Medicines & Healthcare products Regulatory Agency

MHRA

Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed medicines and medicines used outside their licence, to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life-threatening conditions where there are no adequate treatment options. More information about the scheme can be found here: http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the EAMS medicine. This medicine does not yet have a licence (marketing authorisation) and the information is provided to assist physicians in prescribing this unlicensed medicine. Guidance on prescribing unlicensed medicines can be found on the GMC webpage:
https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

The scientific opinion is based on assessment of the information supplied to the MHRA on the benefits and risks of this promising new medicine. As such, this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to license such a medicine, nor should it be regarded as an authorisation to sell or supply such a medicine. A positive scientific opinion is not a recommendation for use of the medicine and should not be interpreted as such. Under EAMS the risk and legal responsibility for prescribing a 'special' remains with the physician, and the opinion and EAMs documentation published by the MHRA are intended only to inform physicians' decision making and not to recommend use. An EAMS scientific opinion does not affect the civil liability of the manufacturer or any physician in relation to the product.

Healthcare professionals should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Scientific opinion period: The MHRA will withdraw the EAMS positive scientific opinion when a marketing authorisation (drug licence) is issued for the EAMS product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

Treatment protocol update(s): In case of substantial new efficacy or safety data, the treatment protocol may need to be updated.

Contact information regarding queries on using this EAMS medicine can be found at the end of this document.

Information for healthcare professionals

1. NAME OF THE MEDICINAL PRODUCT

Risdiplam 0.75 mg/ml powder for oral solution.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 mL bottle contains 60 mg risdiplam in 2.0 g powder for oral solution.

Each mL of the constituted solution contains 0.75 mg risdiplam.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for oral solution.

4. CLINICAL PARTICULARS

4.1 EAMS therapeutic indication

Risdiplam is indicated for the treatment of patients 2 months of age and older with type 1 and type 2 spinal muscular atrophy (SMA) who are not suitable for authorised treatments.

4.2 Posology and method of administration

Treatment with risdiplam should be initiated by a physician with experience in the management of spinal muscular atrophy.

SMA treatment should be initiated as early as possible after SMA diagnosis.

Risdiplam oral solution should be constituted by a healthcare professional (HCP) prior to being dispensed.

Posology

Risdiplam is taken orally once a day after a meal, using the re-usable oral syringe provided, at approximately the same time each day. In infants who are breastfed, risdiplam should be administered after breastfeeding.

The recommended once daily dose of risdiplam for SMA patients is determined by age and body weight (see Table 1).

Table 1 Dosing Regimen by Age and Body Weight

Age	***Recommended Daily Dose***
2 months to < 2 years of age	0.20 mg/kg
≥ 2 years of age (< 20 kg)	0.25 mg/kg
≥ 2 years of age (≥ 20 kg)	5 mg

It is recommended that the prescribing process and weighing process for risdiplam are not dependent upon each other. Therefore, it is recommended that risdiplam is prescribed "take as directed".
Weighing of patients should be carried out by a healthcare professional such as a nurse, GP or health visitor.
The dose should be calculated by the treating physician or pharmacist and communicated to patients/care-givers after each weigh-in.

It is recommended that the HCP determines the most suitable weigh-in frequency on a case-by-case depending on the patient's age, condition or situation.

Dosage changes must be made under the supervision of a healthcare professional. Treatment with a daily dose above 5 mg has not been studied. No data are available in infants below 2 months of age.

Delayed or missed doses

Risdiplam is taken orally once a day after a meal at approximately the same time each day. In infants who are breastfed, risdiplam should be administered after breastfeeding. If a planned dose of risdiplam is missed, administer as soon as possible if still within 6 hours of the scheduled dose. Otherwise, skip the missed dose and administer the next dose at the regularly scheduled time the next day.

If a dose is not fully swallowed or vomiting occurs after taking a dose of risdiplam, do not administer another dose to make up for the lost dose. Wait until the next day to administer the next dose at the regularly scheduled time.

Special Populations

Paediatric population

The safety and efficacy of risdiplam in paediatric patients < 2 months of age have not been studied.

Elderly

The safety and efficacy of risdiplam have not been studied in patients older than 60 years of age. No dose adjustment recommendation can be made based on available data (see section 5.1 and section 5.2).

Renal impairment

The safety and efficacy of risdiplam in patients with renal impairment have not been studied. No dose adjustment recommendation can be made in patients with renal impairment based on available data (see section 5.2).

Hepatic impairment

Mild and moderate hepatic impairment had no impact on the PK of risdiplam. No dose adjustment recommendation can be made based on available data (see section 5.2).

Method of administration

For instructions on reconstitution of the medicinal product before administration, see section 6.6

Risdiplam is taken orally once a day after a meal at approximately the same time each day, using the oral syringe provided to deliver the daily dose of risdiplam. It is recommended that a HCP discusses with the patient or caregiver how to prepare the prescribed daily dose prior to administration of the first dose. For comprehensive instructions on the administration of risdiplam, see Instruction for Use booklet provided separately.

