at each study site. All SUNFISH authors were involved in data interpretation, including employees of F Hoffmann-La Roche. Medical writing and editorial support were funded by F Hoffmann-La Roche.

Results

211 individuals were screened; 180 individuals were enrolled and randomly assigned to receive either risdiplam (n=120) or placebo (n=60; figure 1). Patients were randomly assigned to treatment group between Oct 9, 2017, and Sept 4, 2018. The last individual reached the 12-month assessment on Sept 6, 2019. Four individuals discontinued the study before completing the 12-month placebo-controlled period: three (3%) in the risdiplam group and one (2%) in the placebo group. All four individuals discontinued the study to start a commercially approved treatment.

Enrolled individuals represented a broad range of the late-onset spinal muscular atrophy clinical spectrum, including 128 (71%) individuals with type 2 spinal muscular atrophy and 52 (29%) with non-ambulant type 3 spinal muscular atrophy, with two, three, or four *SMN2* copies. 68 (38%) of 180 individuals were aged 12 years or older at screening (table 1). MFM32 total scores ranged from 16·7 to 71·9 (mean 46·11 [SD 11·46]). 57 (32%) individuals had severe scoliosis (ie, Cobb angle >40°); 46 (26%) individuals underwent scoliosis surgery before screening.

The change from baseline in MFM32 total score at 12 months differed significantly between the risdiplam group (n=115) and the placebo group (n=59). The least squares mean change from baseline in MFM32 total score was 1·36 (95% CI 0·61 to 2·11) in the risdiplam group compared with –0·19 (–1·22 to 0·84) in the placebo group at month 12, resulting in a significant treatment difference of 1·55 (95% CI 0·30 to 2·81; p=0·016; figure 2, table 2).

Significant results were found for the first two of the six key secondary endpoints in the hierarchical testing (ie, family 2 and family 3). A larger proportion of individuals in the risdiplam group had improvement in MFM32 total score of ≥3 points than in the placebo group (table 2; appendix p 19; unadjusted p=0·047, adjusted p=0·047). A significant treatment difference was observed in the change from baseline in RULM total score between individuals in the risdiplam group and those in the placebo group (table 2; appendix p 20; unadjusted p=0·0028, adjusted p=0·047).

In family 4, no difference was observed between groups for the least squares mean change from baseline in HFMSE total score (table 2, appendix p 20; unadjusted p=0·30, adjusted p=0·39). A numerical decline from baseline in best percentage-predicted forced vital capacity at month 12 was observed in individuals in both risdiplam and placebo groups; however, there was no difference between groups (table 2; unadjusted p=0·38, adjusted p=0·39). As p values for these secondary endpoints were not significant, the results of the subsequent two endpoints (ie, family 5 and family 6) in the prespecified hierarchy were also not significant. A numerical increase from baseline in the upper limb total score on SMAIS reported by caregivers was observed in the risdiplam group compared with a decline in the scores of the placebo group (table 2; appendix p 20; unadjusted p=0·0022, adjusted p=0·39). A larger proportion of individuals in the risdiplam group had improved global health from baseline, as measured by CGI-C scale (ie, assessed as "Minimally improved", "Much improved", or "Very much improved"), than in the placebo group (table 2; unadjusted p=0·35, adjusted p=0·39).

Analysis of additional MFM32 secondary endpoints not included in the hierarchical testing showed that a larger proportion of individuals in the risdiplam group had stabilisation or improvement in motor function than in the placebo group, defined as a change from baseline in MFM32 total score of ≥0 (unadjusted p=0·043; table 2). In individual MFM32 domain scores (table 2; appendix p 27), greater improvements from baseline were observed in both D2 and D3 than in D1. The findings for the other secondary endpoints are reported in table 2.

