Risdiplam Trial outcomes / what is known so far in relation to the questions NICE will explore about the treatment

	FIREFISH	SUNFISH	JEWELFISH	RAINBOWFISH
Identifier	NCT02913482[1]	NCT02908685[2]	NCT03032172[3]	NCT03779334[4]
Phase and trial type	2/3, open-label, multi-centre study[1]	2/3, randomised, double-blind, placebo-controlled, multi-centre study[2]	2, exploratory, single-arm, open-label, multi-centre study[3]	2, single-arm, open-label, multi-centre study[4]
Main aims	Investigate safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy[1]	Investigate safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy[2]	Investigate safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy[3]	Investigate safety, pharmacokinetics, pharmacodynamics and efficacy[4]
Parts and timing	**Part 1**: exploratory dose-finding part for 12 weeks[1] **Part 2**: confirmatory part to investigate Risdiplam for 24-months at the dose selected in Part 1[1]	**Part 1**: exploratory dose-finding part for 12 weeks[2] **Part 2**: confirmatory part to investigate Risdiplam for 24-months at the dose selected in Part 1[2]	Parts not applicable. Participants will receive doses of risdiplam orally once daily for 24 months[3]	Parts not applicable. Participants will receive doses of risdiplam orally once daily for 24 months[4]
Type of SMA	Type 1[1]	Types 2 and 3[2]	Types 1, 2 and 3, who have previously having received SMA therapeutic[3] [d]	Genetically diagnosed with 5q SMA, but pre-symptomatic[4]
Age of participants	1 - 7 months[1]	2 - 25 years[2]	6 months - 60 years[3]	Up to six weeks[4]
Participants enrolled	62[1]: 21 (Part 1) and 41 (Part 2)[5]	231[2]: 51 (Part 1) and 180 (Part 2)[6]	174[3]	25[4]
Study start date[a]	December 24, 2016[1]	October 20, 2016[2]	March 3, 2017[3]	August 8, 2019[4]
Primary completion Date[b]	November 14, 2019[1]	September 6, 2019[2]	*(January 31, 2022)*[3]	*(June 21, 2021)*[4]
***(Estimated)* Study completion date**[c]	*(November 17, 2023)*[1]	*(September 2, 2023)*[2]	*(January 31, 2025)*[3]	*(March 4, 2026)*[4]
Safety	**Parts 1 & 2**: No treatment-related safety findings leading to withdrawal[5, 7]	**Parts 1 & 2**: No treatment-related safety findings leading to withdrawal[6-8]	No treatment-related safety findings leading to withdrawal[6]	Not yet reported
Adverse events	**Part 1**: most common were fever (pyrexia; 52%), upper respiratory tract infections (43%), diarrhoea (29%), vomiting (24%), cough (24%)	**Part 1**: most common were fever (pyrexia; 55%), cough (35%), vomiting (33%), upper respiratory tract infections (31%), cold (nasopharyngitis;	Most common were upper respiratory tract infections (13%), headache (12%), fever (8%), diarrhoea (8%),	Not yet reported