The patient should drink water after taking risdiplam to ensure the drug has been completely swallowed. If the patient is unable to swallow and has a nasogastric or gastrostomy tube *in situ*, administer risdiplam via the tube. The tube should be flushed with water after delivering risdiplam.

Selection of the oral syringe for the prescribed daily dose of risdiplam:

Dose strength	*Syringe size*	*Dosing volume*	*Syringe increments*
0.75mg/mL (100mL bottle)	6mL	1.0mL to 6.0mL	0.1mL
	12mL	6.2mL to 6.6mL	0.2mL

For the calculation of dosing volume, the syringe increments need to be considered. Round the dose volume to the closest increment marked on the selected oral syringe.

4.3 Contraindications

Hypersensitivity to risdiplam or any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

Embryo-fetal Toxicity

Embryo-fetal toxicity and teratogenicity (i.e. hydrocephaly) has been observed in animal studies at low exposure margins to human exposure at the recommended dose (see section 5.3). Patients of reproductive potential should be informed of the risks and must use highly effective contraception during treatment and until at least 1 month after the last dose of risdiplam in female patients of childbearing potential, and 4 months after the last dose in male patients (see section 4.6) with partners that are of childbearing potential
The pregnancy status of female patients of reproductive potential should be verified prior to initiating risdiplam therapy. Pregnant women should be clearly advised of the potential risk to the fetus when risdiplam is taken during pregnancy.

Potential Effects on Male Fertility

Due to reversible effects of risdiplam on male fertility based on observations from animal studies, male patients should not donate sperm while on treatment and for 4 months after the last dose of risdiplam (see sections 4.6 and 5.3).

Sodium

Risdiplam contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Risdiplam is primarily metabolized by hepatic enzymes flavin monooxygenase 1 and 3 (FMO1 and 3), and also by CYPs 1A1, 2J2, 3A4, and 3A7. Risdiplam is not a substrate of human multidrug resistance protein 1 (MDR1).

Effects of other medicinal products on risdiplam

Co-administration of 200 mg itraconazole twice daily, a strong CYP3A inhibitor, with a single oral dose of 6 mg risdiplam did not exhibit a clinically relevant effect on the pharmacokinetic (PK) parameters of risdiplam (11% increase in AUC, 9% decrease in C_{max}). No dose adjustments are required when risdiplam is co-administered with a CYP3A inhibitor.

Caution should be used with the concomitant use of sensitive CYP3A4 substrates and CYP3A4 inhibitors for paediatrics patients under 2 years of age.

No drug-drug interactions are expected via the FMO1 and FMO3 pathway.

Effects of risdiplam on other medicinal products

In vitro risdiplam and its major circulating metabolite M1 did not induce CYP1A2, 2B6, 2C8, 2C9, 2C19, or 3A4. *In vitro* risdiplam and M1 did not inhibit (reversible or Time-Dependent Inhibition) any of the CYP enzymes tested (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6) with the exception of CYP3A.

Risdiplam is a weak inhibitor of CYP3A. In healthy adult subjects, administration of risdiplam once daily for 2 weeks slightly increased the exposure of midazolam, a sensitive CYP3A substrate (AUC 11%; Cmax 16%). The extent of the interaction is not considered clinically relevant, and therefore no dose adjustment is required for CYP3A substrates. Using physiologically based pharmacokinetic (PBPK) modelling, a similar magnitude of the effect is expected in children and infants as young as 2 months old.

In vitro studies have shown that risdiplam and its major metabolite are not a significant inhibitor of human MDR1, organic anion-transporting polypeptide (OATP)1B1, OATP1B3, organic anion transporter 1 and 3 (OAT 1 and 3) transporters. Risdiplam and its metabolite are, however, *in vitro* inhibitors of the human

organic cation transporter 2 (OCT2) and the multidrug and toxin extrusion (MATE)1 and MATE2-K transporters. At therapeutic drug concentrations, no interaction is expected with OCT2 substrates. Based on *in vitro* data, risdiplam may increase plasma concentrations of drugs eliminated via MATE1 or MATE2-K.The clinical relevance of the co-administration with MATE1/2-K substrates is unknown.

4.6 Fertility, pregnancy and lactation

Patients of reproductive potential

Contraception in male and female patients

Male and female patients of reproductive potential should use highly effective contraception during treatment with risdiplam and adhere to the following contraception requirements:

- Female patients of childbearing potential should use highly effective contraception during treatment with risdiplam and for at least 1 month after the last dose.

- Male patients with female partners of childbearing potential must both remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during treatment with risdiplam and for at least 4 months after his last dose. Men must refrain from donating sperm during this same period.

Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Pregnancy testing

The pregnancy status of female patients of reproductive potential should be verified prior to initiating risdiplam therapy. Pregnant women should be clearly advised of the potential risk to the fetus.