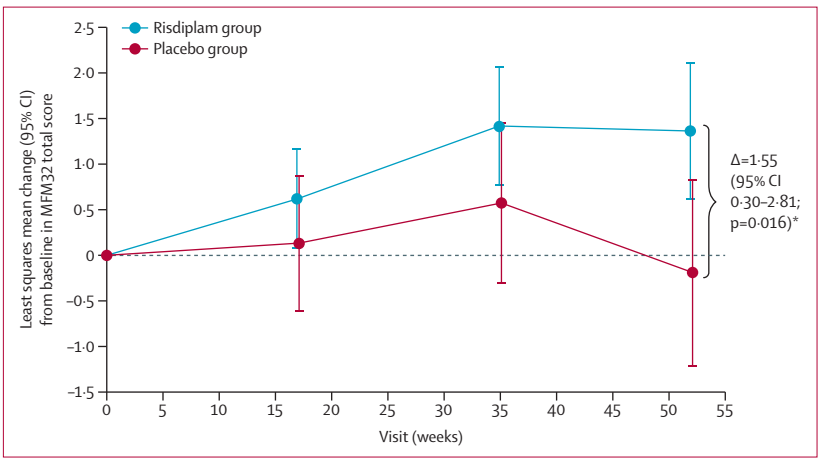

Figure 2: **Change in MFM32 total score from baseline to 12 months of treatment**
Least squares mean change from baseline over 12 months in the MFM32. Absolute scores range from 0 to 96 (ie, 32 items, each with a maximum score of 3), with higher scores indicating better motor function. MFM32 total score is expressed as a percentage of the maximum score. Patients who fulfilled missing item rules were excluded as predefined in the statistical analysis plan (appendix pp 183–291). N at baseline was 115 for the risdiplam group and 59 for the placebo group. Horizontal line at 0 indicates no change. Δ=treatment difference *vs* placebo. MFM32=32-item Motor Function Measure. *Mixed model repeated measures analysis.

Prespecified exploratory subgroup analyses are shown in the appendix (appendix p 22). With regards to age, the largest improvement from baseline in MFM32 total score with risdiplam compared with placebo was observed in the youngest patients (ie, 2–5 years; treatment difference: 3·14 [95% CI 0·81 to 5·46]), followed by the patients aged 6–11 years (1·58 [–0·58 to 3·74]) and 12–17 years (1·04 [–1·31 to 3·39]). No improvement from baseline was seen in the oldest age group (18–25 years; –0·65 [–4·03 to 2·74]). Improvement of ≥3 points in MFM32 total score showed similar age-related trends as the change from baseline; however, stabilisation or improvement (ie, a change of ≥0 points) in MFM32 total score was observed across all age groups (appendix p 19). Although the greatest improvements in the RULM were also in the youngest patients (3·41 [1·55 to 5·26]; appendix p 22), the second greatest improvements were observed in patients aged 18–25 years (1·74 [–1·06 to 4·53]). In HFMSE, the greatest improvements relative to placebo were observed in patients aged 6–11 years and 12–17 years (appendix p 22). Regarding *SMN2* copy number, patients with two *SMN2* copies declined in motor function as assessed by MFM32, RULM, and HFMSE (appendix p 22); however, there were few patients in this subgroup (three patients in the risdiplam group and one patient in the placebo group). Patients with three or four *SMN2* copies improved from baseline in MFM32, RULM, and HFMSE

