

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

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

	<p>pneumonia (19%) and constipation (19%)(7)</p> <p><b>Part 2:</b> most common were upper respiratory tract infection (46%), pneumonia (39%), pyrexia (39%), constipation (20%) nasopharyngitis (12%), rhinitis (12%) and diarrhoea (10%)(5)</p>	<p>24%) and sore throat (oropharyngeal pain; 22%)(6)</p> <p><b>Part 2:</b> most common were upper respiratory tract infection (32%), nasopharyngitis (26%), pyrexia (21%), headache (20%), diarrhoea (17%), vomiting (14%) and cough (14%)(8)</p>	<p>nasopharyngitis (7%) and nausea (7%)(6)</p>	
<b>Serious adverse events</b>	<p><b>Part 1:</b> most common was pneumonia (10/21)(9)</p> <p><b>Part 2:</b> most common were pneumonia (32%), bronchiolitis (5%), respiratory failure (5%) and hypotonia (5%)(5)</p>	<p><b>Part 1:</b> most common was pneumonia (3/51)(6)</p> <p><b>Part 2:</b> 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)</p>	<p>No serious adverse events or risdiplam-related eye complications have been reported so far(10)</p>	<p>Not yet reported</p>
<b>Outcomes:</b>				
<p>Motor function (including, where applicable, age-appropriate motor milestones such as sitting, standing and walking)</p>	<p><b>Part 1:</b> 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</p>	<p><b>Part 1:</b> 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) <math>p &lt; 0.0001</math>) compared with natural history data(6)</p> <p><b>Part 2:</b> treatment significantly improved motor function after 12 months; MFM-32(h) total change from baseline was</p>	<p>Not yet reported</p>	<p>Not yet reported</p>

	<p>milestone of standing (supports weight). 10 out of 17 infants (59%) in the therapeutically dosed group achieved a CHOP-INTEND<sup>(9)</sup> total score of 40 points or more. Median change from baseline to month 12 in CHOP-INTEND<sup>(9)</sup> was 17.5 points. The maximum CHOP-INTEND<sup>(9)</sup> score was 57 points after 12 months treatment, increasing from a maximum of 49 points after 8 months<sup>(7)</sup></p> <p>After 16 months of treatment, 82% (14/17) of high-dose patients had a CHOP-INTEND<sup>(9)</sup> score <math>\geq 40</math><sup>(11)</sup></p> <p><b>Part 2:</b> at 12 months, 29% of infants (12/41; <math>p &lt; 0.0001</math>) sat without support for five seconds (assessed by BSID-III<sup>(e)</sup>), 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<sup>(f)</sup>). 90% (37/41) had a CHOP-INTEND<sup>(9)</sup> score increase of at least 4 points, with 56% (23/41) achieving a</p>	<p>greater in patients receiving risdiplam, compared to placebo (1.55 point mean difference; <math>p = 0.0156</math>). The RULM<sup>(i)</sup> also showed an improvement (1.59 point difference; <math>p = 0.0028</math>). The strongest responses in MFM-32<sup>(h)</sup> versus placebo were observed in the youngest age group (2-5 years) (78% vs 53% achieving <math>\geq 3</math> point increase). Disease stabilisation was observed in the 18-25 years age group (57% vs 38%, with stabilisation defined as a <math>\geq 0</math> point increase)<sup>(8)</sup></p>		
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	score above 40; the median increase was 20 points <sup>(5)</sup>			
<b>Bulbar function (including, for example, swallowing and ability to communicate)</b>	<b>Part 1:</b> no infant lost the ability to swallow during the study <sup>(9)</sup> <b>Part 2:</b> 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 <sup>(5)</sup>	Not identified	Not yet reported	Not yet reported
<b>Respiratory function</b>	<b>Part 1:</b> after 16 months of treatment, no infant has required tracheostomy or reached permanent ventilation <sup>(7, 11)</sup>	Not identified	Not yet reported	Not yet reported
<b>Need for non-invasive or invasive ventilation</b>	<b>Part 1:</b> 86% (18/21) of all infants were event-free after receiving risdiplam for 16 months <sup>(11)</sup> <b>Part 2:</b> at 12 months, 85% (35/41) were event-free <sup>(5)</sup>	Not identified	Not yet reported	Not yet reported
<b>Mortality</b>	<b>Part 1:</b> Three infants experienced fatal complications of their disease after ≈1, 8, and 13 months of treatment <sup>(7)</sup> <b>Part 2:</b> at 12 months, 93% (38/41) of infants were alive <sup>(5)</sup>	Not identified	Not yet reported	Not yet reported
<b>Female menstruation</b>	Not reported, see <sup>(i,k)</sup>	Not reported, see <sup>(i,k)</sup>	Not reported, see <sup>(i,k)</sup>	Not reported, see <sup>(i,k)</sup>
<b>Female fertility and pregnancy</b>	Not reported, see <sup>(i,k)</sup>	Not reported, see <sup>(i,k)</sup>	Not reported, see <sup>(i,k)</sup>	Not reported, see <sup>(i,k)</sup>
<b>Male fertility</b>	Not reported, see <sup>(i,k)</sup>	Not reported, see <sup>(i,k)</sup>	Not reported, see <sup>(i,k)</sup>	Not reported, see <sup>(i,k)</sup>
<b>Other</b>	<b>Part 1:</b> median two-fold increase in blood SMN protein levels after four weeks, which was sustained at 12 <sup>(9)</sup>	Part 1: median two-fold increase in blood SMN protein levels after four weeks, which was sustained at 12 <sup>(11)</sup>	Median two-fold increase in blood SMN protein levels after four weeks, which was sustained at 12 months and 24 months (18 patients) <sup>(6)</sup>	

## 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.<sup>(1-4)</sup>
- (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.<sup>(1-4)</sup>
- (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).<sup>(1-4)</sup>
- (d) Patients previously enrolled in Study BP29420 (“Moonfish”) with the splicing modifier RO6885247 or previously treated with nusinersen, olesoxime or onasemnogene abeparvovec<sup>(4)</sup>. 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.<sup>(6)</sup>
- (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’](#)

25<sup>th</sup> September 2020