Pregnancy

There are no clinical data from the use of risdiplam in pregnant women. Risdiplam has been shown to be embryo-fetotoxic and teratogenic in animals. Based on the findings from animal studies, risdiplam crosses the placental barrier and may cause fetal harm (see section 5.3).

Breast-feeding

It is not known whether risdiplam is excreted in human breast milk. Studies in rats show that risdiplam is excreted into milk (see section 5.3). As the potential for harm to the nursing infant is unknown, a decision must be made with the patient's treating physician. It is recommended not to breast-feed during treatment with risdiplam.

Fertility

Male patients

Male fertility may be compromised while on treatment with risdiplam based on findings in animals (see section 5.3). Prior to initiating treatment with risdiplam, fertility preservation strategies should be discussed with male patients receiving risdiplam. Male patients may consider sperm preservation, prior to treatment initiation or after a treatment free period of at least 4 months. Male patients who wish to father a child should stop treatment with risdiplam for a minimum of 4 months. Treatment may be re-started after conception.

Female patients

Based on animal data (see section 5.3), an impact of risdiplam on female fertility is not expected. There are no existing data to confirm this from humans.

4.7 Effects on ability to drive and use machines

Risdiplam has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the Safety Profile

The safety of risdiplam has been evaluated in three clinical studies (FIREFISH, SUNFISH and JEWELFISH). The studies included patients with infantile-onset SMA and later-onset SMA.

The safety of risdiplam therapy for infantile-onset SMA is based on the pooled analysis of 62 patients from FIREFISH Parts 1 and 2. Of the 62 patients included, 55 patients received more than 12 months of risdiplam treatment (range: 18 days – 35 months). Adverse drug reactions (ADRs) are defined as adverse events occurring in ≥ 5% of patients and where a causal association with risdiplam is possible. The most common adverse reactions observed in clinical trials for infantile-onset SMA are rash (27.4%) and diarrhoea (16.1%).

The safety profile for later-onset SMA patients is based on the SUNFISH Part 2 study, the randomized double-blind, placebo-controlled portion with a follow-up time of at least 12 months. ADRs are defined as adverse events occurring in ≥ 5% of risdiplam treated patients which occurred ≥ 5% more frequently or at least 2 times as frequently than in placebo control patients and where a causal association with risdiplam is possible. The most common adverse reactions observed in the risdiplam treated patients of SUNFISH Part 2 are diarrhoea, rash, and arthralgia.

The adverse reactions diarrhoea and rash occurred without an identifiable clinical or time pattern and resolved despite ongoing treatment in infantile-onset and later-onset SMA patients. These events are not suggestive of the effect on epithelial tissues observed in animal studies (see section 5.3).

Tabulated list of adverse reactions

The corresponding frequency category for each adverse drug reaction is based on the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000). Adverse drug reactions from clinical trials (Table 2) are listed by MedDRA system organ class.

Table 2 summarizes the adverse reactions that have been reported in association with the use of risdiplam in the SUNFISH Part 2 study.

Adverse events (occurring ≥ 10%) reported in FIREFISH part 2 include upper respiratory tract infection (46,3%), pyrexia and pneumonia (39.0% each), constipation (19.5%) and nasopharyngitis and rhinitis (12.2% each).

Table 2. Adverse reactions occurring in patients with later-onset SMA observed in SUNFISH Part 2 study

System Organ Class	Frequency Category
Gastrointestinal Disorders	
Diarrhoea	Very common
Skin and Subcutaneous Tissue Disorders	
Rash*	Very common
Musculoskeletal and Connective Tissue disorders	
Athralgia	Common

* Includes rash, rash maculo-papular, erythema, dermatitis allergic, rash erythematous, folliculitis, rash papular

Safety profile in Patients Previously treated for SMA

The safety profile of risdiplam in treatment non-naive patients in the JEWELFISH study is consistent with the safety profile for treatment naive SMA patients treated with risdiplam in the FIREFISH (Part 1 and Part 2) and SUNFISH (Part 1 and Part 2) studies. In the JEWELFISH study, 76 patients previously treated with nusinersen and 14 patients previously treated with onasemnogene abeparvovec were enrolled (see section 5.1).

4.9 Overdose

There is no experience with overdosage of risdiplam in clinical trials. There is no known antidote for overdosage of risdiplam. In case of overdosage, the patient should be closely supervised and supportive care instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other drugs for disorders of the musculo-skeletal system, ATC code: M09AX10

Mechanism of action

Risdiplam is a survival of motor neuron 2 (SMN2) pre-mRNA splicing modifier designed to treat SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency. Functional SMN protein deficiency is the pathophysiological mechanism of all SMA types.

Findings from animal studies showed that risdiplam corrects the splicing of SMN2 to shift the balance from exon 7 exclusion to exon 7 inclusion into the mRNA transcript leading to an increased production in functional and stable SMN protein.

Risdiplam distributes evenly to all parts of the body, including the central nervous system (CNS) by crossing the blood brain barrier, and thereby leading to SMN protein increase in the CNS and throughout the body. Concentrations of risdiplam in plasma and SMN protein in blood reflect its distribution and pharmacodynamic effects in tissues such as brain and muscle.