	Risdiplam group (n=120)	Placebo group (n=60)	Treatment difference or OR (95% CI)
Primary endpoint			
Least squares mean change from baseline in MFM32 total score	1·36 (0·61 to 2·11); n=115	−0·19 (−1·22 to 0·84); n=59	1·55 (0·30 to 2·81)
Key secondary endpoints			
Proportion of patients with a change of ≥3 points in MFM32 total score	44 (38%) of 115	14 (24%) of 59	OR 2·35 (1·01 to 5·44)
Least squares mean change from baseline in RULM total score	1·61 (1·00 to 2·22); n=119	0·02 (−0·83 to 0·87); n=58	1·59 (0·55 to 2·62)
Least squares mean change from baseline in the best percentage-predicted forced vital capacity*	−5·16% (−7·93 to −2·39); n=83	−3·11% (−6·95 to 0·74); n=40	−2·05% (−6·67 to 2·56)
Least squares mean change from baseline in HFMSE total score	0·95 (0·29 to 1·61); n=120	0·37 (−0·54 to 1·28); n=60	0·58 (−0·53 to 1·69)
Least squares mean change from baseline in the upper limb total score on caregiver-reported SMAIS†	1·65 (0·66 to 2·63); n=116	−0·91 (−2·23 to 0·42); n=60	2·55 (0·93 to 4·17)
Proportion of patients rated as "Improved" on the CGI-C‡	57 (48%) of 120	24 (40%) of 60	1·38 (0·70 to 2·74)
Other secondary endpoints			
Proportion of patients with a change of ≥0 points in MFM32 total score	80 (70%) of 115	32 (54%) of 59	OR 2·00 (1·02 to 3·93)
Proportion of patients with improvement of ≥1 SEM in MFM32 total score§	33 (29%) of 115 (20·65 to 37·88)	10 (17%) of 59 (8·44 to 28·97)	Not calculated
Least squares mean change from baseline in MFM32 domain scores			
D1	0·37 (−0·12 to 0·87); n=118	−0·26 (−0·94 to 0·42); n=60	0·64 (−0·20 to 1·47)
D2	1·04 (−0·38 to 2·46); n=118	−0·93 (−2·87 to 1·02); n=60	1·97 (−0·40 to 4·34)
D3	3·68 (2·31 to 5·04); n=115	1·34 (−0·54 to 3·22); n=59	2·34 (0·05 to 4·62)
D1 and D2	0·69 (−0·07 to 1·45); n=118	−0·59 (−1·64 to 0·45); n=60	1·28 (0·01 to 2·56)
D2 and D3	2·02 (0·84 to 3·20); n=115	−0·14 (−1·76 to 1·48); n=59	2·16 (0·18 to 4·14)
Proportion of patients with a change of ≥0 points in RULM total score	86 (72%) of 119	33 (57%) of 58	OR 1·93 (0·98 to 3·79)
Proportion of patients with a change of ≥2 points in RULM total score	57 (48%) of 119	18 (31%) of 58	OR 2·18 (1·05 to 4·54)
Proportion of patients with a change of ≥0 points in HFMSE total score	81 (68%) of 120	40 (67%) of 60	OR 1·03 (0·52 to 2·04)
Proportion of patients with a change of ≥2 points in HFMSE total score	46 (38%) of 120	20 (33%) of 60	OR 1·23 (0·60 to 2·53)
Change from baseline in the best percentage-predicted sniff nasal inspiratory pressure	3·80% (0·48 to 7·13); n=118	0·5% (−3·87 to 4·87); n=59	2·35% (−3·11 to 7·80)
Change from baseline in best percentage-predicted maximal inspiratory pressure*	1·69% (−7·05 to 10·44); n=81	−1·34% (−12·71 to 10·02); n=40	2·96% (−10·78 to 16·70)

(Table 2 continues on next page)

total scores; patients with four copies showed greater improvements overall than those with three copies on RULM and HFMSE, but not on MFM32.

Adverse events that were more frequently reported (ie, ≥5% difference) with risdiplam than with placebo were pyrexia, diarrhoea, rash, mouth and aphthous ulcers, urinary tract infection, and arthralgias (table 3). Serious adverse events were reported in 24 (20%) of 120 patients in the risdiplam group and in 11 (18%) of 60 patients in the placebo group (table 3). A full list of serious adverse events can be found in the appendix (p 28). Grade 3–4 adverse events were reported in 21 (18%) patients in the risdiplam group compared with eight (13%) in the placebo group. No grade 5 (ie, fatal) adverse events were reported. The incidence of serious adverse events was similar between treatment groups, with the exception of pneumonia (nine [8%] patients in the risdiplam group *vs* one [2%] patient in the placebo group).

