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EVRYSDI®

Risdiplam

1. DESCRIPTION

1.1 THERAPEUTIC / PHARMACOLOGIC CLASS OF DRUG

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

1.2 TYPE OF DOSAGE FORM

Powder for oral solution

1.3 ROUTE OF ADMINISTRATION

Oral or enteral

1.4 STERILE / RADIOACTIVE STATEMENT

Not applicable

1.5 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: risdiplam

Excipients: Ascorbic Acid, Disodium Edetate Dihydrate, Isomalt, Macrogol/Polyethylene Glycol 6000, Mannitol, Sodium Benzoate, Strawberry Flavor, Sucralose, Tartaric Acid

Evrysdi is supplied as a powder in a 100 mL, Type III amber glass bottle. Each bottle is filled with 2.0 g of powder containing 60 mg of 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 *4.2 Special Instructions for Use, Handling and Disposal*).

2. CLINICAL PARTICULARS

2.1 THERAPEUTIC INDICATION(S)

Evrysdi is indicated for the treatment of spinal muscular atrophy (SMA).

2.2 DOSAGE AND ADMINISTRATION

Evrysdi oral solution must be constituted by a health care provider (HCP) prior to being dispensed.

General
SMA treatment should be initiated as early as possible after diagnosis.
Evrysdi is taken orally once daily using the oral syringe provided, at approximately the same time each day.
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
Use the re-usable oral syringe provided to deliver the daily dose of Evrysdi. 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 *4.2 Special Instruction for Use, Handling and Disposal*).

The patient should drink water after taking Evrysdi to ensure the drug has been completely swallowed. If the patient is unable to swallow and has a nasogastric or gastrostomy tube, administer Evrysdi via the tube. The tube should be flushed with water after delivering Evrysdi (see section *4.2 Special Instructions for Use, Handling and Disposal*).

Delayed or Missed Doses
Evrysdi 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, skip the missed dose and take the next dose at the regularly scheduled time the next day.

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

2.2.1 Special Dosage Instructions

Pediatric use
The safety and efficacy of Evrysdi in pediatric patients < 16 days of age have not yet been established (see section *3.1.2 Clinical / Efficacy Studies*). The safety and efficacy of Evrysdi in preterm infants before reaching the corrected age of 16 days have not been established.

Geriatric 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 sections *3.2.5 Pharmacokinetics in Special Populations* and *2.5.5 Geriatric Use*).

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 sections *3.2.5 Pharmacokinetics in Special Populations* and *2.5.6 Renal Impairment*).

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 sections *3.2.5 Pharmacokinetics in Special Populations* and *2.5.7 Hepatic Impairment*).

2.3 CONTRAINDICATIONS

Evrysdi is contraindicated in patients with a known hypersensitivity to risdiplam or any of the excipients.

2.4 WARNINGS AND PRECAUTIONS

2.4.1 General

Embryo-fetal Toxicity
Embryo-fetal toxicity has been observed in animal studies (see section *3.3 Nonclinical Safety*). 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 *2.5 Use in Special Populations*).

Potential Effects on Male Fertility
Due to reversible effects of Evrysdi 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 Evrysdi. (see sections *2.5 Use in Special Populations* and *3.3.3 Impairment of Fertility*).

2.4.2 Drug Abuse and Dependence

Evrysdi does not have the potential to lead to abuse and dependence.

2.4.3 Ability to Drive and Use Machines

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

2.5 USE IN SPECIAL POPULATIONS

Use with SMA gene therapy
Efficacy data of Evrysdi treatment when used in patients that previously received SMN1 gene therapy is not available.

2.5.1 Females and Males of Reproductive Potential

Fertility
Male patients
Male fertility may be compromised while on treatment with Evrysdi based on nonclinical findings. In rat and monkey reproductive organs, sperm degeneration and reduced sperm numbers were observed (see *section 3.3.3 Impairment of Fertility*). The effects on sperm cells are reversible upon discontinuation of risdiplam.
Prior to initiating treatment with Evrysdi, fertility preservation strategies should be discussed with male patients receiving Evrysdi. Male patients may consider sperm preservation, prior to treatment initiation or after a treatment free period of at least 4 months. Male patients who wish to father a child should stop treatment with Evrysdi 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 (see section *3.3.3 Impairment of Fertility*).

Pregnancy testing
The pregnancy status of females of reproductive potential should be verified prior to initiating Evrysdi therapy. Pregnant women should be clearly advised of the potential risk to the fetus.

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

2.5.2 Pregnancy

There are no clinical data from the use of Evrysdi in pregnant women. Risdiplam has been shown to be embryo-fetotoxic and teratogenic in animals. Based on the findings from animal studies, risdiplam crosses the placental barrier and may cause fetal harm (see section *3.3.4 Reproductive toxicity*).

Evrysdi should not be used during pregnancy unless the benefit to the mother outweighs the potential risks to the fetus. If a pregnant woman needs to be treated with Evrysdi, she should be clearly advised on the potential risk to the fetus.