Pharmacodynamic effects

In clinical trials, risdiplam led to a consistent and durable increase in SMN protein with a greater than 2-fold median change from baseline within 4 weeks of treatment initiation, measured in blood, across all SMA types and all age ranges.

Clinical efficacy and safety

The efficacy of risdiplam for the treatment of SMA patients with infantile-onset and later-onset SMA was evaluated in 2 pivotal clinical studies, FIREFISH and SUNFISH. The overall findings of these studies support the effectiveness of risdiplam across the range of SMA patients.

Infantile-onset SMA – FIREFISH (Part 2)

Study BP39056 (FIREFISH) is an open-label, 2-part study to investigate the efficacy, safety, PK and pharmacodynamics (PD) of risdiplam in symptomatic Type 1 SMA patients (all patients had genetically confirmed disease with 2 copies of the *SMN2* gene). Part 1 of FIREFISH was designed as a dose-finding part of the study. The confirmatory Part 2 of the FIREFISH study assessed the efficacy of treatment at the therapeutic dose selected based on the results from Part 1 (see section 4.2). Patients from Part 1 did not take part in Part 2.

In FIREFISH Part 2, 41 patients with Type 1 SMA were enrolled. The median age of onset of clinical signs and symptoms of Type 1 SMA was 1.5 months (range: 1.0-3.0 months), 54% were female, 54% Caucasian and 34% Asian. The median age at enrolment was 5.3 months (range: 2.2-6.9 months) and the median time between onset of symptoms and first dose was 3.4 months (range: 1.0-6.0 months).

The primary efficacy endpoint for FIREFISH Part 2 was met. After 12 months of treatment with risdiplam, 29.3% (95% CI: 17.8%, 14.3%) of patients in Part 2 were sitting without support, as assessed by Item 22 of the Bayley Scales of Infant and Toddler Development – Third Edition (BSID-III) gross motor scale. This proportion is significantly higher than the pre-defined performance criterion of 5% based on natural history data (p<0.0001). A summary of the key efficacy results from FIREFISH Part 2 is provided below.

Table 3. Summary of key efficacy results at month 12 (FIREFISH Part 2)

Efficacy Endpoints	**Proportion of Patients N=41 (90% CI)**
Motor function and development milestones	
BSID-III: sitting without support for at least 5 seconds p-value based on performance criterion of 5%[a]	29.3% (17.8%, 43.1%) <0.0001
CHOP-INTEND: score of 40 or higher p-value based on performance criterion of 17%[a]	56.1% (42.1%, 69.4%) <0.0001
CHOP-INTEND: increase of ⩾4 points from baseline p-value based on performance criterion of 17%[a]	90.2% (79.1%, 96.6%) <0.0001
HINE-2: motor milestone responders[b] p-value based on performance criterion of 12%[a]	78.0% (64.8%, 88.0%) <0.0001
Survival and event-free Survival	
Event-free survival[c] p-value based on performance criterion of 42%[a]	85.4% (73.4%, 92.2%) <0.0001
Alive p-value based on performance criterion of 60%[a]	92.7% (82.2%, 97.1%) 0.0005
Swallowing and feeding	
Ability to swallow	87.8% (76.1%, 95.1%)
Ability to feed orally[d]	82.9% (70.3%, 91.7%)
Healthcare utilization	
No hospitalizations[e]	48.8% (35.1%, 62.6%)

Abbreviations: CHOP-INTEND=Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2=Module 2 of the Hammersmith Infant Neurological Examination.

[a] p-values for survival and ventilation-free survival are based on a Z-test; p-values for all other endpoints (BSID-III, CHOP-INTEND, HINE-2) are based on an exact binomial test. Survival proportions estimated using Kaplan-Meier methodology.

[b] According to HINE-2: ⩾2 point increase [or maximal score] in ability to kick, OR ⩾1 point increase in the motor milestones of head control, rolling, sitting, crawling, standing or walking, AND improvement in more categories of motor milestones than worsening is defined as a responder for this analysis.

[c] An event is meeting the endpoint of permanent ventilation defined as tracheostomy or ⩾16 hours of non-invasive ventilation per day or intubation for > 21 consecutive days in the absence of, or following the resolution of, an acute reversible event. Three patients met the endpoint of permanent ventilation before Month 12. All 3 patients achieved an increase of at least 4 points in their CHOP-INTEND score from baseline.

[d] Includes patients who were fed exclusively orally (28 patients overall) and those who were fed orally in combination with a feeding tube (6 patients overall) at Month 12.

[e] Hospitalizations include all hospital admissions which spanned at least two days.

Later Onset SMA – SUNFISH (Part 2)

Study BP39055 (SUNFISH), is a 2-part, multicentre trial to investigate the efficacy, safety, PK and PD of risdiplam in SMA Type 2 or Type 3 patients between 2-25 years of age. Part 1 was the exploratory dose-

finding portion and Part 2 was the randomized, double-blind, placebo-controlled confirmatory portion. Patients from Part 1 did not take part in Part 2.