No adverse events led to dose modification of risdiplam; interruptions of treatment were short term and occurred in both groups (ie, ten adverse events led to dose interruption in eight patients in the risdiplam group, lasting 1–4 days; three adverse events led to dose interruption in two patients in the placebo group, lasting 6–7 days). Review of available laboratory results, vital signs, and electrocardiograms did not show any clinically significant adverse findings. Ophthalmological assessments did not show evidence of risdiplam-induced retinal toxicity.

Discussion

SUNFISH part 2 was designed to show the clinical efficacy of risdiplam in a broad sample of patients with spinal muscular atrophy, similar to a real-world population of patients who are non-ambulant but are able to sit. At month 12, patients treated with risdiplam had a significantly greater change from baseline in MFM32 total score than did patients who received placebo. This increase was largely driven by the axial and proximal (ie, D2) and distal (ie, D3) domains, which are of particular relevance in a population with non-ambulant spinal muscular atrophy.

MFM32 is a scale that has been developed and validated in a broad range of neuromuscular diseases;[14] additional evaluation has shown strong evidence of reliability and validity in a population aged 2–25 years with non-ambulant type 2 or type 3 spinal muscular atrophy.[18,19] A clinically meaningful change estimate for MFM32 in spinal muscular atrophy has not yet been published and SUNFISH part 2 is, to our knowledge, the first to investigate its performance in a broad population with spinal muscular atrophy.

Given the precedent for assessing clinically meaningful change at a patient level (US Food and Drug Administration Patient-focused Drug Development Discussion Document for Guidance 3),[20] an improvement of at least 3 points in motor function on MFM32 total

score was used for the responder analysis. This change represents gaining a new function or improvement in several functions at the item level and thus could be considered a marked improvement. A greater proportion of patients in the risdiplam group had a treatment response of at least 3 points than did patients in the placebo group.

Selecting a single meaningful change threshold is challenging, and clinicians increasingly acknowledge that what constitutes a meaningful change is patient dependent.[21] Survey data have shown that patients with spinal muscular atrophy and their caregivers consider stabilisation of disease to be important,[22,23] which might reflect a fear of the progressive loss of function that is inherent to spinal muscular atrophy.[24–26] In this context, the minor improvements observed on the primary and RULM and SMAIS secondary endpoints in this diverse population can be considered to be clinically meaningful.

Stabilisation or improvement (ie, a change from baseline of ≥0 in MFM32 total score), an important treatment outcome for patients, was also explored. A larger proportion of patients receiving risdiplam had stabilisation or improvement in motor function than did those receiving placebo. More importantly, this difference was observed across all age subgroups in an exploratory analysis, indicating a benefit of risdiplam, even in older individuals with more advanced disease.

Although significant improvements relative to placebo were seen in patients who received risdiplam overall, improvements were most pronounced in younger individuals, whereas older individuals had stabilisation in MFM32. Contractures and scoliosis, which are unlikely to be affected by increased functional SMN expression, worsen with age and negatively affect motor function. Therefore, younger individuals have a higher potential for improvement in motor function earlier in their disease course than do older individuals. Functional improvement would therefore be expected in younger patients, whereas for older patients with more advanced disease, functional stabilisation would be considered an important treatment benefit.

Risdiplam was also associated with a significantly greater increase in upper limb function relative to placebo. Due to the progressive nature of spinal muscular atrophy, and the importance of upper limb function in non-ambulant individuals with spinal muscular atrophy, it is essential to note that although the greatest improvement in upper limb function was observed in the youngest age group, the second greatest improvement was observed in the oldest patients. Differences between the risdiplam and placebo groups for the other secondary endpoints were not significant.

