PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

Evrysdi 0,75 mg/mL powder for oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Risdiplam

Evrysdi is supplied as a powder in an amber glass bottle. Each bottle is filled with 2,0 g of powder which contains 60 mg risdiplam. Each mL of the constituted solution contains 0,75 mg risdiplam.

The powder is constituted with purified water or water for injection to yield an oral solution containing 0,75 mg/mL of risdiplam (see section 6.6).

For the full list of excipients, see section 6.1

Contains sodium benzoate 1,5 % (m/v) as a preservative

Contains sugar: sucralose 0,2 mg/mL, isomalt2,97 mg/mL & mannitol 16,81 mg/mL

Contains antioxidant: ascorbic acid 0,18 mg/mL

3. PHARMACEUTICAL FORM

Powder for oral solution: 60 mg as a light yellow, yellow, greyish yellow, greenish yellow or light green powder for constitution. Following constitution, the volume of the greenish yellow to yellow solution is 80 mL, providing 60 mg/80 mL (0,75 mg/mL) risdiplam.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Evrysdi is indicated for the treatment of spinal muscular atrophy (SMA) in patients with a clinical diagnosis of SMA Type 1, Type 2 and Type 3.

4.2 Posology and method of administration

General

Treatment with Evrysdi should be initiated by a medical practitioner with experience in the management of SMA.

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

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

Posology

Evrysdi is taken orally once daily using the oral syringe provided, at approximately the same time each day.

Recommended dosage

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

Table 1: Dosing Regimen by Age and Body Weight

Age[a] and Body Weight	***Recommended Daily Dose***
16 days to < 2 months of age	0,15 mg/kg
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

[a] based on corrected age for preterm infants

Dose changes must be made under the supervision of a HCP. Treatment with a daily dose above 5 mg has not been studied. No data are available in infants below 16 days of age.

Method of administration

Evrysdi is taken orally once a day at approximately the same time each day, using the re-usable oral syringe provided. It is recommended a HCP discuss with the patient or caregiver how to prepare the

prescribed daily dose prior to administration of the first dose (see section 6.6).

For comprehensive instructions on the administration, see Instructions for Use booklet provided.

The patient should drink water after taking Evrysdi to ensure the medicinal product has been completely swallowed. If the patient is unable to swallow and has a nasogastric or gastrostomy tube *in situ*, risdiplam should be administered via the tube. The tube should be flushed with water after delivering Evrysdi (see section 6.6).

Delayed or Missed Doses

Risdiplam is taken orally once daily at approximately the same time each day. If a dose of Evrysdi is missed, administer as soon as possible if still within 6 hours of the scheduled dose. Otherwise, the missed dose should be skipped and the next dose should be administered at the regularly scheduled time the next day.

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

Special Dosage Instructions

Elderly use

The pharmacokinetics (PK) and safety of Evrysdi have been assessed in subjects without SMA up to 69 years of age. Evrysdi has not been studied in patients with SMA above 60 years of age (see section 5.2).

Renal Impairment

The safety and efficacy of Evrysdi in patients with renal impairment have not been studied. No dose adjustment is expected to be required in patients with renal impairment (see section 5.2).

Hepatic Impairment

The PK, safety and tolerability of a single dose of 5 mg risdiplam were evaluated in subjects with mild or moderate hepatic impairment in a dedicated clinical study. Mild or moderate hepatic impairment had no impact on the PK of risdiplam. No dose adjustment is therefore required in patients with mild or moderate hepatic impairment. Evrysdi has not been studied in patients with severe hepatic impairment (see section 4.2 and 5.2)

Paediatric population

The safety and efficacy of Evrysdi in paediatric patients < 16 days of age have not yet been established (see section 5.2). The safety and efficacy of Evrysdi in preterm infants before reaching the corrected age of 16 days have not been established.

4.3 Contraindications

- Hypersensitivity to the Risdiplam or to any of the excipients listed in section 6.1.
- Women and men of reproductive potential who are not using highly effective contraception
- Pregnancy

4.4 Special warnings and precautions

Embryo-foetal toxicity

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 Evrysdi in female patients, and 4 months after the last dose of Evrysdi in male patients (see section 5.2).