In SUNFISH Part 2, 180 patients were randomized with 2:1 ratio to receive either risdiplam at the therapeutic dose (see section 4.2) or placebo. Randomization was stratified by age group (2 to 5, 6 to 11, 12 to 17, 18 to 25 years old).

The median age of patients at the start of treatment was 9.0 years old (range 2-25 years old), the median time between onset of initial SMA symptoms to first treatment was 102.6 (1-275) months. Patients had a mean baseline MFM32 score of 46.1 and Revised Upper Limb Module (RULM) score of 20.1.

When compared to placebo, patients treated with risdiplam demonstrated a significant improvement in primary analysis for SUNFISH Part 2, which was the change from baseline score on the Motor Function Measure-32 (MFM32) scale after 12 months of treatment (1.55 points mean difference; 95% CI: 0.30, 2.81, p=0.0156). Patients 2-5 years old treated with risdiplam demonstrated the greatest improvement on MFM32 compared to placebo control (≥3 points increase in 78.1 % vs 52.9 %). Patients ≥18 years old treated with risdiplam achieved stabilization of disease (change from baseline MFM32 total score ≥ 0 point(s): 57.1% vs. 37.5%). Consistent improvement compared to baseline MFM32 was observed in both Type 2 and 3 SMA patients (1.54 points [95% CI: 0.06, 3.02]; 1.49 points [95% CI: -0.94, 3.93] respectively) treated with risdiplam compared to placebo control. The results of the primary analysis and key secondary endpoints are provided in Table 4 and Figure 1 below.

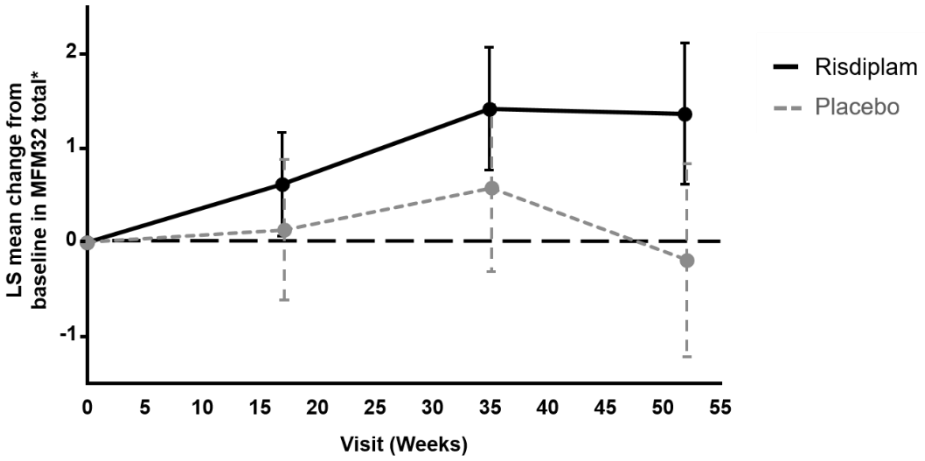
Table 4. Summary of efficacy in patients with later-onset SMA at month 12 of treatment (SUNFISH Part 2)

Endpoint	**Risdiplam n=120**	**Placebo n=60**
Primary Endpoint:		
Change from baseline in MFM32 total score[1] at Month 12 LS mean (95%, CI)	1.36 (0.61, 2.11)	-0.19 (-1.22, 0.84)
Difference from placebo Estimate (95% CI) p-value[2]	1.55 (0.30, 2.81) 0.0156	
Secondary Endpoints:		
Proportion of patients with a change from baseline in MFM32 total score[1] of 3 or more at Month 12 (95% CI)[1]	38.3% (28.9, 47.6)	23.7% (12.0, 35.4)
Odds ratio for overall response (95% CI) Adjusted (unadjusted) p-value[3,4]	2.35 (1.01, 5.44) 0.0469 (0.0469)	
Change from baseline in RULM total score[5] at Month 12 LS mean (95% CI)	1.61 (1.00, 2.22)	0.02 (-0.83, 0.87)
Difference from placebo estimate (95% CI) Adjusted (unadjusted) p-value[2,4]	1.59 (0.55, 2.62) 0.0469 (0.0028)	

LS=least squares

1. Based on the missing data rule for MFM32, 6 patients were excluded from the analysis (risdiplam n=115; placebo control n=59).
2. Data analysed using a mixed model repeated measure with baseline total score, treatment, visit, age group, treatment-by-visit and baseline-by-visit.
3. Data analysed using logistic regression with baseline total score, treatment and age group.
4. The adjusted p-value was obtained for the endpoints included in the hierarchical testing and was derived based on all the p-values from endpoints in order of the hierarchy up to the current endpoint
5. Based on the missing data rule for RULM, 3 patients were excluded from the analysis (risdiplam n=119; placebo control n=58).