An absence of significance in HFMSE and forced vital capacity results can be partly explained by the study design. Few data are available for respiratory outcomes in patients with late-onset spinal muscular atrophy. Values of pulmonary function are sensitive to several factors, including scoliosis, scoliosis surgery, use of airway clearance, and respiratory tract infections.[27,28] This information was not available when the study was designed, and these factors were not considered in the randomisation. SUNFISH part 2 is one of the first clinical trials to have assessed respiratory function as a secondary endpoint in patients with type 2 or type 3 spinal muscular atrophy, and our findings emphasise the challenge of showing clinically meaningful respiratory outcomes in a broad and clinically heterogeneous population.

A study of nusinersen in children with spinal muscular atrophy who had onset of symptoms at older than 6 months (CHERISH) showed significant improvements in HFMSE scores compared with sham controls;[29] MFM32 was not used as an outcome measure. Important distinctions between the two studies might explain differences in HFMSE results. CHERISH had more restrictive inclusion and exclusion criteria than did SUNFISH part 2, with a maximum age at enrolment of 12 years and HFMSE scores at screening of 10–54.[29] CHERISH participants were younger (ie, median age of 4·0 years [range 2–9 years] in the nusinersen group and 3·0 years [range 2–7 years] in the sham control group *vs* 9·0 years [range 2–25 years] in the risdiplam group

	Risdiplam group	Placebo group	Treatment difference or OR (95% CI)
(Continued from previous page)			
Change from baseline in best percentage-predicted maximal expiratory pressure*	–2·38% (–6·09 to 1·34); n=83	–3·58 (–8·77 to 1·61); n=41	–0·43% (–6·30 to 5·45)
Change from baseline in best percentage-predicted forced expiratory volume in 1 s*	–4·15% (–7·76 to –0·55); n=83	–0·95% (–5·22 to 3·33); n=40	–2·87% (–8·36 to 2·62)
Change from baseline in best percentage-predicted peak cough flow*	0·84% (–1·46 to 3·13); n=83	–0·12% (–2·97 to 2·73); n=42	1·28% (–2·42 to 4·99)
Number of disease-related adverse events per 100 patient-years	101·51 (84·23 to 121·29)	119·77 (93·71 to 150·82)	0·85¶
Proportion of patients rated by clinicians as "No change" or "Improved" on the Clinical Global Impression of Change scale‖	103 (86%) of 120	50 (83%) of 60	OR 1·21 (0·52 to 2·83)
Change from baseline in the upper limb total score on patient-reported SMAIS†**	1·04 (–0·26 to 2·35); n=43	–0·40 (–2·13 to 1·32); n=23	1·45 (–0·68 to 3·57)

Data are change from baseline (95% CI), n (%) of N, or n (95% CI). Safety analyses included data from all patients who received at least one dose of risdiplam or placebo. Efficacy analyses included the total number of patients with available baseline scores in the risdiplam and placebo groups. For each efficacy endpoint, patients who fulfilled the corresponding missing item rules were excluded, as pre-defined in the statistical analysis plan. HFMSE=Hammersmith Functional Motor Score Expanded. MFM32=32-item Motor Function Measure. OR=odds ratio. RULM=Revised Upper Limb Module. SMAIS=Spinal Muscular Atrophy Independence Scale. *Assessments were conducted in patients aged ≥6 years. †SMAIS scores range from 0 to 44 following rescoring to a 0–2 response scale for each item. Higher scores indicate greater independence in completing daily activities than do lower scores. Scoring manual is available in the appendix (pp 10–17). ‡Assessed as either "Minimally improved", "Much improved", or "Very much improved" by the clinician. §SEM was calculated on the basis of the MFM32 items scores and total score at baseline. The SEM of the MFM32 scores in SUNFISH part 2 was 3·26; therefore, a change of ≥1 SEM is equivalent to a change of ≥4 in MFM32 total score. ¶The disease-related adverse event rate ratio (risdiplam:placebo). ‖Assessed as "Minimally improved", "Much improved", "Very much improved", or "No change" by the clinician. **Reported by patients aged ≥12 years.

