Risdiplam Information Summary - September 2020

1. How does risdiplam work?

Risdiplam is a small molecule drug that specifically modulates how effectively the *survival motor neuron 2* (*SMN2*) gene is used to make SMN protein. Signals (called messenger RNAs) are generated from *SMN2,* and risdiplam selectively interacts with these, resulting in more SMN protein being made by cells throughout body. **Read more**.

2. How is risdiplam administered / taken?

Risdiplam is given daily in liquid form. It is taken at the prescribed dose, at approximately the same time each day. This is by mouth or feeding tube, using the syringe provided.

3. Where does risdiplam get to in the body?

Risdiplam distributes throughout the body to many different types of cell, tissue and organ, including the brain, spinal cord, muscles and blood.

4. Where do you have to be to take risdiplam and where is it stored between doses?

Risdiplam is imported as a powder, which has to be reconstituted with purified water by a pharmacy, usually within the hospital. The first treatment will normally be at the treating centre. Subsequent doses may then be taken at home, if this is a local possibility and agreed by the treating clinician.

Risdiplam must be kept between 2°C and 8°C, so can be stored in a regular, domestic fridge.

5. When did human clinical trials of risdiplam begin?

The first in-human trials of risdiplam, which were conducted in healthy volunteers (*i.e*. a Phase 1 clinical trial), were initiated in late 2015, with the first volunteers enrolled in early 2016 (clinicaltrials.gov trial identifier: NCT02633709). SMA patients were first enrolled in clinical trials of risdiplam in late 2016: the FIREFISH trial involving infants with Type 1 SMA and the SUNFISH trial involving participants with SMA Type 2 and 3 (see below). JEWELFISH and RAINBOWFISH trials followed later.

6. What clinical trials with SMA patients have been initiated/conducted so far?

Trial Name	Identifier	Type of SMA	Age of participants	Participants enrolled
FIREFISH	NCT02913482	Type 1	1 - 7 months	62
SUNFISH	NCT02908685	Types 2 and 3	2 - 25 years	231
JEWELFISH	NCT03032172	Type 1, 2 and 3, previously receiving SMA therapeutic	6 months - 60 years	174
RAINBOWFISH	NCT03779334	Genetically diagnosed with 5q SMA, but pre-symptomatic	Up to 6 weeks	25

7. What are the major results to date from the four key clinical trials of risdiplam?

Please also see the summary table

Treatment with risdiplam was associated with an increase in SMN protein that was maintained over at least a 12-month treatment period in FIREFISH, SUNFISH and JEWELFISH trials. Data is not yet available for RAINBOWFISH.

(You can find information about some physiotherapy-based measures used to monitor outcomes here

FIREFISH

➢ **Patients enrolled via Part 1 of the trial**

Patients involved in Part 1 continued to receive treatment at the dose selected from the 12-week dose-finding study.

Outcomes for infants with SMA Type 1 following 12 months of risdiplam treatment were:

- 7 out of 17 (41%) able to sit without support for at least five seconds, compared to 0% of untreated infants (natural history data).
- 11 (65%) able to sit (with or without support),
- 9 (53%) achieved upright head control (assessed by HINE-2)
- 1 (6%) achieved the milestone of standing (supporting own weight).

- 10 out of 17 (59%) achieved a CHOP-INTEND total score of 40 points or more.
    - Median change from baseline to month 12 in CHOP-INTEND was 17.5 points.
    - The maximum CHOP-INTEND score was 57 points after 12 months treatment, increasing from a maximum of 49 points after 8 months.
    - After 16 months of treatment, 82% (14/17) of high-dose patients had a CHOP-INTEND score ≥40.

- After 16 months of treatment, no infant required tracheostomy or reached permanent ventilation

- 86% (18/21) of all infants were event-free after receiving risdiplam for 16 months. An event is defined as the time when ventilation support for breathing is required for at least 16 hours a day for 14 consecutive days, or sadly when a patient dies.

➢ **Patients enrolled via Part 2 of the trial**

Outcomes for infants with SMA Type 1 receiving 12 months of risdiplam treatment:

- 29% of infants (12/41; $p<0.0001$) able to sit without support for at least five seconds, compared to 0% of untreated infants (natural history data).
- 18 (43.9%) able to hold their head upright.
- 13 (31.7%) able to roll to the side.
- 2 (4.9%) able to stand with support (measured with HINE-2).

- 90% (37/41) had a CHOP-INTEND score increase of at least 4 points.
- 56% (23/41) achieved a score above 40; the median increase was 20 points.

- 85% (35/41) were event-free

SUNFISH

Outcomes for those with SMA Type 2 or 3 aged 2 – 25 years

➢ **Patients enrolled via Part 1 of the trial**

Patients involved in Part 1 continued to receive treatment at the dose selected from the 12-week dose-finding study.

- risdiplam significantly improved motor function after 24 months of risdiplam treatment:
  - MFM-32 (Motor function measure which assesses 32 items) 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.

➢ **Patients enrolled via Part 2 of the trial**

- risdiplam significantly improved motor function after 12 months of treatment:
  - MFM-32 total change from baseline was greater in patients receiving risdiplam, compared to placebo (1.55 point mean difference; $p=0.0156$).
  - the RULM (Revised Upper Limb Module which assesses the functioning of the arm) also showed an improvement (1.59 point difference; $p=0.0028$).