Potential effects on male fertility

Due to reversible effects 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 5.2).

Excipients

Isomalt

Evrysdi contains isomalt (2,97 mg per mL). Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Sodium

Evrysdi contains 0,375 mg of sodium benzoate per mL. Sodium benzoate may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old).

Evrysdi contains less than 1 mmol sodium (23 mg) per 5 mg dose, i.e. is essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

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

Effects of other medicinal products on Evrysdi

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

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

Effects of Evrysdi on concomitant medicines

In vitro Evrysdi and its major circulating metabolite M1 did not induce CYP1A2, 2B6, 2C8, 2C9, 2C19, or 3A4. *In vitro* Evrysdi 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.

Evrysdi is a weak inhibitor of CYP3A. In healthy adult subjects, oral administration of Evrysdi 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. Based on 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 Evrysdi and its major metabolite are not significant inhibitors of human MDR1, organic anion-transporting polypeptide (OATP) 1B1, OATP1B3, organic anion transporter 1 and 3 (OAT 1 and 3). However, Evrysdi and its metabolite are *in vitro* inhibitors of the human organic cation transporter 2 (OCT2) and the multimedicine and toxin extrusion (MATE) 1 and MATE2-K transporters. At therapeutic medicine concentrations, no interaction is expected with OCT2 substrates. Based on *in vitro* data, Evrysdi may increase plasma concentrations of medicines 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

Pregnancy

Evrysdi should not be used during pregnancy. The safety during labour and delivery has not been established.

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

Lactation

Women taking Evrysdi should not breastfeed their infants.

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).

Fertility

Male patients

Male fertility may be compromised while on treatment, based on nonclinical findings. In rat and

monkey reproductive organs, sperm degeneration and reduced sperm numbers were observed. The effects on sperm cells are reversible upon discontinuation of Evrysdi.

Prior to initiating treatment, fertility preservation strategies should be discussed with male patients. 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 for a minimum of 4 months. Treatment may be re-started after conception.

Female patients

Based on nonclinical data, an impact of Evrysdi on female fertility is not expected.

Contraception

Male and female patients of reproductive potential should adhere to the following contraception requirements:

- Female patients of childbearing potential should use highly effective contraception during treatment and for at least 1 month after the last dose.
- Male patients, with female partners of childbearing potential, should both use highly effective contraception during treatment and for at least 4 months after his last dose.

Pregnancy testing

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a. Summary of the Safety Profile

The safety profile of Evrysdi is based on four clinical trials FIREFISH, SUNFISH, RAINBOWFISH and

JEWELFISH.

The FIREFISH study is a two-part, open-label study that enrolled 62 patients with infantile-onset (Type 1) SMA between 2,2 and 6,9 months of age. The median exposure duration was 27,8 months (range: 0,6 to 46,5 months) (see section 5.1). The adverse drug reactions (ADRs) observed in clinical trials for infantile-onset SMA in Table 2 are based on the pooled analysis of patients from FIREFISH Part 1 and 2. ADRs are defined as adverse events occurring in ≥ 5 % of patients and where a causal association with Evrysdi is possible.

The SUNFISH study is a two-part study with later-onset (Type 2 and 3) SMA between 2-25 years of age (see section 5.1). The ADRs observed in clinical trials for later-onset SMA in Table 2 are based on SUNFISH Part 2 (n=180), the randomised double-blind, placebo-controlled portion with a follow-up duration of at least 12 months. ADRs are defined as adverse events occurring in ≥ 5 % more frequently or at least 2 times as frequently as in placebo control patients and where a causal association with Evrysdi is possible.

The common adverse reactions of 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.

b. Tabulated list of adverse reactions

The corresponding frequency category for each adverse medicine 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 medicine reactions from clinical trials (Table 2) are listed by MedDRA system organ class.