Table 2: **Primary and secondary endpoints at month 12**

	Risdiplam group (n=120)	Placebo group (n=60)
Total number of adverse events	789	354
Patients with at least one adverse event	111 (93%)	55 (92%)
Patients with at least one serious adverse event	24 (20%)	11 (18%)
Most frequently reported adverse events*		
Upper respiratory tract infection	38 (32%)	18 (30%)
Nasopharyngitis	31 (26%)	15 (25%)
Pyrexia	25 (21%)	10 (17%)
Headache	24 (20%)	10 (17%)
Diarrhoea	20 (17%)	5 (8%)
Vomiting	17 (14%)	14 (23%)
Cough	17 (14%)	12 (20%)
Bronchitis	8 (7%)	10 (17%)
Most frequently reported serious adverse events†		
Pneumonia	9 (8%)	1 (2%)
Gastroenteritis	2 (2%)	2 (3%)
Bacteraemia	2 (2%)	0
Influenza	2 (2%)	0
Pyrexia	2 (2%)	0
Lung infection	1 (1%)	1 (2%)
Adverse events with an incidence ≥5 percentage points higher in the risdiplam group than in the placebo group		
Pyrexia‡	25 (21%)	10 (17%)
Diarrhoea	20 (17%)	5 (8%)
Rash§	20 (17%)	1 (2%)
Mouth and aphthous ulcers	8 (7%)	0
Urinary tract infection¶	8 (7%)	0
Arthralgia	6 (5%)	0
Serious adverse events with an incidence ≥5 percentage points higher in the risdiplam group than in the placebo group		
Pneumonia	9 (8%)	1 (2%)
Total number of deaths	0	0
Patients with at least one event		
Treatment-related adverse event	16 (13%)	6 (10%)
Related adverse event leading to withdrawal from treatment	0	0
Related adverse event leading to dose modification or interruption	0	0
Serious adverse event leading to withdrawal from treatment	0	0
Serious adverse event leading to dose modification or interruption	4 (3%)	2 (3%)
Treatment-related serious adverse event	0	0
Grade 3 to 4 adverse event	21 (18%)	8 (13%)
Adverse event with fatal outcome (ie, grade 5)	0	0
Adverse event leading to dose interruption	8 (7%)	2 (3%)

Data are number of patients (%), unless otherwise stated. Events were classified according to Medical Dictionary for Regulatory Activities (version 22.0) preferred terms. For frequency counts by preferred term, multiple occurrences of the same adverse event in a patient are counted only once. For frequency counts of total number of events, multiple occurrences of the same adverse event in a patient are counted separately. *Events occurred in more than 15% of patients in either treatment group. †Events occurred in more than one patient in either treatment group. ‡Includes pyrexia and hyperpyrexia. §Includes rash, maculo-papular rash, erythema, allergic dermatitis, erythematous rash, and folliculitis. ¶Includes urinary tract infection and cystitis.

Table 3: **Summary of adverse events**

and 9·0 years [range 2–24 years] in the placebo group of SUNFISH part 2), with shorter disease duration.[29] Moreover, when assessed by the HFMSE, patients in SUNFISH part 2 had lower mean baseline motor function (16·10 points [SD 12·46] in the risdiplam group, 16·62 points [12·09] in the placebo group) than did patients in CHERISH[29] (22·4 points [8·3] in the nusinersen group, 19·9 [7·2] in the sham control), with 74 (41%) of 180 patients in SUNFISH part 2 having an HFMSE total score below 10. Finally, patients with substantial contractures or severe scoliosis (ie, Cobb angle of >40°) and those dependent on enteral feeding and non-invasive ventilatory support were excluded in CHERISH but not in SUNFISH part 2.[29]

