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)]
***(Estimated)* Primary completion Date**[(b)]	November 14, 2019[(1)]	September 6, 2019[(2)]	*(December 27, 2024)*[(3)]	February 20, 2023[(4)]
***(Estimated)* Study completion date**[(c)]	*(November 17, 2023)*[(1)]	*(September 2, 2023)*[(2)]	*(December 27, 2024)*[(3)]	*(January 21, 2029)*[(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)]	PRELIMINARY: No treatment related safety findings leading to withdrawal[(12)]
Adverse events	**Part 1**: most common were fever (pyrexia; 52%), upper respiratory tract infections (43%), diarrhoea (29%),	**Part 1**: most common were fever (pyrexia; 55%), cough (35%), vomiting (33%), upper respiratory tract infections	Most common were upper respiratory tract infection (17%), pyrexia (17%), headache (16%), nausea	PRELIMINARY: Most common were nasal congestion (33%), cough (25%), teething (25%),

	vomiting (24%), cough (24%) 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]	(31%), cold (nasopharyngitis; 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]	(12%), diarrhoea (11%), nasopharyngitis (10%) vomiting (8%)[12]	vomiting (25%), eczema (17%), abdominal pain (17%), diarrhoea (17%), nasal congestion (33%), cough (25%), teething (25%), vomiting (25%), eczema (17%), abdominal pain (17%), diarrhea (17%), gastroenteritis (17%), papule (rash; 17%) and pyrexia (fever; 17%)[12]
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]	The most common serious adverse events were pneumonia (2%) lower respiratory tract infection (2%), upper respiratory tract infection (2%) and respiratory failure (2%)[12]	PRELIMINARY: No serious adverse events or risdiplam related eye complications have been reported so far[12]
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	**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	Not yet reported	Not yet reported

	1 infant (6%) achieved the 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	change from baseline was 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,l]	Not reported, see[j,l]	Not reported, see[j,l]	Not reported, see[j,l]
Male fertility	Not reported, see[j,l]	Not reported, see[j,l]	Not reported, see[j,l]	Not reported, see[j,l]
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 April 6, 2023)
(2) https://clinicaltrials.gov/ct2/show/NCT02908685 (last accessed April 6, 2023)
(3) https://clinicaltrials.gov/ct2/show/NCT03032172 (last accessed April 6, 2023)
(4) https://clinicaltrials.gov/ct2/show/NCT03779334 (last accessed April 6, 2023)
(5) Roche Press Release, April 28, 2020: https://www.roche.com/media/releases/med-cor-2020-04-28.htm (last accessed April 6, 2023)
(6) Roche Press Release, June 12, 2020: https://www.roche.com/media/releases/med-cor-2020-06-12.htm (last accessed April 6, 2023)
(7) Roche press release, May 7, 2019: https://www.roche.com/media/releases/med-cor-2019-05-07.htm (last accessed April 6, 2023)
(8) Roche press release, February 6, 2020: https://www.roche.com/investors/updates/inv-update-2020-02-06.htm (last accessed April 6, 2023)
(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 April 6, 2023)
(12) Roche Press Release, June 11, 2021: https://www.roche.com/media/releases/med-cor-2021-06-11.htm (last accessed April 6, 2023)

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 (last accessed April 6, 2023)
(k) Risdiplam Information Summary - https://smauk.org.uk/risdiplam-what-how-faqs (last accessed April 6, 2023)
(l) Electronic Medicines Compendium: https://www.medicines.org.uk/emc/product/12582/pil (last accessed April 6, 2023)