The safe use of Evrysdi during labor and delivery has not been established.

2.5.3 Lactation

It is not known whether Evrysdi is excreted in human breast milk. Studies in rats show that risdiplam is excreted into milk (see section *3.3.4 Reproductive toxicity*). As the potential for harm to the nursing infant is unknown, a decision must be made with the patient's treating physician. It is recommended not to breastfeed during treatment with Evrysdi.

2.5.4 Pediatric Use

(See sections *2.1 Therapeutic Indication(s), 2.2 Dosage and Administrations, 3.1.2 Clinical / Efficacy Studies, 3.2.5 Pharmacokinetics in Special Populations, 2.6 Undesirable Effects* and *3.3.5 Other, Juvenile animal studies.*)

2.5.5 Geriatric Use

The PK and safety of Evrysdi have been studied 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 sections *3.2.5 Pharmacokinetics in Special Populations* and *3.1.2 Clinical Studies*).

2.5.6 Renal Impairment

The safety and efficacy of Evrysdi in patients with renal impairment have not been studied. A change in dose is not expected to be required for patients with renal impairment (see sections *2.2.1 Special Dosage Instructions, 3.2.3 Metabolism, 3.2.4 Elimination*, and *3.2.5 Pharmacokinetics in Special Populations*).

2.5.7 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 sections *2.2.1 Special Dosage Instructions* and *3.2.5 Pharmacokinetics in Special Populations*).

2.6 UNDESIRABLE EFFECTS

2.6.1 Clinical Trials

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 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 *3.1.2 Clinical / Efficacy Studies*). 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 SMA between 2-25 years of age (see section *3.1.2 Clinical / Efficacy Studies*). The ADRs observed in clinical trials for later-onset SMA in Table 3 are based on SUNFISH Part 2 (n=180), the randomized double-blind, placebo-controlled portion with a follow-up duration of at least 12 months. ADRs are defined as adverse events occurring in ≥ 5% of Evrysdi treated patients which occurred ≥ 5% more frequently or at least 2 times as frequently as in placebo control patients and where a causal association with Evrysdi is possible.

In infantile-onset SMA patients, the most common adverse reactions observed in Evrysdi clinical studies were pyrexia (48.4%), rash (27.4%) and diarrhoea (16.1%).

In later-onset SMA patients, the most common adverse reactions observed in Evrysdi clinical studies were pyrexia (21.7%), headache (20.0%), diarrhoea (16.7%), and rash (16.7%).

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

System Organ Class	Adverse Reaction	Incidence N=62 n (%)	Number of events/ 100 patient years Total exposure in patient years = 142.4	Frequency Category
Gastrointestinal Disorders	Diarrhea	12 (19.4)	9.8	Very common
Skin and Subcutaneous Tissue Disorders	Rash*	18 (29.0)	16.2	Very common

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

Table 3 Summary of adverse drug reactions for later-onset SMA patients observed in SUNFISH Part 2 study

System Organ Class	Adverse Reaction	Evrysdi N=120 n (%)	Placebo N=60 n (%)	Frequency Category
Gastrointestinal Disorders	Diarrhea	20 (16.7)	5 (8.3)	Very common
Skin and Subcutaneous Tissue Disorders	Rash*	20 (16.7)	1 (1.7)	Very common

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

The adverse reactions diarrhea 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 (see section *3.3.5 Nonclincal Safety*).

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 *3.1.2 Clinical / Efficacy Studies*). 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.

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), SUNFISH (Part 1 and Part 2), and RAINBOWFISH studies. In the JEWELFISH study, 76 patients previously treated with nusinersen and 14 patients previously treated with onasemnogene abeparvovec were enrolled (see section *3.1.2 Clinical / Efficacy Studies*).

2.6.2 Postmarketing Experience

The following adverse drug reaction has been identified from postmarketing experience with Evrysdi (Table 4). Adverse drug reaction is listed according to system organ classes in MedDRA.

Table 4 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.

2.7 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.

2.8 INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

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

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

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

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

Evrysdi is a weak inhibitor of CYP3A. In healthy adult subjects, administration of Evrysdi once daily for 2 weeks slightly increased the exposure of midazolam, a sensitive CYP3A substrate (AUC 11%; C_{max} 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 risdiplam 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). Risdiplam and its metabolite are, however, *in vitro* inhibitors of the human organic cation transporter 2 (OCT2) and the multidrug and toxin extrusion (MATE)1 and MATE2-K transporters. At therapeutic drug concentrations, no interaction is expected with OCT2 substrates. Based on *in vitro* data, Evrysdi may increase plasma concentrations of drugs eliminated via MATE1 or MATE2-K. The clinical relevance of the co-administration with MATE1/2-K substrates is unknown.

Based on in vitro data, risdiplam may increase plasma concentrations of medicinal products eliminated via MATE1 or MATE2-K, such as metformin. If coadministration cannot be avoided, drug-related toxicities should be monitored and dosage reduction of the co-administered medicinal product should be considered if needed.