Table 2 Summary of adverse drug reactions for infantile-onset SMA patients observed in FIREFISH (Part 1 and 2) study and later-onset SMA patients observed in SUNFISH Part 2 study

System Organ Class	Infantile-onset SMA patients observed in FIREFISH (Part 1 and 2) study	Later-onset SMA patients observed in SUNFISH Part 2 study
Gastrointestinal Disorders		
Diarrhoea	Very common	Very common
Nausea	Not applicable	Common
Mouth ulcerations and aphthous ulcers	Common	Common
Skin and Subcutaneous Tissue Disorders		
Rash*	Very common	Very common
Nervous system disorders		
Headache	Not applicable	Very common
General disorders and administration site conditions		
Pyrexia (including hyperxia)	Very common	Very common
Infections and infestations		
Urinary tract infections (including cystitis)	Common	Common
Musculoskeletal and connective tissue disorders		
Arthralgia	Not applicable	Common

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

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

The RAINBOWFISH study is an open-label, single-arm study. At the time of interim analysis, the study had enrolled 18 patients with pre-symptomatic SMA between 16 and 40 days of age at first dose. The median exposure duration was 8,7 months (range: 0,5 to 22,8 months) (see section 5.1). The safety profile of Evrysdi in pre-symptomatic patients in the RAINBOWFISH study is consistent with the safety profile for symptomatic SMA patients treated with Evrysdi in clinical trials.

c. Safety Profile in Patients Previously Treated with Other SMA Modifying Therapies

Based on the primary analysis of the JEWELFISH study, the safety profile of Evrysdi in treatment non-naive patients who received Evrysdi for up to 59 months (including those previously on treatment with nusinersen (n=76) or with onasemnogene abeparvovec (n=14)) is consistent with the safety profile for treatment naive SMA patients treated with Evrysdi in the FIREFISH (Part 1 and Part 2) and SUNFISH (Part 1 and Part 2), and RAINBOWFISH studies. (see section 5.1).

Postmarketing Experience

The following adverse drug reaction has been identified from postmarketing experience with Evrysdi (Table 3). Adverse drug reaction is listed according to system organ classes in MedDRA.

Table 3 Adverse drug reactions from postmarketing experience

System Organ Class	Adverse Reaction	Frequency Category
Skin and subcutaneous disorders	Cutaneous vasculitis[1]	Unknown

[1] Incidence rate and frequency category cannot be estimated based on available data

Cutaneous vasculitis was identified during postmarketing experience. Symptoms recovered after permanent discontinuation of Evrysdi.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

There is no experience with overdosage of Evrysdi in clinical trials. There is no known antidote for

overdosage of Evrysdi. In case of overdosage, the patient should be closely supervised and supportive care instituted

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other medicines 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. 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. Thus, risdiplam treats SMA by increasing and sustaining functional SMN protein levels.

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.

In FIREFISH, SUNFISH and JEWELFISH clinical trials for infantile-onset SMA and later-onset SMA patients, 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 as measured in blood. This increase in SMN protein was sustained throughout the treatment period of at least 24 months.

Pharmacodynamic effects

In all clinical trials for infantile-onset SMA and later-onset SMA patients, 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 as measured in blood. This increase in SMN protein was sustained throughout the treatment period of up to 2 years (see section 5.1).

Clinical efficacy and safety

The efficacy of risdiplam for the treatment of SMA patients with infantile-onset (Type 1) and later-onset (Type 2 and 3) SMA was evaluated in 2 pivotal clinical studies, FIREFISH and SUNFISH, and supported by additional data from the JEWELFISH study. The efficacy of risdiplam for the treatment of pre-symptomatic SMA patients was evaluated based on an interim analysis of the ongoing RAINBOWFISH study. The overall findings of these studies support the effectiveness of risdiplam for SMA patients.

Infantile-onset SMA

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.

A total of 62 patients with symptomatic Type 1 SMA were enrolled in FIREFISH Part 1 (n=21) and Part 2 (n=41), of which 58 patients received the therapeutic dose. The median age of onset of clinical signs and symptom was 1,5 months (range: 0,9 to 3.0 months). The median age at enrolment was 5,6 months (range: 2,2 to 6,9 months), and the median time between onset of symptoms and the first dose was 3.7 months (range 1,0 to 6,0 months). Of these patients, 60 % were female, 57 % were Caucasian, and 29 % were Asian. At baseline the median CHOP-INTEND score was 23 (range: 8 to

37), and the median HINE-2 score was 1 (range: 0 to 5). The baseline demographics and disease characteristics of those enrolled in Part 1 were comparable to those in Part 2.