The HFMSE is an appropriate scale to assess stronger individuals who are non-ambulant but might be less sensitive to detect changes in the weaker SUNFISH part 2 population who have more progressed disease.[30,31] Some HFMSE items are assessed in the prone position, and so cannot be performed in individuals who have undergone spinal fusion or have substantial hip flexor contractures; 46 (26%) of 180 patients in this study had already undergone scoliosis surgery before screening. The MFM32 includes items to measure head, trunk, lower and upper limb, and distal motor function.[14] Distal motor function is of crucial importance in individuals with severe spinal muscular atrophy as it is preserved until late in the disease course.[24] Items that assess distal upper limb motor function in the MFM32 and RULM can therefore overcome the floor effects of the HFMSE.

The placebo group in SUNFISH part 2 showed different disease progression from published natural history cohorts, as assessed by the HFMSE. Two natural history studies report declines in HFMSE total score of 0·96 points per year between the ages of 5 and 14 years and of 2·15 points per year between the ages of 5 and 13 years, with slower decline or stabilisation at older ages;[26,30] we report a decrease of 0·39 in the subgroup aged 6–11 years and an increase of 0·67 in the subgroup aged 12–17 years. A greater increase in HFMSE total score was also seen in the SUNFISH part 2 placebo group in the subgroup aged 2–5 years (ie, increase of 2·59) versus natural history (ie, increase of 0·04).[26] A mild placebo effect lasting 6 months was also observed in CHERISH.[29]

The SMAIS scale, which has undergone validation,[32] assesses the level of assistance that is needed to perform basic personal tasks that have been described as a priority for individuals with type 2 or type 3 spinal muscular atrophy.[22,23] A numerical improvement in caregiver-assessed independence associated with patients needing less assistance to perform daily tasks was observed, providing complementary insights into MFM32 and RULM results. SMAIS reported by patients (completed by patients aged 12–25 years), a secondary endpoint that was not included in the predefined hierarchy, similarly showed numerical improvement in favour of risdiplam; however,

the magnitude of change was smaller than in the SMAIS reported by caregivers, which might be explained by the inclusion of younger individuals (ie, aged ≥2 years) in the caregiver report, who have greater capacity for improvement.

The CGI-C reported by clinicians with a recall period of 1 year showed that similar proportions of patients receiving risdiplam and placebo had improvements. Given the limitations of CGI-C items in terms of subjectivity, recall bias, and absence of sensitivity due to the generic nature of the items,[33] the outcome was positioned as the seventh and final endpoint in the predefined hierarchy.

Risdiplam treatment was not associated with any drug-related safety findings leading to withdrawal. Intensive ophthalmological monitoring did not show any clinically significant findings. Non-clinical findings of bone marrow depression and epithelial effects associated with risdiplam were not observed.

Reports of diarrhoea, rash, mouth and aphthous ulcers, urinary tract infection, and arthralgias were more frequent in patients receiving risdiplam than in those receiving placebo. There was, however, no time pattern to their recording, and events resolved with ongoing treatment. These adverse events are included in the prescribing information of risdiplam. There was also increased incidence of serious pneumonia in the risdiplam group relative to placebo; however, this increase was due to an unexpectedly low incidence of serious pneumonia in the placebo group, which did not increase after these patients switched to risdiplam in the open-label period, indicating that occurrences of serious pneumonia were due to underlying disease rather than a risdiplam-induced adverse event.

A possible limitation of our study is that participants were stratified only by age at randomisation. The absence of other stratification led to an imbalance in baseline characteristics: baseline motor scale total scores were higher in the placebo group than in the risdiplam group, whereas the risdiplam group had a lower proportion of patients with four *SMN2* copies and severe scoliosis. Also, a higher proportion of patients in the placebo group were receiving pulmonary care at baseline.

Overall, SUNFISH part 2 showed a significant difference in motor function in a population aged 2–25 years treated with risdiplam relative to placebo, with improvement observed in younger individuals and stabilisation in older individuals. SUNFISH part 2 is, to our knowledge, the first randomised, double-blind, placebo-controlled clinical study of an oral treatment for spinal muscular atrophy to report such a result in a patient population with a broad range of ages and functional status, including individuals with advanced disease and comorbidities.