The potential for synergistic effects of concomitant administration of risdiplam with retinotoxic drugs has not been studied. Therefore, caution in using concomitant medications with known or suspected retinal toxicity is recommended.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 PHARMACODYNAMIC PROPERTIES

3.1.1 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 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 *3.1.2 Clinical / Efficacy Studies*).

3.1.2 Clinical / Efficacy Studies

The efficacy of Evrysdi for the treatment of SMA patients with infantile-onset and later-onset SMA was evaluated in 2 pivotal clinical studies, FIREFISH and SUNFISH, and supported by additional data from the JEWELFISH study. The efficacy of Evrysdi 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 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 the dose-finding part of the study. The confirmatory Part 2 of the FIREFISH study assessed the efficacy of Evrysdi at the therapeutic dose selected based on the results from Part 1 (see *section 2.2 Dosing and Administration*). 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 Evrysdi treated patients in FIREFISH Part 1 and Part 2 are shown in Table 5, and displayed in Figure 1 and Figure 2.

Table 5: 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 hospitalizations[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] Hospitalizations include all hospital admissions which spanned at least two days.

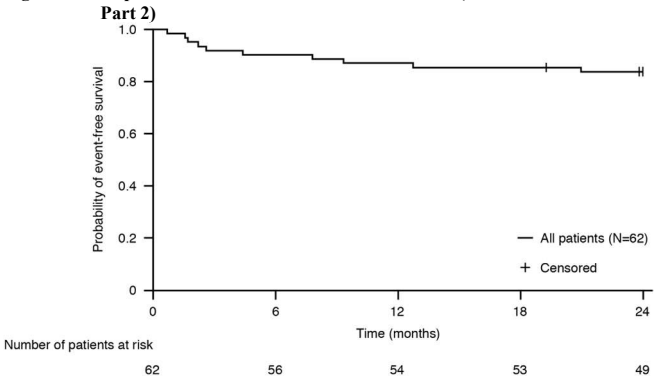
[e] An event is meeting the endpoint of permanent ventilation defined as tracheostomy or ≥16 hours of non-invasive ventilation per day or intubation for > 21 consecutive days in the absence of, or following the resolution of, an acute reversible event. Four patients met the endpoint of permanent ventilation 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, see Figure 1. 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.

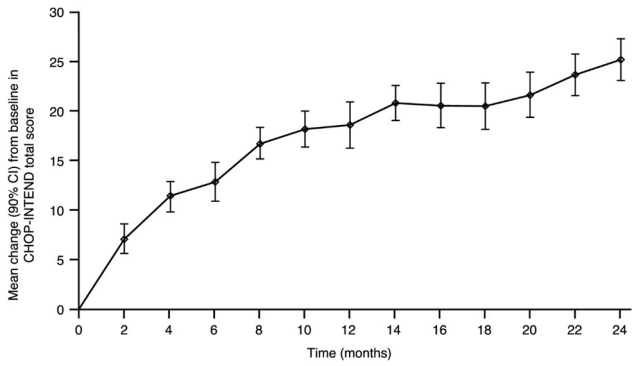
These results indicate a clinically meaningful deviation from the natural history of untreated infantile-onset SMA. Untreated patients with infantile-onset SMA would never be able to sit without support and only 25% would be expected to survive without permanent ventilation beyond 14 months of age.

Figure 1 Kaplan-Meier Plot of Event-Free Survival (FIREFISH Part 1 and Part 2)



+ Censored: two patients were censored because they attended the Month 24 visit early, 1 one patient was censored after discontinuing treatment and died 3.5 months later

Figure 2 Mean change from baseline in CHOP-INTEND Total Score (FIREFISH Part 1 and Part 2)



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 randomized, 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 randomized, 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 randomized with 2:1 ratio to receive either Evrysdi at the therapeutic dose (see section *2.2 Dosage and Administration*) or placebo. Randomization was stratified by age group (2 to 5, 6 to 11, 12 to 17, 18 to 25 years old).

The median age of patients at the start of treatment was 9.0 years old (range 2-25 years old), the median time between onset of initial SMA symptoms to first treatment was 102.6 (1-275) months. 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 6, Figure 3, and Figure 4.