The primary endpoint was the proportion of patients with the ability to sit without support for at least 5 seconds (BSID-III gross motor scale, Item 22) after 12 months of treatment in Part 2; 29 % of patients (n=12/41, 90 % CI: 17,8 %, 43,1 %, p <0.0001) achieved this milestone.

The key efficacy endpoints of risdiplam treated patients in FIREFISH Part 1 and Part 2 are shown in Table 4.

Table 4: Summary of Key Efficacy Endpoints at Month 12 and Month 24 (FIREFISH Part 1 and Part 2)

Efficacy Endpoints	**Month 12**	**Month 24**
	Proportion of Patients (90% CI)	
Motor Function and Development Milestones	**N = 58**[a]	
BSID-III: sitting without support for at least 5 seconds	32,8% (22,6%, 44,3%)	60,3% (48,7%, 71,2%)
CHOP-INTEND: score of 40 or higher	56,9% (45,3%, 68,0%)	74,1% (63,0%, 83,3%)
CHOP-INTEND: increase of ≥4 points from baseline	89,7% (80,6%, 95,4%)	87,9% (78,5%, 94,2%)
HINE-2: motor milestone responders[b]	77,6% (66,7%, 86,2%)	82,8% (72,5%, 90,3%)
Feeding		
Ability to feed orally[c]	84,5% (74,5%, 91,7%)	82,8% (72,5%, 90,3%)
Healthcare Utilization		
No hospitalisations[d]	48,3% (36,9%, 59,8%)	34,5% (24,2%, 46,0%)
Survival and Event-Free Survival	**N=62**[a]	
Event-free survival[e]	87,1% (78,1%, 92,6%)	83,8% (74,3%, 90,1%)
Alive	91,9% (83,9%, 96,1%)	90,3% (81,9%, 94,9%)

Abbreviations: BSID-III: Bayley Scales of Infant and Toddler Development – Third Edition; CHOP-INTEND=Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2=Module 2 of the Hammersmith Infant Neurological Examination.

[a] For survival and ventilation-free survival, data were pooled from all patients who received any dose of risdiplam in Part 1 and Part 2 (n=62). For the motor function and development milestone, feeding, and healthcare utlization efficacy endpoints, data were pooled from all patients who received the therapeutic dose of risdiplam (all patients in Part 2 and those in the high-dose cohort of Part 1; n=58).

[b] HINE-2 responder definition: ≥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] Includes patients who were fed exclusively orally (41 patients at Months 12 and 24) and those who were fed orally in combination with a feeding tube (8 patients at Month 12 and 7 patients at Month 24).

[d] Hospitalisations include all hospital admissions which spanned at least two days.

[e] 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. Four patients met the endpoint of permanent ventilation before Month 24. These 4 patients achieved an increase of at least 4 points in their CHOP-INTEND score from baseline.

At Month 24, 40 % (23/58) of patients who received the therapeutic dose achieved sitting without support for 30 seconds (BSID-III, Item 26). In addition, patients continued to achieve additional motor milestones as measured by the HINE-2 at Month 24; 78% of patients were able to roll (31 % of patients could roll to the side, 7 % could roll from prone to supine and 40 % could roll from supine to prone), and 28 % of patients achieved a-standing measure (16 % supporting weight and 12 % standing with support).

The proportion of patients alive without permanent ventilation (event-free survival) was 84 % for all patients at Month 24. Six infants died (4 within the first 3 months following study enrolment) and one additional patient withdrew from treatment and died 3,5 months later. Four patients required permanent ventilation by Month 24.

These results indicate a clinically meaningful deviation from the natural history of untreated infantile-onset SMA. Untreated patients with infantile-onset SMA would never be able to sit without support and only 25 % would be expected to survive without permanent ventilation beyond 14 months of age.