Figure 1. Mean change from baseline in MFM32 total score over 12 months in SUNFISH Part 2[1]



[1]The least squares (LS) mean difference for change from baseline in MFM32 score [95% CI]

Use in Patients Previously treated with SMA

Study BP39054 (JEWELFISH) is a single arm, open-label study to investigate the safety, tolerability, PK and PD of risdiplam in patients with infantile-onset and later-onset SMA between 6 months and 60 years of age, who had previously received treatment with SMA therapies (including nusinersen and onasemnogene abeparvovec). Of the 174 patients enrolled, 76 patients were previously treated with nusinersen (9 patients with Type 1 SMA, 43 with Type 2 SMA and 24 with Type 3 SMA) and 14 patients were previously treated with onasemnogene abeparvovec (4 patients with Type 1 SMA and 10 with Type 2 SMA). After 4 weeks of treatment, patients had on average a greater than 2-fold increase in SMN protein levels in blood compared to baseline.

5.2 Pharmacokinetic properties

Pharmacokinetic parameters for risdiplam have been characterised in healthy adult subjects and in patients with SMA.

After administration of risdiplam as an oral solution, pharmacokinetics of risdiplam were approximately linear between 0.6 and 18 mg. Risdiplam's pharmacokinetics was best described by a population PK model with three-transit-compartment absorption, two-compartment disposition and first-order elimination. Body weight and age were found to have significant effect on the pharmacokinetics.

The estimated exposure (mean $AUC_{0\text{-}24h}$) for infantile-onset SMA patients (age 2-7 months at enrolment) at the therapeutic dose of 0.2 mg/kg once daily was 1930 ng.h/mL. The estimated exposure for later-onset SMA patients (2-25 years old at enrolment) in the SUNFISH (Part 2) study at the therapeutic dose (0.25 mg/kg once daily for patients with a body weight <20kg; 5 mg once daily for patients with a body weight ≥20 kg) was 2070 ng.h/mL. The observed maximum concentration (mean C_{max}) was 194 ng.h/mL at 0.2mg/kg in FIREFISH and 120 ng.h/mL in SUNFISH Part 2.

Absorption

Risdiplam was rapidly absorbed in the fasted state with a plasma t_{max} ranging from 1 to 4 hours after oral administration. Food (high-fat, high calorie breakfast) had no relevant effect on the exposure of risdiplam.

Distribution

The population pharmacokinetic parameter estimates were 98 L for the apparent central volume of distribution, 93 L for the peripheral volume, and 0.68 L/hour for the inter-compartment clearance

Risdiplam is predominantly bound to serum albumin, without any binding to alpha-1 acid glycoprotein, with a free fraction of 11%.
Animal studies have shown that risdiplam readily crosses the blood-brain-barrier.

Biotransformation

Risdiplam is primarily metabolized by flavin monooxygenase 1 and 3 (FMO1 and FMO3), and also by CYPs 1A1, 2J2, 3A4 and 3A7.

Co-administration of 200 mg itraconazole twice daily, a strong CYP3A inhibitor, with a single oral dose of 6 mg risdiplam showed no clinically relevant effect on the PK of risdiplam (11% increase in AUC, 9% decrease in C_{max}).

Elimination

Population PK analyses estimated an apparent clearance (CL/F) of 2.6 L/h for risdiplam.
The effective half-life of risdiplam was approximately 50 hours in SMA patients.

Risdiplam is a weak substrate of human MDR-1 in vitro. Risdiplam is a highly permeable compound, so active transport proteins are not expected to impact its oral bioavailability or distribution. Human MDR-1 inhibitors are not expected to result in a clinically significant increase of risdiplam concentrations.

Approximately 53% of the dose (14% unchanged risdiplam) was excreted in the feces and 28% in urine (8% unchanged risdiplam). Parent drug was the major component found in plasma, accounting for 83% of drug related material in circulation. The pharmacologically inactive metabolite M1 was identified as the major circulating metabolite.

Pharmacokinetics in special populations

Paediatric Population

Body weight and age were identified as covariates in the population PK analysis. The dose is therefore adjusted based on age (below and above 2 years) and body weight (up to 20 kg) to obtain similar exposure across the age and body weight range. No data are available in patients less than 2 months of age.

Geriatric Population
No dedicated studies have been conducted to investigate PK in patients with SMA above 60 years of age. Patients with SMA up to 60 years of age were included in the JEWELFISH study. Subjects without SMA up to 69 years of age were included in the clinical PK studies, which indicates that no dose adjustment is required for patients up to 69 years of age.

Renal impairment

No studies have been conducted to investigate the pharmacokinetics of risdiplam in patients with renal impairment. Elimination of risdiplam as unchanged entity via renal excretion is minor (8%).