Table 6 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 (unadjusted) p-value[3,4]	2.35 (1.01, 5.44) 0.0469 (0.0469)	
Change from baseline in RULM total score[5] at Month 12 LS Mean (95% CI)	1.61 (1.00, 2.22)	0.02 (-0.83, 0.87)
Difference from Placebo Estimate (95% CI) adjusted (unadjusted) p-value[2,4]	1.59 (0.55, 2.62) 0.0469 (0.0028)	

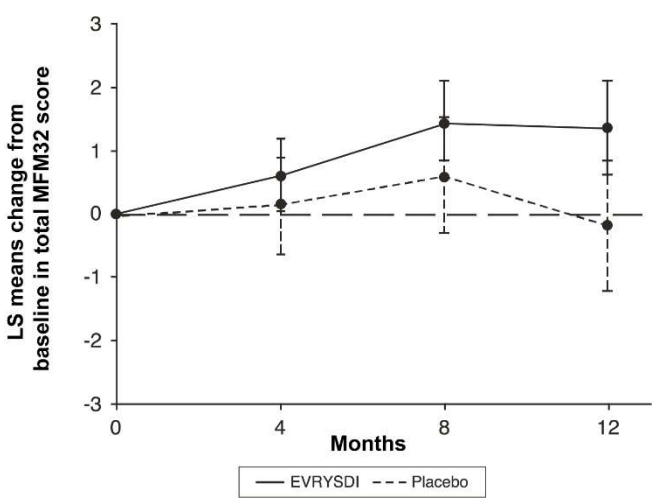
LS=least squares

1. Based on the missing data rule for MFM32, 6 patients were excluded from the analysis (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 stabilization of disease (change from baseline MFM32 total score ≥ 0 point(s): 57.1% vs. 37.5%). Consistent improvement compared to baseline MFM32 was observed in both Type 2 and 3 SMA patients (1.54 points [95% CI: 0.06, 3.02]; 1.49 points [95% CI: -0.94, 3.93] respectively) treated with Evrysdi compared to placebo control.

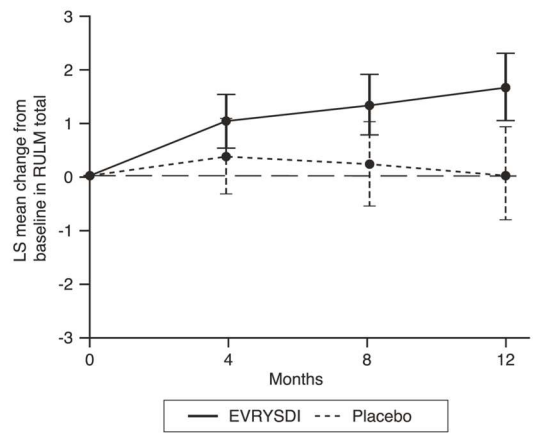
The study also met a secondary independent motor function outcome, RULM. On the RULM, statistically significant and clinically meaningful improvements in motor function were observed after 12 months of treatment compared to baseline. The patients 2-5 years old treated with Evrysdi demonstrated the greatest 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])

Figure 3 Mean Change from Baseline in Total MFM32 Score Over 12 months in SUNFISH Part 2[1]



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

Figure 4 Mean Change from Baseline in Total RULM Score Over 12 months in SUNFISH Part 2[1]



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

Upon completion of 12 months of treatment, 117 patients continued to receive Evrysdi. At the time of the 24 month analysis, these patients who were treated with Evrysdi 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 Evrysdi 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 Evrysdi 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 Evrysdi 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 Evrysdi 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 Evrysdi 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 7 and displayed in Figure 5.

Table 7: 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 hospitalizations[b]	100% (65.2%, 100.0%)
Event-Free Survival[c]	100%

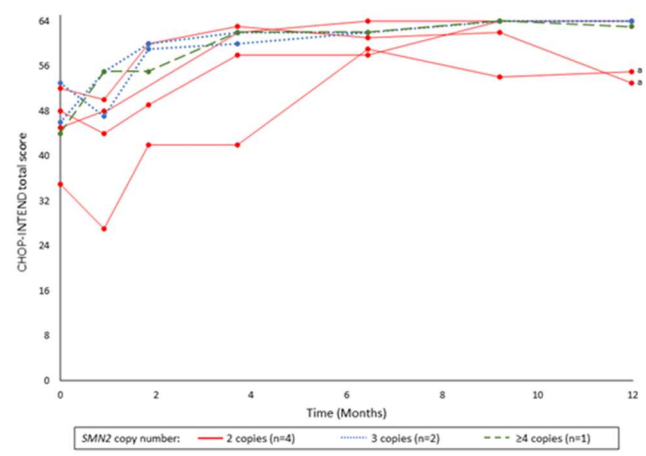
Abbreviations: CHOP-INTEND=Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI=Confidence Interval

a All patients were fed exclusively by mouth.

b Hospitalizations 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.

Figure 5 Plot of Individual CHOP-INTEND Total Score Over Time (RAINBOWFISH; N=7)



Abbreviations: SMN2=Survival of Motor Neuron 2; CMAP=Compound Muscle Action Potential

a Baseline CMAP negative peak amplitude for two patients were 0.5 mV and 0.6 mV. All other patients had baseline CMAP negative peak amplitude of ≥1.5 mV.

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 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 SMA 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.

3.1.3 Immunogenicity

Not applicable

3.2 PHARMACOKINETIC PROPERTIES

Pharmacokinetic parameters for Evrysdi have been characterized 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 $AUC_{0\text{-}24h}$) 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. 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 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 C_{max}) was 194 ng/mL at 0.2 mg/kg in FIREFISH and 120 ng/mL in SUNFISH Part 2, and the estimated maximum concentration at 0.15 mg/kg in RAINBOWFISH is 113 ng/mL.