Later Onset SMA

Study BP39055 (SUNFISH), is a 2-part, multicenter 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 dose-finding portion and Part 2 was the randomised double-blind placebo-controlled confirmatory portion. Patients from Part 1 did not take part in Part 2.

The primary endpoint was the change from baseline score at Month 12 on the Motor Function Measure-32 (MFM32). The MFM32 has the ability to assess a wide range of motor function across a broad range of SMA patients. The total MFM32 score is expressed as a percentage (range: 0 to 100) of the maximum possible score, with higher scores indicating greater motor function. The MFM32 measures motor function abilities, which relate to important daily functions. Small changes in motor function can result in meaningful gain or loss of daily function(s).

SUNFISH Part 2

SUNFISH Part 2 is the randomised, double-blinded, placebo-controlled portion of the SUNFISH study in 180 non-ambulant patients with Type 2 (71 %) or Type 3 (29 %) SMA. Patients were randomised with 2:1 ratio to receive either risdiplam at the therapeutic dose (see Section 4,2) or placebo. Randomisation 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. Of the 180 patients included in the trial, 51 % were female, 67 % Caucasian and 19 % Asian. At baseline, 67 % of patients had scoliosis (32 % of patients with severe scoliosis). Patients had a mean baseline MFM32 score of 46,1 and Revised Upper Limb Module (RULM) score of 20,1. The overall baseline demographic characteristics were well balanced between risdiplam and placebo groups with the exception of an imbalance of patients with scoliosis (63,3 % of patients in the risdiplam arm and 73,3 % of patients in the placebo control).

The primary analysis for SUNFISH Part 2, the change from baseline in MFM32 total score at Month 12 showed a clinically meaningful and statistically significant difference between patients treated with risdiplam and placebo. The results of the primary analysis and key secondary endpoints are shown in Table 5.

Table 5. Summary of Efficacy in Patients with Later-Onset SMA at Month 12 of Treatment (SUNFISH Part 2)

Endpoint	Evrysdi (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)	38,3 % (28,9; 47,6)	23,7 % (12,0; 35,4)
Odds ratio for overall response (95 % CI) Adjusted[4] (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[4] (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 (Evrysdi 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. Unadjusted p-value was tested at the 5 % significance level.
5. Based on the missing data rule for RULM, 3 patients were excluded from the analysis (Evrysdi n=119; placebo control n=58)

When compared to placebo, patients treated with risdiplam demonstrated significant improvements in motor function assessed by the MFM32 (1,55 points mean difference; p = 0,0156) after 12 months of treatment. Patients 2-5 years old treated with risdiplam demonstrated the greatest improvement on MFM32 compared to placebo control (≥3 points increase 78,1 % vs 52,9 %). Patients ≥18 years old treated with risdiplam achieved stabilisation 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 study also met a secondary independent motor function outcome, RULM. On the RULM, statistically significant and clinically meaningful improvements in motor function were observed after 12 months of treatment compared to baseline. The patients 2-5 years old treated with risdiplam

demonstrated the greatest improvement on the RULM (3,41 points [95 % CI: 1,55; 5,26]) and improvement was also observed in the patients ≥18 years old (1,74 points [95 % CI: -1,06; 4,53]).
Upon completion of 12 months of treatment, 117 patients continued to receive risdiplam. At the time of the 24 month analysis, these patients who were treated with risdiplam for 24 months overall experienced maintenance of improvement in motor function between month 12 and month 24. The mean change from baseline for MFM32 was 1.83 (95 % CI: 0,74, 2,92) and for RULM was 2,79 (95 % CI: 1,94, 3,64) at month 24.

SUNFISH Part 1

The efficacy of risdiplam in later-onset SMA patients was also supported by results from Part 1, the dose-finding part of SUNFISH. In Part 1, 51 patients with Type 2 and 3 SMA (including 7 ambulatory patients) between 2 to 25 years old were enrolled. After 1 year of treatment at the therapeutic dose (the dose selected for Part 2), there was a clinically meaningful improvement in motor function as measured by MFM32 with a mean change from baseline of 2,7 points (95 % CI: 1,5; 3,8). The improvement in MFM32 was maintained up to 2 years on risdiplam treatment (mean change of 2.7 points [95% CI: 1,2; 4,2]).