	pneumonia (19%) and constipation (19%)[7] **Part 2**: most common were upper respiratory tract infection (46%), pneumonia (39%), pyrexia (39%), constipation (20%) nasopharyngitis (12%), rhinitis (12%) and diarrhoea (10%)[5]	24%) and sore throat (oropharyngeal pain; 22%)[6] **Part 2**: most common were upper respiratory tract infection (32%), nasopharyngitis (26%), pyrexia (21%), headache (20%), diarrhoea (17%), vomiting (14%) and cough (14%)[8]	nasopharyngitis (7%) and nausea (7%)[6]	
Serious adverse events	**Part 1**: most common was pneumonia (10/21)[9] **Part 2**: most common were pneumonia (32%), bronchiolitis (5%), respiratory failure (5%) and hypotonia (5%)[5]	**Part 1**: most common was pneumonia (3/51)[6] **Part 2**: While the rate of lower respiratory tract infections overall was similar between risdiplam (19%) and placebo (20%), serious lower respiratory tract infections occurred in more patients in the risdiplam group (10% versus placebo 2%)[8]	No serious adverse events or risdiplam-related eye complications have been reported so far[10]	Not yet reported
Outcomes:				
Motor function (including, where applicable, age-appropriate motor milestones such as sitting, standing and walking)	**Part 1:** after 12 months of treatment, among the infants who received the dose selected for the confirmatory Part 2 of the study (n=17), 7 (41%) were able to sit without support for at least five seconds (assessed by BSID-III[e]). 11 (65%) infants were able to sit (with or without support), 9 (53%) achieved upright head control (assessed by HINE-2[f]), and 1 infant (6%) achieved the	**Part 1:** treatment significantly improved motor function after 24 months; MFM-32[h] total change from baseline was greater in patients receiving risdiplam (3.99 point difference (95% CI: 2.34, 5.65) $p < 0.0001$) compared with natural history data[6] **Part 2:** treatment significantly improved motor function after 12 months; MFM-32[h] total change from baseline was	Not yet reported	Not yet reported

	milestone of standing (supports weight). 10 out of 17 infants (59%) in the therapeutically dosed group achieved a CHOP-INTEND[g] total score of 40 points or more. Median change from baseline to month 12 in CHOP-INTEND[g] was 17.5 points. The maximum CHOP-INTEND[g] score was 57 points after 12 months treatment, increasing from a maximum of 49 points after 8 months[7] After 16 months of treatment, 82% (14/17) of high-dose patients had a CHOP-INTEND[g] score ≥40[11] **Part 2:** at 12 months, 29% of infants (12/41; *p*<0.0001) sat without support for five seconds (assessed by BSID-III[e]), compared with natural history data indicating no untreated patients achieve this milestone. 18 (43.9%) infants were able to hold their head upright, 13 (31.7%) were able to roll to the side and 2 (4.9%) were able to stand with support (measured with HINE-2[f]). 90% (37/41) had a CHOP-INTEND[g] score increase of at least 4 points, with 56% (23/41) achieving a	greater in patients receiving risdiplam, compared to placebo (1.55 point mean difference; *p*=0.0156). The RULM[i] also showed an improvement (1.59 point difference; *p*=0.0028). The strongest responses in MFM-32[h] versus placebo were observed in the youngest age group (2-5 years) (78% vs 53% achieving ≥3 point increase). Disease stabilisation was observed in the 18-25 years age group (57% vs 38%, with stabilisation defined as a ≥0 point increase)[8]		

	score above 40; the median increase was 20 points[5]			
Bulbar function (including, for example, swallowing and ability to communicate)	**Part 1:** no infant lost the ability to swallow during the study[9] **Part 2:** 95% of infants who were alive at 12 months (36/38) maintained the ability to swallow and 89% (34/38) were able to feed orally[5]	Not identified	Not yet reported	Not yet reported
Respiratory function	**Part 1:** after 16 months of treatment, no infant has required tracheostomy or reached permanent ventilation[7, 11]	Not identified	Not yet reported	Not yet reported
Need for non-invasive or invasive ventilation	**Part 1:** 86% (18/21) of all infants were event-free after receiving risdiplam for 16 months[11] **Part 2:** at 12 months, 85% (35/41) were event-free[5]	Not identified	Not yet reported	Not yet reported
Mortality	**Part 1:** Three infants experienced fatal complications of their disease after ≈1, 8, and 13 months of treatment[7] **Part 2:** at 12 months, 93% (38/41) of infants were alive[5]	Not identified	Not yet reported	Not yet reported
Female menstruation	Not reported, see[j,k]	Not reported, see[j,k]	Not reported, see[j,k]	Not reported, see[j,k]
Female fertility and pregnancy	Not reported, see[j,k]	Not reported, see[j,k]	Not reported, see[j,k]	Not reported, see[j,k]
Male fertility	Not reported, see[j,k]	Not reported, see[j,k]	Not reported, see[j,k]	Not reported, see[j,k]
Other	**Part 1:** median two-fold increase in blood SMN protein levels after four weeks, which was sustained at 12[9]	Part 1: median two-fold increase in blood SMN protein levels after four weeks, which was sustained at 12[11]	Median two-fold increase in blood SMN protein levels after four weeks, which was sustained at 12 months and 24 months (18 patients)[6]	