3.2.1 Absorption

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

3.2.2 Distribution

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

Risdiplam is predominantly bound to serum albumin, without any binding to alpha-1 acid glycoprotein, with a free fraction of 11%.

3.2.3 Metabolism

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

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

3.2.4 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 multidrug resistance protein 1 (MDR1).

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

3.2.5 Pharmacokinetics in Special Populations

Pediatric 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.

Geriatric 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.

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 C_{max} and AUC were 0.95 and 0.80 in mild (n=8) and 1.20 and 1.08 in moderate hepatic impaired subjects (n=8) versus matched healthy controls (n=10). The safety and PK in patients with severe hepatic impairment have not been studied.

Ethnicity

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

3.3 NONCLINICAL SAFETY

3.3.1 Carcinogenicity

A 2-year carcinogenicity study in rat is ongoing. A study using rasH2 transgenic mice with 6 months duration of treatment did not generate any evidence for a tumorigenic potential.

3.3.2 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.

3.3.3 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.

3.3.4 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.

3.3.5 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 hematological 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 hematological effects were seen with chronic treatment of rats over 26 weeks at the same exposure. The NOAEL for hematological effects in rats treated for 26 weeks was attained at approximately 3.5 times higher than exposure achieved in humans at the therapeutic dose. 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.

4. PHARMACEUTICAL PARTICULARS

4.1 STORAGE

Storage

As registered locally.

Keep in the original amber bottle.

Powder: Do not store above 25°C.

After constitution, the oral solution should be stored in the refrigerator (2°C to 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 bottle and keep the bottle always in an upright position with the cap tightly closed.

Shelf life

As registered locally.

This medicine should not be used and should be discarded:

- after the expiry date ("EXP" for the powder, and "Discard After" for the constituted oral solution) on the pack 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.

4.2 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 *2.4 Warning and Precautions*). Avoid inhalation and avoid direct contact with skin or mucous membranes with the dry powder and the constituted solution.

Wear disposable gloves during constitution and while wiping the outer surface of the bottle/cap and cleaning the working surface after constitution. If contact occurs, wash thoroughly with soap and water; rinse eyes with water.

Selecting the Oral Syringe for the Prescribed Daily Dose

Table 8 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.

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.

Instructions for administration

Dosing of Evrysdi oral solution (0.75 mg/mL)

Refer to section *2.1 Dosage and Administration* for the proper dosing regimen instructions.

For detailed instructions on constitution and administration please refer to the Instructions for Constitution and Instructions for Use.

Incompatibilities

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

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment must be minimized. Medicines must not be disposed of via wastewater and disposal through household waste should be avoided.

Local requirements should be followed for the disposal process of unused/expired medicines.

4.3 PACKS

Bottle containing powder for oral solution 1

Medicine: keep out of reach of children

Current at July 2022

Roche F. Hoffmann-La Roche Ltd, Basel, Switzerland

Instructions For Constitution (0.75 mg/mL)

EVRYSDI®

Risdiplam

Instructions for Constitution

(FOR HEALTHCARE PROFESSIONALS ONLY)

Each Evrysdi carton contains (See figure A):

1. 1 Cap
2. 1 Evrysdi bottle
3. 2 Oral syringes 12 mL (in pouches)
4. 2 Oral syringes 6 mL (in pouches)
5. 1 Press-in bottle adapter

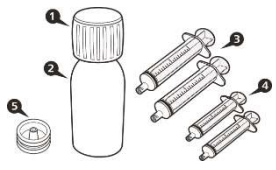


Figure A

Important information about Evrysdi

- **Avoid inhaling** Evrysdi powder.
- **Use gloves.**
- **Do not** use if the powder expiry date has passed. The powder expiration date is printed on the bottle label.
- **Do not** dispense the constituted solution if the solution's Discard After date exceeds the original powder expiration date.
- **Avoid getting contact** with the medicine on your skin. If the medicine gets on your skin, wash the area with soap and water.
- **Do not** use the medicine if any of the supplies are damaged or missing.
- Use Purified Water or Water for Injection (WFI) to constitute the medicine.
- Do not add oral syringes other than the ones provided in the carton.

How to store Evrysdi

- Store the powder (unconstituted medicine) at room temperature, below 25°C (77°F) and keep it in the carton.
- Store the solution (constituted medicine) in a refrigerator between 2°C to 8°C (35°F to 46°F).
- Keep the oral solution in the original bottle and always keep the bottle in an upright position with the cap tightly closed.

Constitution

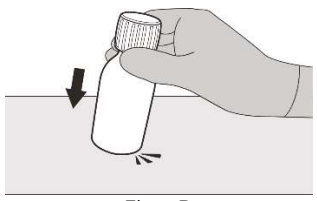


Figure B

Step 1
Gently tap the bottom of the bottle to loosen the powder (see Figure B).