In an exploratory analysis, the motor function assessed by MFM was compared between SUNFISH Part 1 and a natural history cohort (weighted based on key prognostic factors). The MFM total change from baseline after 1 year and 2 years was greater in patients receiving risdiplam compared to the natural history cohort (after 1 year: 2.7 point difference; p< 0.0001; after two years; 4.0 point difference; p< 0.0001). The natural history cohort experienced a decline in motor function as expected based on the natural progression of SMA (after 1 year: -0,6 mean change; after 2 years: -2.0 mean change).

Pre-symptomatic SMA

Study BN40703 (RAINBOWFISH) is an open-label, single-arm, multicenter clinical study to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of risdiplam in infants from birth to 6 weeks of age (at first dose) who have been genetically diagnosed with SMA but do not yet present

with symptoms.

At the time of the interim analysis, a total of 18 patients with pre-symptomatic SMA were enrolled in RAINBOWFISH. The efficacy in pre-symptomatic SMA patients was evaluated in 7 of 18 patients who had been treated with risdiplam for at least 12 months. Of these patients, the median age at first dose was 35 days (range: 16 to 40 days), 71% were female, 100% were Caucasian. Four patients had 2 copies of the SMN2 gene, 2 patients had 3 copies of the SMN2 gene, and 1 patient had 4 or more copies of the SMN2 gene. At baseline the median CHOP-INTEND score was 46 (range: 35 to 53) and the median ulnar nerve compound muscle action potential (CMAP) amplitude was 3,0 mV (range: 0,5 to 6,6 mV). The baseline median HINE-2 score was 1 (range: 0 to 4) and is in the expected range for this age group of patients.

The results of the interim analysis in RAINBOWFISH are shown in Table 6.

Table 6: Summary of Key Efficacy Endpoints for Pre-symptomatic Patients Completing 12 Months of Treatment (RAINBOWFISH Interim Analysis)

Efficacy Endpoints	**Proportion of Patients N=7 (90 % CI)**
Motor Function and Development Milestones	
CHOP-INTEND: Total score of 40 or higher	100 % (65,2 %, 100,0 %)
CHOP-INTEND: Total score of 50 or higher	100% (65,2 %, 100,0 %)
Feeding	
Ability to feed orally[a]	100% (65,2 %, 100,0 %)
Healthcare Utilization	
No hospitalisations[b]	100% (65,2 %, 100,0 %)
Event-Free Survival[c]	100 %

Abbreviations: CHOP-INTEND=Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI=Confidence Interval

a All patients were fed exclusively by mouth.

b Hospitalisations include all hospital admissions which spanned at least two days, and which are not due to study requirements.

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.

At the time of interim analysis, patients achieved additional motor milestones as measured by the HINE-2 at Month 12 (N=7); 100 % patients could sit (6 patients could pivot/rotate and 1 patient achieved stable sit), 71 % of patients could stand (3 patients could stand unaided and 2 patients could stand with support), and 57 % of patients could walk or bounce (3 patients could walk independently and 1 patient could bounce; the remaining patients were not tested at Month 12).

Use in Patients Previously Treated with Other SMA Modifying Therapies

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 were previously treated 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 previously received treatment with onasemnogene abeparvovec (4 patients with Type 1 SMA and 10 with Type 2 SMA). The median age of patients at the start of risdiplam treatment was 14 years (range 1-60 years). At baseline, 83 % of patients of the 168 patients 2–60 years had scoliosis (39 % of patients had severe scoliosis) and 63 % of patients had a Hammersmith Functional Motor Scale Expanded (HFMSE) score <10 points. The study also included 16 ambulant patients (2 – 46 years of age).

Patients had a greater than 2-fold median increase in SMN protein levels in blood compared to baseline after 4 weeks of risdiplam treatment. The increase in SMN protein was maintained throughout the treatment period of at least 2 years.

