

Evrysdi™ (risdiplam) Clinical Summary
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INDICATIONS AND USAGE¹

Evrysdi is a survival of motor neuron 2 (SMN2) splicing modifier indicated for the treatment of spinal muscular atrophy (SMA) in patients 2 months of age and older.

DOSAGE AND ADMINISTRATION¹

- Evrysdi is a solution constituted from powder that is taken orally once daily and can be administered via feeding tube if the patient is unable to swallow.
- Dose is determined by age and body weight.
 - 2 months to less than 2 years of age: 0.2 mg/kg/day
 - 2 years of age and older weighing less than 20 kg: 0.25 mg/kg/day
 - 2 years of age and older weighing 20 kg or more: 5 mg/day

SMA EPIDEMIOLOGY

- The incidence of SMA is approximately 1 in 10,000 live births. In 2016, the estimated U.S. prevalence of SMA was approximately 1,610 individuals with Type 1 (17%), 3,944 with Type 2 (42%), and 3,875 with Type 3 (41%). Types 0 and 4 are rarely observed.²
- Historically, SMA was classified into 5 types (0-4) based on age of onset and highest motor milestone achieved. Individuals with Type 0 have a prenatal onset and a short life expectancy of < 6 months. Type 1 exhibits a more severe expression of the disease with an onset appearing at ≤ 6 months of age. Type 2 onset occurs at ≤18 months of age, whereas Type 3 onset occurs at >18 months of age. Type 4 presents in adulthood (onset >18 years) with a slower progression of muscle weakness.³ However, as more treatments become available, patient phenotypes are changing.

SMA BURDEN OF ILLNESS

- SMA, a leading genetic cause of infant mortality, is a rare, progressive neuromuscular disease (NMD) characterized by degeneration of spinal cord motor neurons. This results in muscle atrophy, overall weakness, loss of motor function, feeding and breathing difficulties, and disease-related complications that can impact survival.^{4,5}
- Infants with **Type 1** SMA demonstrate reduced motor function over time and are not expected to gain the ability to roll or sit independently. Symptoms progress rapidly and historically the majority succumb to respiratory failure before 2 years of age without treatment.⁵⁻⁷
- Children with **Type 2** SMA achieve the ability to sit unassisted, but are never able to stand or walk independently. Long-term follow-up shows clear and progressive decline in motor function. Most develop progressive scoliosis and respiratory muscle weakness which leads to impaired lung function.^{5,8,9}
- Individuals with **Type 3 SMA** are able to stand and walk unassisted at some point during their lifetime; however, progressive muscular weakness is the predominant concern and may result in motor impairment, including loss of ambulation over time requiring assistance, as well as potential development of scoliosis.^{3,9,10}

PLACE OF EVRYSDI IN THERAPY

- SMA may lead to irreversible loss of motor function across patient types; therefore, it is crucial to begin treatment as soon as possible to prevent further disease progression by stabilizing motor function.¹⁰ Despite the availability of new disease-modifying therapies (DMTs), many patients remain untreated.
- Evrysdi is the only liquid oral formulation DMT for adult and pediatric patients with SMA, allowing for home administration.¹
- The clinical development program for Evrysdi assessed the efficacy and safety across a comprehensive population of SMA patients, from infants (≥2 months of age) to adults, as well as patients with severe scoliosis.^{1,11-14}

EFFICACY IN INFANTILE-ONSET SMA (TYPE 1) (FIREFISH; PI Study 1)^{1,11,12}

A Phase II/III, open-label, multicenter, 2-part study assessed Evrysdi in infants (2-7 months old) with infantile-onset SMA (Type 1). **Part 1** (n=21) was a dose-finding study that enrolled two cohorts. Patients in the recommended-dosage cohort (n=17) had their dosage adjusted to 0.2 mg/kg/day before 12 months of treatment, while patients in the low-dosage cohort (n=4) did not. **Part 2** (n=41) was the confirmatory efficacy and safety part where patients received Evrysdi for 12 months at the recommended dose of 0.2 mg/kg/day. After 12 months of treatment with Evrysdi:

- In **Part 1**, 41% (7/17) of patients treated with the recommended-dose were able to sit without support for at least 5 seconds, as measured by item 22 of the Bayley Scale of Infant and Toddler Development - Third Edition (BSID-III) gross motor scale.^{1,11}
 - 90% (19/21) of all patients were alive without permanent ventilation and reached ≥15 months of age. Permanent ventilation was defined as requiring a tracheostomy or more than 21 consecutive days of either non-invasive ventilation (≥16 hours per day) or intubation, in the absence of an acute reversible event. After a minimum of 23 months of treatment, 81% (17/21) of all patients were alive without permanent ventilation, and reached ≥28 months of age.
- In **Part 2**, 29% of patients were able to sit without support for at least 5 seconds, as assessed by item 22 of the BSID-III gross motor scale (primary endpoint).¹²
 - 93% of patients were alive and 85% of patients were alive without permanent ventilation.
 - A ≥4-point increase in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) total score was achieved by 90% of infants, with a median change from baseline of +20 points after 12 months. A

CHOP-INTEND total score of ≥ 40 was achieved by 56% of infants. Median baseline CHOP-INTEND total score was 22 points (range: 8-36).

- 78% of infants were Hammersmith Infant Neurological Examination Module 2 (HINE-2) responders, defined as if more motor milestones showed improvement than worsening.
- Of the 38 infants alive at Month 12, 89% were able to feed orally, and 74% were able to feed exclusively orally.

EFFICACY IN LATER-ONSET SMA (TYPE 2 OR 3) (SUNFISH; PI Study 2)^{1,13}

A Phase II/III, multicenter, randomized, double-blind, placebo-controlled, 2-part study assessed Evrysdi in pediatric and adult patients (2-25 years old) with later-onset SMA (Type 2 or 3). **Part 1** (n=51) was the exploratory dose-finding portion, and evaluated safety, tolerability, pharmacokinetics, and pharmacodynamics of Evrysdi in ambulant and non-ambulant patients. **Part 2** was the randomized (2:1), double-blind, placebo-controlled confirmatory portion in 180 non-ambulant patients with Type 2 (71%) and Type 3 (29%) SMA. At baseline (median age: 9 years [range 2-25 years]), 67% of patients had scoliosis, of which 32% had severe scoliosis.

- In **Part 2**, after 12 months of treatment:
 - All patients treated with Evrysdi showed significant improvement in total Motor Function Measure-32 (MFM-32) score from baseline (least squares [LS] mean change 1.36 [95% CI: 0.61, 2.11]) compared to placebo (LS mean change -0.19 [95% CI: -1.22, 0.84]; 1.55 difference vs. placebo [95% CI: 0.30, 2.81], $p=0.0156$).
 - More patients on Evrysdi had a change of ≥ 3 points in the total MFM-32 score (38% [95% CI: 28.9, 47.6]) vs. placebo (24% [95% CI: 12.0, 35.4]; odds ratio for overall response 2.35 [95% CI: 1.01, 5.44], $p=0.0469$).
 - Greater improvement in total Revised Upper Limb Module (RULM) was observed from baseline with Evrysdi vs. placebo (LS mean change 1.61 [95% CI: 1.00, 2.22] vs. placebo LS mean change 0.02 [95% CI: -0.83, 0.87]; 1.59 difference vs. placebo [95% CI: 0.55, 2.62]), $p=0.0469$).

USE IN PREVIOUSLY TREATED SMA (JEWELFISH)¹⁴

An ongoing Phase II, single arm, open-label study is investigating the safety, tolerability, pharmacokinetics and pharmacodynamics of Evrysdi in SMA patients (1 to 60 years of age) who received treatment with investigational and approved SMA therapies prior to receiving Evrysdi. As of January 31, 2020, 173 patients received Evrysdi for a median of 3 months (range: 0-32.8). The overall adverse event profile of Evrysdi in previously-treated patients observed in this trial is consistent with the safety profile observed in patients who were treatment-naïve prior to receiving Evrysdi in FIREFISH and SUNFISH.

IMPORTANT SAFETY INFORMATION¹

Avoid coadministration with drugs that are substrates of multidrug and toxin extrusion (MATE) transporters. Based on animal data, Evrysdi may cause fetal harm and may compromise male fertility. Avoid use in patients with hepatic impairment.

ADVERSE REACTIONS

The most common adverse reactions were:¹

- Infantile-onset SMA (incidence $\geq 10\%$): upper respiratory tract infection, fever, rash, pneumonia, constipation, diarrhea, and vomiting.
- Later-onset SMA (incidence $\geq 10\%$ of Evrysdi treated patients and more frequent than on placebo): diarrhea, rash and arthralgia.

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