JEWELFISH

➢ Key efficacy findings not yet reported: the first patients were enrolled in March 2017.

RAINBOWFISH

➢ Key results not yet reported: the first patients were enrolled in August 2019.

8. What is the safety profile of risdiplam?

To date, there have been no drug-related safety findings leading to withdrawal of patients from FIREFISH, SUNFISH or JEWELFISH. There are no data available for RAINBOWFISH.

All trials and testing to date indicate that risdiplam has a tolerable safety profile.

9. What adverse events were reported from the clinical trials?

Overall, reported adverse events were designated as "not risdiplam-related", because they are issues commonly observed in untreated SMA patients. Detailed reports were as follows:

FIREFISH

➢ **Patients enrolled via Part 1 of the trial**

- Most common adverse events were fever (pyrexia; 52%), upper respiratory tract infections (43%), diarrhoea (29%), vomiting (24%), cough (24%) pneumonia (19%) and constipation (19%).
- Most common serious adverse event was pneumonia (10/21).
- Three infants experienced fatal complications of their disease after approximately 1, 8, and 13 months of treatment.

➢ **Patients enrolled via Part 2 of the trial**

- Most common adverse events were upper respiratory tract infection (46%), pneumonia (39%), pyrexia (39%), constipation (20%) nasopharyngitis (12%), rhinitis (12%) and diarrhoea (10%).
- Most common serious adverse events were pneumonia (32%), bronchiolitis (5%), respiratory failure (5%) and hypotonia (5%).
- At 12 months, 93% (38/41) of infants were alive.

SUNFISH

➢ **Patients enrolled via Part 1 of the trial**

- Most common adverse events fever (pyrexia; 55%), cough (35%), vomiting (33%), upper respiratory tract infections (31%), cold (nasopharyngitis; 24%) and sore throat (oropharyngeal pain; 22%).
- Most common serious adverse event was pneumonia (3/51).

➢ **Patients enrolled via Part 1 of the trial**

- Most common adverse events were upper respiratory tract infection (32%), nasopharyngitis (26%), pyrexia (21%), headache (20%), diarrhoea (17%), vomiting (14%) and cough (14%).
- 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%).

JEWELFISH

- Most common adverse events were upper respiratory tract infections (13%), headache (12%), fever (8%), diarrhoea (8%), nasopharyngitis (7%) and nausea (7%).
- No serious adverse events or risdiplam-related eye complications have been reported thus far.

Across clinical studies

➢ **Impact of risdiplam on menstruation**

Across clinical studies, approximately 20% of patients (90 in total) were of child-bearing potential. Adverse events related to the menstrual cycle were reported in some patients:

- Menstrual pain and cramps (dysmenorrhea) reported by 35/90
- Irregular menstrual bleeding (metrorrhagia) reported by 3/90
- Menstrual disorder reported by 1/90
- Absent menstruation (amenorrhea) reported by 1/90

Roche report that trial investigators stated that there was no indication that these events were related to any risdiplam-related safety issues on the menstrual cycle.

➢ **Pregnancy, contraception, breast-feeding and male fertility**

In risdiplam trials, no female participants were pregnant and no participants – male or female – were trying to conceive; it is ethically unacceptable for any clinical trials of new treatments to include participants from these groups.

The following information is part of the **patient information** for anyone receiving risdiplam treatment via the Early Access to Medicines Scheme (EAMS) in the UK as a pre-licensed treatment approved by the Medicines and Health Regulatory Products Agency (MHRA). It was published by the MHRA on 17th September 2020 following their assessment of all the trial evidence about risdiplam and preceding related studies.

➢ **Pregnancy**

- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. This is because taking this medicine while you are pregnant could harm your unborn baby.
- Before you start treatment with risdiplam, your doctor should do a pregnancy test. This is because risdiplam may harm your unborn baby. Your doctor will consider the benefit of you taking risdiplam against the risk to your baby.
- If you do become pregnant during your treatment with risdiplam, tell your doctor straight away. You and your doctor will decide what is best for you and your unborn baby.

➢ **Contraception**

For women
Do not become pregnant:
- during your treatment with risdiplam and
- for at least one month after you stop taking risdiplam.

Talk to your doctor about highly effective methods of birth control that you and your partner should use during treatment and for one month after you stop treatment.

For men

If your female partner is of childbearing potential, you both need to avoid pregnancy. Remain abstinent or use condoms plus an additional contraceptive method that results in highly effective contraception during your treatment with risdiplam and continue to use them for at least 4 months after treatment has finished. You should not donate sperm for the same period.

Please be aware that no method of contraception is 100% effective.

- **Breast-feeding**

Do not breast-feed while taking this medicine. This is because risdiplam may pass into breast milk and may therefore harm your baby.

Discuss with your doctor if you should stop breast-feeding or if you should stop taking risdiplam.

- **Male fertility**

Risdiplam may affect male fertility. For your family planning, ask your doctor for advice.

Do not donate sperm during your treatment and for 4 months after your last dose of risdiplam.

We have sent a request to Roche for more information about the studies that led to these conclusions and will publish their reply here as soon as it is available.

25th September 2020