Exploratory efficacy was assessed with age appropriate motor function measures including MFM-32 and RULM scales for patients 2-60 years of age, BSID-III and HINE-2 for patients less than 2 years of age and the Six-Minute Walk Test (6MWT) in ambulant patients ≥ 6 years of age. At the primary analysis scheduled at month 24 of treatment, patients 2-60 years of age showed overall stabilization in motor function in MFM-32 and RULM (n=137, and n=133, respectively). Patients less than 2 years (n=6) maintained or gained motor milestones such as head control, rolling and sitting independently. The 6MWT results showed a mean improvement of 30.88 meters (95 % CI: -5,54, 67,29, n=8). All ambulatory patients retained their ability to walk. The safety data in JEWELFISH are consistent with the known safety profile of treatment naïve SMA patients receiving risdiplam.

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, PK of risdiplam were approximately linear between 0,6 and 18 mg. risdiplam's PK 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 PK.

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. For pre-symptomatic infants age 16 days to <2 months in the RAINBOWFISH study, the estimated exposure is 2080 ng.h/mL at 0.15 mg/kg after 2 weeks once daily administration. The estimated exposure for later-onset SMA patients (2-25 years old at enrolment) in the SUNFISH study (Part 2) at the therapeutic dose (0,25 mg/kg once daily for patients with a body weight < 20 kg; 5 mg once daily for patients with a body weight ≥ 20 kg) was 2070 ng.h/mL. The observed maximum concentration (mean Cmax) was 194 ng.h/mL at 0,2 mg/kg in FIREFISH and 120 ng.h/mL in SUNFISH Part 2, and the estimated maximum concentration at 0.15 mg/kg in RAINBOWFISH is 113 ng/mL.

Absorption: Risdiplam was rapidly absorbed in the fasted state with a plasma tmax 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 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 %.

Metabolism: Risdiplam is primarily metabolised 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 Cmax).

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 not a substrate of human multimedicine resistance protein 1 (MDR1).

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

Pharmacokinetics in Special Populations

Elderly Population

No dedicated studies have been conducted to investigate the PK of risdiplam 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 clinical PK studies, which indicates that no dose adjustment is required for patients up to 69 years of age.

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 months and 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 16 days of age.

Renal impairment

No studies have been conducted to investigate the PK 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 Cmax 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.

5.3 Preclinical safety data

5.3.1 Carcinogenicity

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 therapeutic dose.

5.3.2 Genotoxicity

Risdiplam is not mutagenic in a bacterial reverse mutation assay. In mammalian cells in vitro and in bone marrow of rats, risdiplam increases the frequency of micronucleated cells. Micronucleus induction in bone marrow was observed in several toxicity studies in rats (adult and juvenile animals). 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 therapeutic 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 gastrointestinal (GI) tract, in male germ cells, in embryonal toxicity, and in the bone marrow. Risdiplam does not possess a potential to damage DNA directly.

5.3.3 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 therapeutic 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.

5.3.4 Reproductive toxicity

In studies in pregnant rats treated with risdiplam, embryofoetal toxicity with lower foetal weight and delayed development was evident. The NOAEL for this effect was approximately two fold above the exposure levels reached at the 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 foetuses (4 %) from 4 litters (22 %) with hydrocephaly. The NOAEL was approximately four times the exposure levels reached at the therapeutic 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 (behavioural 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.

5.3.5 Other

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 therapeutic dose. No such findings were observed in albino or pigmented rats when dosed chronically with risdiplam at exposures exceeding those in the monkey. Such findings have not been observed in clinical trials in SMA patients with regular ophthalmological monitoring (including SD OCT and visual function assessment).

Effect on epithelial tissues

Effects on skin, 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 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 level with exposure in excess of 15-times the average exposure in humans at the therapeutic 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 therapeutic 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 haematological effects in rats treated for 26 weeks was attained at approximately 3,5 times higher than exposure achieved in humans at the therapeutic dose. Micronucleus induction in bone marrow was observed in several toxicity studies in rats (adult and juvenile animals) with a NOAEL exposure of approximately 1,5 fold the average exposure in humans at the therapeutic dose. Haematological parameters remained unchanged during treatment with risdiplam in clinical trials in SMA patients.