Hepatic impairment

Mild and moderate hepatic impairment had no impact on the PK of risdiplam. After administration of 5 mg risdiplam, the mean ratios for C_{max} and AUC were 0.95 and 0.80 in mild (n=8) and 1.20 and 1.08 in moderate hepatic impaired subjects (n=8) versus matched healthy controls (n=10). The safety and PK in patients with severe hepatic impairment have not been studied.

Ethnicity

The pharmacokinetics of risdiplam do not differ in Japanese and Caucasian subjects.

5.3 Preclinical safety data

Carcinogenicity

The carcinogenic potential of risdiplam has not been fully evaluated. A carcinogenicity study with risdiplam in rasH2 transgenic mice did not give any evidence for a tumorigenic potential of risdiplam with animals exposed up to 7-fold the exposure in humans at the recommended therapeutic dose.

Genotoxicity

Risdiplam was negative in an in vitro Ames assay. In an in vivo combined bone marrow micronucleus and comet assay in rat, risdiplam was clastogenic, as evidenced by an increase in micronuclei in bone marrow, but was negative in the comet assay. A pronounced increase in bone marrow micronuclei was also observed in toxicity studies in adult and juvenile rats.
The no observed adverse effect level (NOAEL) across the studies is associated with an exposure of approximately 1.5-fold the exposure in humans at the recommended dose. Data indicated that this effect is indirect and secondary to an interference of risdiplam with the cell cycle of dividing cells. These effects also manifest in other tissues with high cell turnover with changes on the skin, the GI tract, in male germ cells, in embryonal toxicity, and in the bone marrow. Risdiplam does not possess a potential to damage DNA directly.

Impairment of Fertility

Treatment with risdiplam has been associated with male germ cell arrest in rats and monkeys. These effects led to degenerated spermatocytes, degeneration/necrosis of the seminiferous epithelium, and oligo/aspermia in the epididymis. Further, decreased sperm concentrations and motility associated with an increased number of spermatozoa morphology abnormalities were observed. In young rats, effects were seen at exposure levels reached at the recommended dose of risdiplam in patients. However, there was no impairment on male fertility seen in a respective study in rats. Sperm cell effects of risdiplam are likely related to an interference of risdiplam with the cell cycle of dividing cells and are stage specific and reversible. No effects were seen on female reproductive organs in rats and monkeys after treatment with risdiplam.

Reproductive Toxicity

In studies in pregnant rats treated with risdiplam, embryofetal toxicity with lower fetal weight and delayed development was evident. The NOAEL for this effect was approximately 2 fold above the exposure levels reached at the recommended therapeutic dose of risdiplam in patients. In studies with pregnant rabbits, dysmorphogenic effects were observed at exposures also associated with maternal toxicity. These consisted of four fetuses (4%) from 4 litters (22%) with hydrocephaly. The NOAEL was approximately 4 times the exposure levels reached at the recommended dose of risdiplam in patients.

In a pre- and post-natal study in rats treated daily with risdiplam, risdiplam caused a slight delay in gestation length. No adverse effects were recorded on the survival, growth, functional (behavioral or reproductive) performance of the offspring. There were no effects on female germ cells, as assessed by primordial follicle counts and ovarian histopathology.

Studies in pregnant and lactating rats showed that risdiplam crosses the placenta barrier and is excreted into milk.

Effect on retinal structure

Chronic treatment of monkeys with risdiplam yielded evidence for an effect on the retina in terms of photoreceptor degeneration starting in the periphery of the retina. Upon cessation of treatment, the effects on the retinogram were partially reversible but the photoreceptor degeneration did not reverse. The effects were monitored by optical coherence tomography (OCT) and in the electroretinography (ERG). Some experimental data indicate that the effect may be caused by an impairment of photoreceptor recycling in the retinal pigment epithelium. The effect has a clear NOAEL at the clinical dose used for risdiplam. Effects were seen with exposures in excess of 2 times the exposure in humans at the recommended dose.

No such findings were observed in albino or pigmented rats when dosed chronically with risdiplam at exposures exceeding those in the monkey.

Effect on epithelial tissues

Effects on skin (reversible parakeratosis with flaky skin correlating histologically with squamous hyperplasia observed in the epidermis; at high doses, reddening, peeling and shedding with erosions/ulcer), larynx and eyelid histology and the GI tract were evident in rats and monkeys treated with risdiplam. Changes started to be seen at high doses with treatment of 2 weeks and longer. With chronic treatment for 39 weeks in monkeys, the NOAEL was at an exposure in excess of 2-times the average exposure in humans at the recommended therapeutic dose. Skin epithelial effects as observed in animal studies have not been observed in clinical trials in SMA patients.

Effect on haematological parameters

In the acute bone marrow micronucleus test in rats, a reduction of more than 50% in the ratio of polychromatic (young) to normochromatic (adult) erythrocytes, indicative of substantial bone marrow toxicity, was observed at the high dose with exposure in excess of 15-times the average exposure in humans at the recommended dose. With treatment of rats for 4 weeks, such effects were not seen up to the highest dose with an exposure of approximately 7-times the average exposure in humans at the recommended dose while early deaths and sacrifices likely based on haematological effects were seen with chronic treatment of rats over 26 weeks at the same exposure. The NOAEL for hematological effects in rats treated for 26 weeks was attained at approximately 3.5 times higher than exposure achieved in humans at the therapeutic dose.