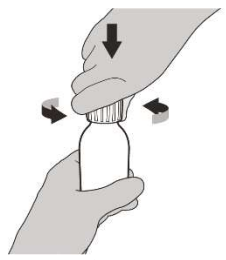


Figure C

Step 2
Remove the cap by pushing it down and then twisting to the left (counter-clockwise) (see Figure C). Do not throw away the cap.

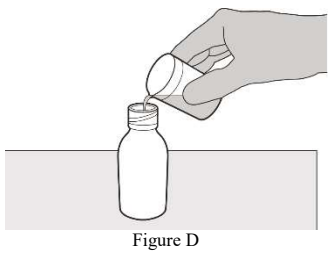


Figure D

Step 3
Carefully pour 79 mL of Purified Water or Water for Injection (WFI) into the medicine bottle (see Figure D).

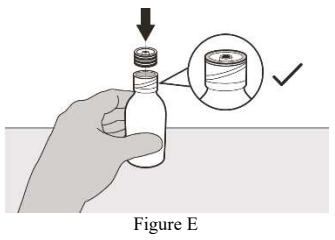


Figure E

Step 4
Hold the medicine bottle on a table with one hand.

Insert the press-in bottle adapter into the opening by pushing it down with the other hand. Ensure it is completely pressed against the bottle lip (see Figure E).

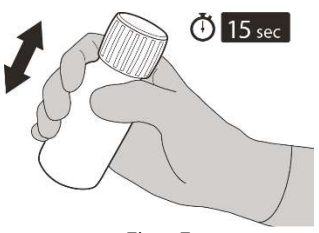


Figure F

Step 5
Put the cap back on the bottle. Turn the cap to the right (clockwise) to close the bottle.

Ensure it is completely closed and then shake well for 15 seconds (see Figure F).

Wait for 10 minutes. You should have obtained a **clear solution**.

Afterwards, shake well again for another 15 seconds.

Figure G

Step 6
Calculate the Discard After date **as 64 days** after constitution *(*Note: the day of constitution is counted as day 0. For example, if constitution is on the 1st of April, the Discard After date will be the 4th of June).

Write the Discard After date of the solution on the bottle label (see Figure G) and carton.

Put the bottle back in its original carton, with syringes (in pouches). Store the carton into the refrigerator.

Instructions For Use – Administration (0.75 mg/mL)

EVRYSDI®

Risdiplam

Instructions for Use

Be sure to read and understand this **Instructions for Use** before you start using Evrysdi for information on how to prepare and give Evrysdi through an oral syringe, gastrostomy tube (G-tube), or nasogastric tube (NG-tube).

If you have any questions about how to use Evrysdi, contact your healthcare provider.

Evrysdi should come as a liquid in a bottle when you receive it. Do not use if the medicine in the bottle is a powder and contact your healthcare provider.

Important information about Evrysdi

- Ask your healthcare provider to show you the correct syringe you should use and how to measure your prescribed daily dose.
- Always use the re-usable the oral syringes provided in the pack to measure your prescribed daily dose. The oral syringe protects the medicine from light.
- Two oral syringes of each size are provided in case one gets lost or damaged. Contact your healthcare provider if both oral syringes are lost or damaged. They will advise you on how to continue to take your medicine.
- See "**How to select the correct oral syringe to use for your prescribed daily dose of Evrysdi**" for the correct oral syringe you should use. Ask your healthcare professional if you have questions on how to select the right oral syringe.
- If the bottle adapter is not in the bottle, **do not** use Evrysdi and then contact your healthcare professional.
- **Do not** use Evrysdi after the **Discard after** date written on the bottle label. Ask your healthcare professional for the **Discard after** date if it is not written on the bottle label.
- **Do not** mix Evrysdi into food or liquids (e.g. milk or formula milk).
- **Do not** use Evrysdi if the bottle or oral syringes are damaged.
- **Avoid** getting Evrysdi on your skin. If Evrysdi gets on your skin, wash the area with soap and water.

- If you spill Evrysdi, dry the area with a dry paper towel and clean with soap and water. Throw away the paper towel in the waste and wash your hands well with soap and water.
- If there is not enough Evrysdi left in the bottle for your prescribed dose, discard the bottle with remaining Evrysdi and used oral syringes according to your local requirements; use a new bottle of Evrysdi to obtain your prescribed daily dose. **Do not mix** Evrysdi from the new bottle with the bottle you are currently using.

Each Evrysdi carton contains (See figure A):

1. 1 Evrysdi bottle with bottle adapter and cap
2. 2 Oral syringes 6 mL (in pouches)
3. 2 Oral syringes 12 mL (in pouches)

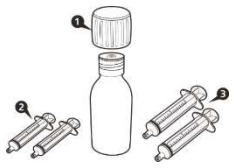
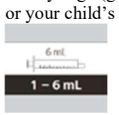


Figure A

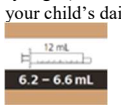
How to store Evrysdi
Please see section *4.1 Storage* of the Package Leaflet for full information.