Juvenile animal studies

Risdiplam was studied for toxicity with chronic administration in rats and monkeys including juvenile animal studies. Studies in juvenile animals did not indicate any specific effect of treatment with risdiplam on developing organ systems. 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 differences in sensitivity between juvenile, adolescent and adult animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ascorbic acid (E300)

disodium edetate dehydrate

isomalt

macrogol/polyethylene glycol 6000

mannitol (E421)

sodium benzoate (E211)

strawberry flavour

sucralose

tartaric acid (E334)

6.2 Incompatibilities

No incompatibilities between Evrysdi and the oral syringes provided have been observed.

6.3 Shelf life

Powder for oral solution

24 months

Constituted oral solution

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

Patients should take Evrysdi immediately after it is drawn up into the oral syringe. If it is not taken within 5 minutes, the dose should be discarded and a new dose should be prepared.

This medicine should not be used

- after the expiry date ("EXP" for the powder, and "Discard After" for the constituted oral solution) on the carton and on the bottle.
- if the oral solution is kept outside of the refrigerator for more than a total combined time of 5 days at room temperature (below 40˚C),
- or if the oral solution is kept above 40˚C.

6.4 Special precautions for storage

Powder for oral solution

Keep in the original amber bottle.

Do not store above 25 °C.

Constituted oral solution

Store in a refrigerator at 2 °C – 8 °C for up to 64 days.

If necessary, the patient or their caregiver may store the oral solution at room temperature (below 40 ˚C) for no more than a total combined time of 5 days.

Do not freeze.

Do not store the oral solution above 40 ˚C

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

6.5 Nature and contents of container

Evrysdi 0,75 mg/mL powder for oral solution is supplied as powder in an amber glass bottle.

Each 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, 1 press-in bottle adapter, two 1 mL re-usable oral syringes, two 6 mL re-usable amber oral syringes and two 12 mL re-usable amber oral syringes.

6.6 Special Instructions for Use, Handling and Disposal

Evrysdi powder must be constituted to the oral solution by an HCP prior to being dispensed.

Preparation of the 60 mg Evrysdi Powder for Oral solution (0,75 mg/mL)

Caution should be exercised in the handling of Evrysdi powder for oral solution (see Section 4.4). Avoid inhalation and 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 contact occurs, wash thoroughly with soap and water; rinse eyes with water.

Selecting the Oral Syringe for the Prescribed Daily Dose

Table 7. Selecting the Oral Syringe for the Prescribed Daily Dose of Evrysdi

Syringe size	*Dosing volume*	*Syringe Markings*
1 mL	0,3 mL to 1,0 mL	0,01 mL
6 mL	1,0 mL to 6,0 mL	0,1 mL
12 mL	6,2 mL to 6,6 mL	0,2 mL

For the calculation of dosing volume, the syringe markings need to be considered. Round the dose volume to the nearest graduation mark on the selected oral syringe.

Instructions for administration

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 Evrysdi bottle to yield the 0,75 mg/mL oral solution.
4. Hold the medicine bottle on the table with one hand. Insert the press-in bottle adapter into the opening by pushing it down with the other hand. Ensure the adapter is completely pressed against the bottle lip.
5. Put the cap back on the bottle and close the bottle tightly. Ensure it is completely closed and then shake well for 15 seconds. Wait for 10 minutes. You should have obtained a clear solution. If not, shake well again for after 15 seconds.
6. Write the “Discard after” date of the solution on the bottle label and carton. (The “Discard after” date is calculated as 64 days after constitution, the day of constitution is counted as day 0). Put the bottle back in its original carton with syringes (in pouches), Professional Information, and Instructions for Use booklet.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Roche Products (Pty) Ltd

90 Bekker Road, Hertford Office Park,

Building E, Vorna Valley, Midrand

Johannesburg, 1686

South Africa

Roche Ethical Assistance Line (REAL) toll-free: 0800 21 21 25

8. REGISTRATION NUMBER

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 23 August 2022

10. DATE OF REVISION OF THE TEXT

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Botswana: S2 BOT2304010

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