Juvenile animal studies

Risdiplam was studied for toxicity with chronic administration in rats and monkeys including juvenile animal studies. In terms of toxicity seen after treatment with risdiplam in various organ systems with high cell turnover (skin, GI-tract, bone marrow), animal studies do not indicate any clinically relevant differences in sensitivity between juvenile, adolescent and adult animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

mannitol (E421)
tartaric acid (E334)
sodium benzoate (E211)
ascorbic acid (300)
isomalt
polyethylene glycol 6000
disodium edetate dihydrate
sucralose
strawberry flavor

6.2 Incompatibilities

No incompatibilities between risdiplam and the recommended oral syringes have been observed.

6.3 Shelf life

Powder for oral solution

3 years

Constituted oral solution

64 days stored in a refrigerator (2°C–8°C).

6.4 Special precautions for storage

Powder for oral solution

Do not store above 25°C.

Keep in the original amber bottle to protect from light.

Constituted oral solution

Store in a refrigerator (2°C–8°C).

Do not freeze.

Keep the oral solution in the original bottle and keep the bottle always in an upright position with the cap tightly closed.

This medicine should not be used after the expiry date ("EXP" for the powder, and "Discard After" for the constituted oral solution) written on the pack and on the bottle.

6.5 Nature and contents of container

Risdiplam 0.75 mg/mL powder for oral solution is supplied as powder in an amber glass bottle.

Each100 mL amber glass bottle contains 60 mg risdiplam in 2.0 g powder for oral solution. When constituted, the volume of the oral solution is 80 mL. Each mL of the constituted oral solution contains 0.75 mg risdiplam.

Each carton contains; one bottle

6.6 Special precautions for disposal and other handling

Risdiplam powder must be constituted to the oral solution by a healthcare professional prior to being dispensed.

Preparation of the 60 mg risdiplam Powder for Oral solution (*0.75 mg/mL)*

Avoid exposure to airborne dust of risdiplam powder and follow local guideline(s). It is recommended to use appropriate equipment.

Avoid direct contact with skin or mucous membranes with the dry powder and the constituted solution. Wear disposable gloves during constitution and while wiping the outer surface of the bottle/cap and cleaning the working surface after constitution. If such contact occurs, wash thoroughly with soap and water; rinse eyes with water.

Instructions for constitution:

1. Gently tap the bottom of the closed glass bottle to loosen the powder.
2. Remove the cap. Do not throw away the cap.
3. Carefully pour 79 mL of purified water or sterile water for injection (SWFI) into the risdiplam bottle to yield the 0.75 mg/mL oral solution.

4. Insert a Press-In bottle adapter into the opening by pushing it down against the bottle lip. Ensure it is completely pressed against the bottle lip.
5. Re-cap the bottle tightly and shake well for 15 seconds. Wait for 10 minutes. You should have obtained a clear solution. Thereafter, shake well again for after 15 seconds.
6. Write the date of expiration of the constituted oral solution on the bottle label. (calculated as 64 days after constitution, the day of constitution is counted as day 0).
7. Put the bottle back in its original carton with syringes (in pouches).
8. Dispense with the "Instructions for Use" with risdiplam and applicable Treatment Protocol for Patients. Alert patients to read the important handling information described in the instructions for use.

Store the constituted oral solution in the refrigerator at 2°C - 8°C. Do not freeze. Discard any unused portion 64 days after constitution.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. SCIENTIFIC OPINION HOLDER

Roche Products Limited
6 Falcon Way, Shire Park
Welwyn Garden City
AL7 1TW
United Kingdom

8. EAMS NUMBER

00031/0011

9. DATE OF SCIENTIFIC OPINION

Additional information

Each prescribing physician will be required to complete the initial application and drug supply request form to confirm patient eligibility within the scheme, once the patient has signed the informed consent form. These forms can be requested by sending an email to welwyn.risdiplameams@roche.com

A Physician Agreement and Safety Data Exchange agreement will be signed by the prescribing physician. Once the signed documents are returned, Roche will arrange safety training and each prescribing physician will also be provided with a physician pack containing all the relevant documents needed, including the adverse events reporting form needed to manage patients receiving risdiplam under the EAMS.

Contact information

Contact details for reporting Adverse Events/Special Situations/Pregnancies:

SAE Email Address: welwyn.uk_dsc@roche.com

SAE Facsimile Transmission: 01707 367582

SAE TELEPHONE CONTACT (24 hours): 01707 367554

Name: UK Drug Safety Centre

Contact email for the EAMS programme (excluding AE reporting):

welwyn.risdiplameams@roche.com

Contact Details for Medical Information

Roche Medical Information on 0800 328 1629 or email medinfo.uk@roche.com