A) Preparing and withdrawing your daily dose
How to select the correct oral syringe to use for your prescribed daily dose of Evrysdi

- If your prescribed daily dose of Evrysdi is between 1 mL and 6 mL, use a 6 mL oral syringe (grey label). Ask your healthcare professional about rounding your or your child's daily dose to the nearest 0.1 mL.



- If your prescribed daily dose of Evrysdi is 6.2 mL or higher, use a 12 mL oral syringe (brown label). Ask your healthcare professional about rounding your or your child's daily dose to the nearest 0.2 mL.



How to prepare your daily dose of Evrysdi

Figure B

Step A1
Remove the cap by pushing it down and then twisting the cap to the left (counter-clockwise) (See Figure B). Do not throw away the cap.

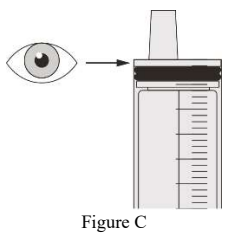


Figure C

Step A2
Push the plunger of the oral syringe all the way down to remove any air in the oral syringe (See Figure C).

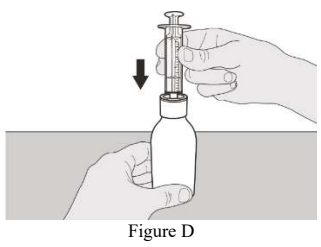


Figure D

Step A3
Keeping the bottle in an upright position, insert the syringe tip into the bottle adapter (See Figure D).

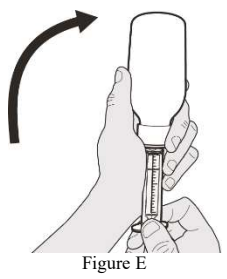


Figure E

Step A4
Carefully turn the bottle upside down with the syringe tip firmly inserted into the bottle adapter (See Figure E).

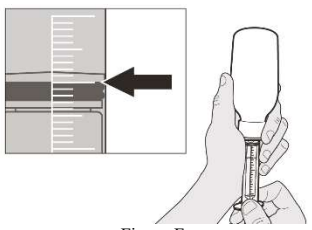


Figure F

Step A5
Slowly pull back on the plunger to withdraw your prescribed daily dose of Evrysdi. The top of the black plunger stopper must line up with the mL marking on the oral syringe for your prescribed daily daily dose (See Figure F).

After the correct dose is withdrawn, **hold the plunger in place to keep the plunger from moving.**

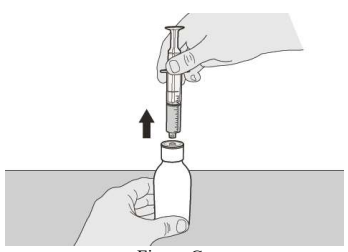


Figure G

Step A6
Continue to hold the plunger in place to keep the plunger from moving. Leave the oral syringe in the bottle adapter and turn the bottle to an upright position. Place the bottle onto a flat surface. Remove the oral syringe from the bottle adapter by gently pulling straight up on the oral syringe (See Figure G).

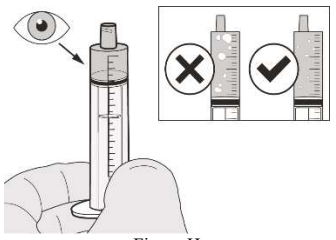


Figure H

Step A7
Hold the oral syringe with the syringe tip pointing up. Check the medicine in the oral syringe. **If** there are large air bubbles in the oral syringe (See Figure H) **or if** you have drawn up the wrong daily dose of Evrysdi, insert the syringe tip firmly into the bottle adapter. Push the plunger all the way down so that the medicine flows back into the bottle and repeat Steps A4 through A7.

Take or give Evrysdi immediately after it is drawn up into the oral syringe.

If it is not taken **within 5 minutes**, discard from oral syringe and prepare a new dose.

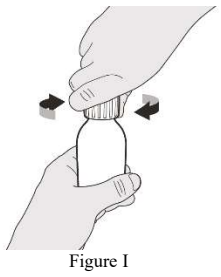


Figure I

Step A8
Put the cap back on the bottle. Turn the cap to the right (clockwise) to tightly close the bottle (See Figure I). Do not remove the bottle adapter from the bottle.

If you are taking your daily dose of Evrysdi by mouth, follow the instructions in "**B) How to take a daily dose of Evrysdi by mouth**".

If you are taking your daily dose of Evrysdi through a gastrostomy tube, follow the instructions in "**C) How to give a daily dose of Evrysdi through a gastrostomy tube**".

If you are taking your daily dose of Evrysdi through a nasogastric tube, follow the instructions in "**D) How to give a daily dose of Evrysdi through a nasogastric tube**".