Contributors

CM, HK, KG, MG, OK, WYY, and PF contributed to the study conception and design. Data were collected by EM, ND, ESM, AN, MO, KS, CV, GB, OB-T, NG, JK, AK-P, and LS. Analysis and interpretation were performed by all authors. All authors reviewed and edited drafts of the manuscript and approved the final submitted manuscript. All authors attest to the integrity of the data. EM, WYY, and MG accessed and verified the data. All authors had full access to all the data in the study on request and had final responsibility for the decision to submit for publication. Lauren Walmsley of MediTech Media, Manchester, UK, wrote the first draft of the manuscript on the basis of an outline agreed by all authors and provided medical writing assistance with subsequent drafts. Medical editorial support was provided by Megan Speakman of MediTech Media, Manchester, UK.

Declaration of interests

EM has received fees for serving on scientific advisory boards; speaker fees from F Hoffmann-La Roche, Biogen, AveXis/Novartis, Scholar Rock, and Cytokinetics; and grants from Biogen during the conduct of the study. ND served on scientific advisory boards for F Hoffmann-La Roche and Novartis pharmaceuticals; he has received personal fees from Biogen for congress and travel support. ESM reports that she has served on advisory boards for Biogen and Scholar Rock. She has received consulting fees, travel support, and speaker honoraria as an independent contractor from F Hoffmann-La Roche, Biogen, AveXis, and Scholar Rock. AN has received fees for serving on scientific advisory boards and speaker fees from F Hoffmann-La Roche. MO reports grants from F Hoffmann-La Roche during the conduct of the study and has received grants as a clinical trial investigator from Biogen. KS reports grants from F Hoffman-La Roche/Chugai Pharmaceutical during the conduct of the study and grants from Biogen Japan and lecture fees from Novartis Pharmaceuticals, outside the submitted work. CV reports personal fees and financial support to her institution from F Hoffmann-La Roche for activities outside the submitted work. GB received consultancy fees and speaker honoraria from F Hoffmann-La Roche and AveXis and speaker fees from PTC Therapeutics. NG reports fees for serving on advisory boards and presentations at symposia from F Hoffmann-La Roche, Biogen, and AveXis. JK received grants or contracts from Novartis Gene Therapies and Biogen. He has received consulting and speaker fees from F Hoffmann La Roche, Biogen, and Novartis Gene Therapies and consulting fees from Scholar Rock. AK-P reports that she received an institutional support grant from Biogen; serving on scientific advisory boards for and receiving speaker honoraria from Biogen, F Hoffmann-La Roche, Novartis, and PTC Therapeutics; and receiving personal fees from Biogen and F Hoffmann-La Roche for travel support. LS received grants and personal fees from F Hoffman-La Roche, Biogen, and AveXis/Novartis Gene Therapy and personal fees from Cytokinetics, outside the submitted work. OK reports that he was previously an employee and stockholder in F Hoffmann-La Roche during the submitted work and that he now holds the position of honorary chief medical officer at The Spinal Muscular Atrophy Foundation. JWD has received fees for serving on scientific advisory boards from Biogen, Novartis, Sarepta, and Avidity; has received consulting fees from Affinia Therapeutics and Shift Therapeutics for a therapeutic platform; and has received grant support for clinical trials from F Hoffman-La Roche, Biogen, Novartis Gene Therapies, Cytokinetics, Scholar Rock, and Sarepta. CM, PF, MG, KG, HK, HS, RSS, and WYY report that they are current employees and stockholders in F Hoffmann-La Roche. OB-T declared no competing interests.

Data sharing

Qualified researchers can request access to individual patient level data through the clinical study data request platform (https://vivli.org/). Further details on F Hoffman-La Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on F Hoffman-La Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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