References

[1] https://clinicaltrials.gov/ct2/show/NCT02913482 (last accessed September 23, 2020)
[2] https://clinicaltrials.gov/ct2/show/NCT02908685 (last accessed September 23,2020)
[3] https://clinicaltrials.gov/ct2/show/NCT03032172 (last accessed September 23,2020)
[4] https://clinicaltrials.gov/ct2/show/NCT03779334 (last accessed September 23, 2020)
[5] Roche Press Release, April 28, 2020: https://www.roche.com/media/releases/med-cor-2020-04-28.htm (last accessed September 23, 2020)
[6] Roche Press Release, June 12, 2020: https://www.roche.com/media/releases/med-cor-2020-06-12.htm (last accessed September 23, 2020)
[7] Roche press release, May 7, 2019: https://www.roche.com/media/releases/med-cor-2019-05-07.htm (last accessed September 23, 2020)
[8] Roche press release, February 6, 2020: https://www.roche.com/investors/updates/inv-update-2020-02-06.htm (last accessed September 23, 2020)
[9] Baranello, G *et al.* Survival, ventilation and swallowing ability in infants with Type 1 SMA receiving risdiplam (RG7916) (1-year results). Presented at the CureSMA Congress, 28 June-1 July 2019, Anaheim, California.
[10] Chiriboga CA, *et al.* JEWELFISH: Risdiplam (RG7916) increased survival of motor neuron (SMN) protein levels in non-naïve patients with spinal muscular atrophy (SMA). Presented at the CureSMA Congress, 28 June-1 July 2019, Anaheim, California.
[11] Cision PR Newswire article, October 2, 2019: https://www.prnewswire.com/news-releases/risdiplam-spinal-muscular-atrophy-data-demonstrating-continued-benefit-presented-at-world-muscle-society-congress-300929363.html (last accessed September 23, 2020)

Footnotes

[a] **Study Start Date**: The actual date on which the first participant was enrolled in a clinical study.[1-4]
[b] **Primary Completion Date**: The date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure.[1-4]
[c] ***(Estimated)*** **Study Completion Date**: The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and adverse events (that is, the last participant's last visit).[1-4]
[d] Patients previously enrolled in Study BP29420 ("Moonfish") with the splicing modifier RO6885247 or previously treated with nusinersen, olesoxime or onasemnogene abeparvovec[4]. Of the 174 patients enrolled, 76 were previously treated with nusinersen and 14 with onasemnogene abeparvovec. The remaining 83 patients had been treated with compounds then being developed by Roche.[6]
[e] **BSID-III**: Gross Motor Scale of the Bayley Scales of Infant and Toddler Development Third Edition (uses a series of play tasks to assess the development of babies/infants aged 1–42 months).
[f] **HINE-2**: Hammersmith Infant Neurological Examination Module 2 (a scale used to assess an infant's ability to move their head, kick, roll on their side, walk, crawl, sit up and grasp objects).
[g] **CHOP-INTEND**: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (a scale used for infants with Type 1 SMA)
[h] **MFM-32**: Motor Function Measure-32 (a scale designed to detect motor function changes in a broad range of SMA patients, from weak Type 2 to strong Type 3)
[i] **RULM**: Revised Upper Limb Module (a scale developed to assess arm movement and coordination in individuals with SMA).
[j] Roche letter to SMA UK about fertility and menstruation: https://smauk.org.uk/blog/treatments-research/effect-of-risdiplam-on-female-fertility-and-menstruation
[k] **See: Risdiplam Information Summary - September 2020 Page 5 'Across All Clinical Studies'**

25th September 2020