Evrysdi's oral syringes are specifically designed to be compatible with the ENFit® system. If your feeding tube is not ENFit® compatible, you may need an ENFit® transition connector to connect the Evrysdi syringe to your G-tube or NG-tube.

B) How to take a daily dose of Evrysdi by mouth
Sit upright when taking a daily dose of Evrysdi by mouth.

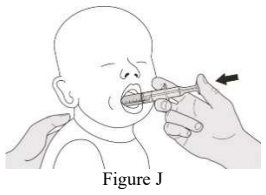


Figure J

Step B1
Place the oral syringe into the mouth **with the tip along either cheek.**

Slowly push the plunger all the way down to take the full dose of Evrysdi (See Figure J).

Giving Evrysdi into the throat or too fast may cause choking.

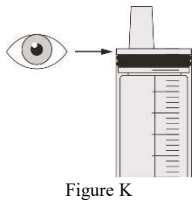


Figure K

Step B2
Check that there is no medicine left in the oral syringe (See Figure K).

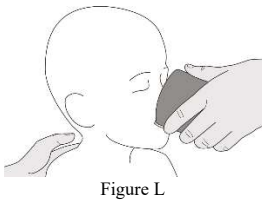


Figure L

Step B3
Drink some water right after taking the prescribed dose of Evrysdi (See Figure L).

Go to Step E for cleaning of the syringe.

C) How to give a daily dose of Evrysdi through a gastrostomy tube
If you are giving Evrysdi through a gastrostomy tube, ask your doctor to show you how to inspect the gastrostomy tube before giving Evrysdi.

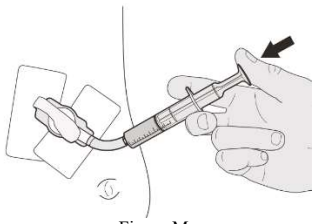


Figure M

Step C1
Place the oral syringe tip into the gastrostomy tube. Slowly push the plunger all the way down to give the full dose of Evrysdi (See Figure M).

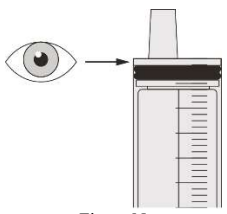


Figure N

Step C2
Check that there is no medicine left in the oral syringe (See Figure N).

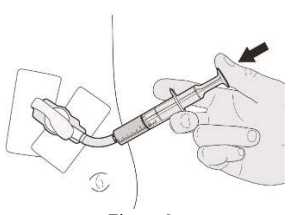


Figure O

Step C3
Flush the gastrostomy tube with 10-20 mL of water right after giving the prescribed dose of Evrysdi (See Figure O).

Go to Step E for cleaning of the syringe.

D) How to give a daily dose of Evrysdi through a nasogastric tube
If you are giving Evrysdi through a nasogastric tube, ask your doctor to show you how to inspect the nasogastric tube before giving Evrysdi.

Figure P

Step D1
Place the oral syringe tip into the nasogastric tube. Slowly press the plunger all the way down to give the full dose of Evrysdi (See Figure P).

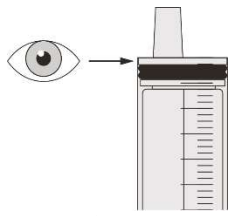


Figure Q

Step D2
Check that there is no medicine left in the oral syringe (See Figure Q).

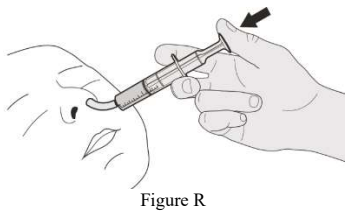


Figure R

Step D3
Flush the nasogastric tube with 10-20 mL of water right after giving the prescribed dose of Evrysdi (See Figure R).

Go to Step E for cleaning of the syringe.

E) How to clean the oral syringe after use

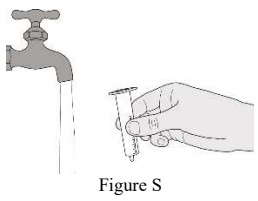


Figure S

Step E1
Remove the plunger from the oral syringe.
Rinse the oral syringe barrel well under clean water (See Figure S).

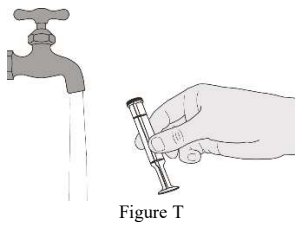


Figure T

Step E2
Rinse the plunger well under clean water (See Figure T).

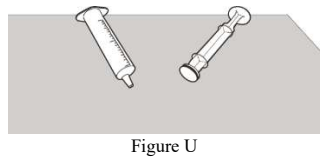


Figure U

Step E3
Check that the oral syringe barrel and plunger are clean.

Place the oral syringe barrel and plunger on a clean surface in a safe place to dry (See Figure U).

Wash your hands.

Once dry, reassemble the plunger into the oral syringe barrel and store the syringe with your medicine.