# 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 sterile 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 16 mg & mannitol 1344,70 mg

Contains antioxidant – ascorbic acid 14,10 mg

## 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, in patients 2 months of age and older.

## 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 and Body Weight*** | ***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 |

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 2 months 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***

No dose adjustment is required in patients with mild or moderate hepatic impairment. Evrysdi has not been studied in patients with severe hepatic impairment (see section 5.2).

***Paediatric population***

The safety and efficacy of Evrysdi in paediatric patients < 2 months of age have not yet been established (see section 5.2).

## 4.3 Contraindications

- Hypersensitivity to the Risdiplam or to any of the excipients listed in section 6.1.
- Women and med 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).

## 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 three clinical trials FIREFISH, SUNFISH, 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. Fifty-five patients received Evrysdi treatment for more than 12 months (range: 18 days – 35 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 3 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.

Tables 2 and 3 summarise the adverse reactions that have been reported in association with the use of Evrysdi in clinical trials (FIREFISH, SUNFISH and JEWELFISH).

**Table 2. Adverse reactions occurring in patients with infantile-onset (Type 1) SMA observed in FIREFISH (Part 1 and 2) study**

| **System Organ Class** | Number of events/ 100 patients years<br>Total exposure in patient years = 87,9 | Frequency Category |
|---|---|---|
| **Gastrointestinal Disorders** | | |
| Diarrhoea | 13,7 | Very common |
| **Skin and Subcutaneous Tissue Disorders** | | |
| Rash* | 23,9 | Very common |

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

**Table 3. Adverse reactions occurring in patients in patients with later-onset (Type 2 and 3) 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 |

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

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.

***c. Safety profile in Patients Previously treated for SMA***

The safety profile of Evrysdi in treatment non-naive patients in the JEWELFISH study 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) 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).

**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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Medicine Reaction Report Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

**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.

**Pharmacodynamic effects**

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

**Clinical efficacy and safety**

The efficacy of Evrysdi 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 overall findings of these studies support the effectiveness of Evrysdi 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 Evrysdi 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 Parts 1 and 2, the key efficacy endpoint was the ability to sit without support for at least 5 seconds, as measured by Item 22 of the Bayley Scales of Infant and Toddler Development – Third Edition (BSID-III) gross motor scale, after 12 months of treatment.

*FIREFISH 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). At

baseline, the median CHOP-INTEND score was 22,0 points (range: 8,0-37,0) and the median HINE-2 score was 1,0 (range: 0,0-5,0).

The primary endpoint was the proportion of patients with the ability to sit without support for at least 5 seconds after 12 months of treatment (BSID-III gross motor scale, Item 22). The efficacy endpoints of Evrysdi treated patients were compared to similar cohorts of untreated patients with infantile-onset SMA from natural history (defined as performance criteria) as shown in Table 4.

**Table 4. 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<br>p-value based on performance criterion of 5 %[a] | 29,3 % (17,8 %, 43,1 %)<br><0,0001 |
| CHOP-INTEND: score of 40 or higher<br>p-value based on performance criterion of 17 %[a] | 56,1 % (42,1 %, 69,4 %)<br><0,0001 |
| CHOP-INTEND: increase of ≥ 4 points from baseline<br>p-value based on performance criterion of 17 %[a] | 90,2 % (79,1 %, 96.6 %)<br><0,0001 |
| HINE-2: motor milestone responders[b]<br>p-value based on performance criterion of 12 %[a] | 78,0 % (64,8 %, 88,0 %)<br><0,0001 |
| Survival and Event-Free Survival | |
| Event-Free Survival[c]<br>p-value based on performance criterion of 42 %[a] | 85,4 % (73,4 %, 92,2 %)<br><0,0001 |
| Alive<br>p-value based on performance criterion of 60 %[a] | 92,7 % (82,2 %, 97,1 %)<br>0,0005 |
| Swallowing and Feeding | |
| Ability to swallow | 85,4 % (73,15 %, 93,43 %) |
| Ability to feed orally[d] | 82,9 % (70,3 %, 91,7 %) |
| Healthcare Utilisation | |
| No hospitalisations[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, CHOPINTEND, 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. Hospitalisations include all hospital admissions, which spanned at least two days.

After 12 months of treatment with Evrysdi, 29 % (12/41) of patients met the criteria for sitting without support (BSID-III, Item 22), 93 % (38/41) of patients were alive, and 85 % (35/41) of patients were alive and event-free (without permanent ventilation).

***Later Onset SMA***

Study BP39055 (SUNFISH), is a 2-part, multicenter trial to investigate the efficacy, safety, PK and PD of Evrysdi 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 Evrysdi 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 Evrysdi and placebo groups with the exception of an imbalance of patients with scoliosis (63,3 % of patients in the Evrysdi 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 Evrysdi and placebo. The results of the primary analysis and key secondary endpoints are shown in Table 5, Figure 3, and Figure 4.

**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<br>LS Mean (95 %, CI) | 1,36<br>(0,61, 2,11) | -0,19<br>(-1,22, 0,84) |
| Difference from Placebo<br>Estimate (95 % CI)<br>p-value[2] | 1,55<br>(0,30; 2,81)<br>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 %<br>(28,9; 47,6) | 23,7 %<br>(12,0; 35,4) |
| Odds ratio for overall response (95 % CI)<br>Adjusted[4] (unadjusted) p-value[3,4] | 2,35 (1,01; 5,44)<br>0,0469 (0,0469) | |
| Change from baseline in RULM total score[5] at Month 12<br>LS Mean (95 % CI) | 1,61<br>(1,00; 2,22) | 0,02<br>(-0,83; 0,87) |
| Difference from Placebo<br>Estimate (95 % CI) adjusted[4] (unadjusted) p-value[2,4] | 1,59<br>(0,55; 2,62)<br>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 Evrysdi 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 Evrysdi demonstrated the greatest improvement on MFM32 compared to placebo control (≥3 points increase 78,1 % vs 52,9 %). Patients ≥18 years old treated with Evrysdi 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 Evrysdi 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 Evrysdi 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]).

***Use in Patients Previously Treated for SMA***

Study BP39054 (JEWELFISH) is a single arm, open-label study to investigate the safety, tolerability, PK and PD of Evrysdi in patients with infantile-onset and later-onset between 6 months and 60 years of age, who 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). Patients had on average a greater than 2-fold increase in SMN protein levels in blood compared to baseline after 4 weeks of Evrysdi treatment.

## 5.2 Pharmacokinetic Properties

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

After administration of Evrysdi 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 AUC0-24h) for infantile-onset SMA patients (age 2-7 months at enrollment) 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 enrollment) 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.

***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 Evrysdi 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 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.

***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 narrow. 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, embryofetal toxicity with lower fetal 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 fetuses (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 (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.

### 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. Hematological parameters remained unchanged during treatment with Evrysdi 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.

### 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.

Do not freeze.

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 6 mL re-usuable 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 a 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 6. Selecting the Oral Syringe for the Prescribed Daily Dose of Evrysdi**

| *Syringe size* | *Dosing volume* | *Syringe increments* |
|---|---|---|
| 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 increments need to be considered. Round the dose volume to the closest increment marked 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

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

55/17.3/0466

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

**Date of registration:** 23 August 2022

## 10. DATE OF REVISION OF THE TEXT

n/a