

Some things get **everywhere**

like Evrysdi, an oral
treatment for spinal
muscular atrophy (SMA)^{1,2}



**Available in liquid and
tablet formulations¹**

For illustrative purposes only.

**Evrysdi is designed to reach the CNS and
peripheral tissues, increasing SMN protein
production throughout the body.^{1,2*}**

*As observed in animal models.²

CNS=central nervous system; SMN=survival motor neuron.

Indication

EVERYSDI is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

Important Safety Information

Interactions with Substrates of MATE Transporters

- Based on in vitro data, Evrysdi may increase plasma concentrations of drugs eliminated via MATE1 or MATE2-K, such as metformin
- Avoid coadministration of Evrysdi with MATE (multidrug and toxin extrusion) substrates. If coadministration cannot be avoided, monitor for drug-related toxicities and consider dosage reduction of the coadministered drug if needed

**Please see additional Important Safety
Information throughout and accompanying
full Prescribing Information.**



EVERYWHERE

FOR HEALTHCARE PROFESSIONALS

The first and only oral treatment for SMA^{1,3,4}

Evrysdi is a small molecule that crosses the blood-brain barrier and is designed to target the CNS and beyond, getting everywhere the body needs it²

Evrysdi is designed to reach parts of the body SMA affects, such as the larynx, GI system, and heart.^{2*}

*As observed in animal models.²

Evrysdi is non-invasive, which means^{1,4}:

- ✓ No needles
- ✓ No lab monitoring
- ✓ No hospital stays

The Evrysdi community is **everywhere**

16,000+
people globally,
including people up to
75 years of age^{5†}

⁵Based on individuals with SMA receiving Evrysdi worldwide as of August 2024.⁵

[†]Clinical trials of Evrysdi did not include people aged 65 and older to determine whether they respond differently from those who are younger.¹

CNS=central nervous system; GI=gastrointestinal.

Two oral options for your patients to choose from^{1§}

Evrysdi tablets have the same demonstrated efficacy and safety as the liquid formulation^{1,6}



[§]Patients must be ≥ 2 years of age and weigh ≥ 20 kg (44 lb) to take Evrysdi tablets. Tablet dispersion cannot be used in a gastrostomy or nasogastric tube.¹

Evrysdi is designed to **fit your patients' lifestyles**—it's non-invasive, so they have flexibility in how they plan their day.^{1,4}

Important Safety Information (continued)

Pregnancy & Breastfeeding

- Evrysdi may cause embryofetal harm when administered to a pregnant woman. In animal studies, administration of Evrysdi during pregnancy and/or lactation resulted in adverse effects on development. Advise pregnant women of the potential risk to the fetus
- Pregnancy testing is recommended prior to initiating Evrysdi. Advise female patients to use contraception during treatment with Evrysdi and for at least 1 month after the last dose

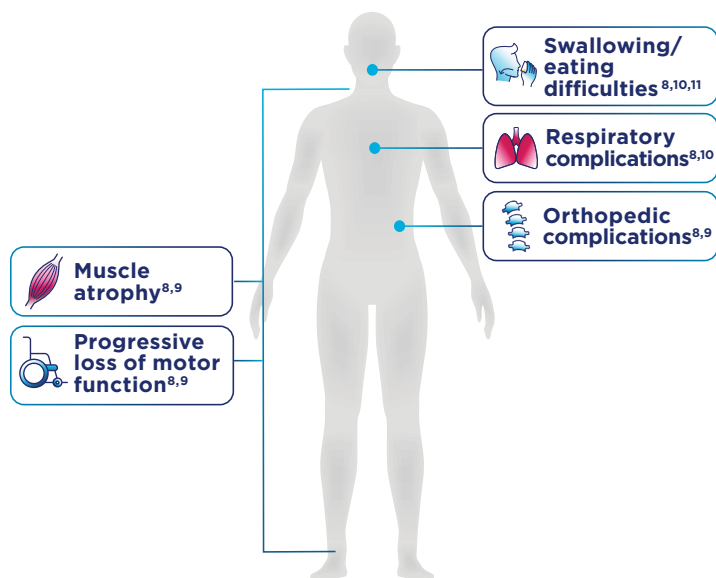
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Effects of SMA can be seen throughout the body⁷

SMA is caused by a genetic mutation, which results in deficiency of a key protein called survival motor neuron (SMN)²



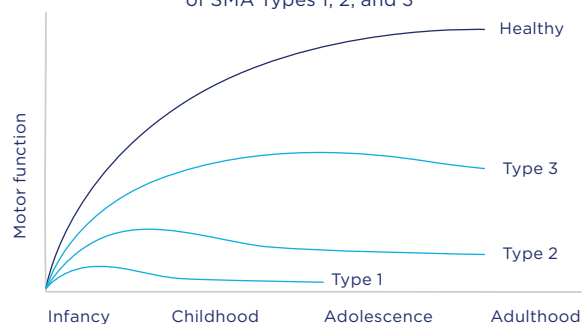
The human body needs SMN protein, found in all cells and tissues, to function properly. The **progressive and multi-organ** nature of SMA causes muscles to atrophy and weaken, and results in **disease-related complications**^{2,8-10}

Untreated individuals with SMA face relentless loss of motor function with lifelong consequences^{8,11,12}

✗ Many individuals with SMA are not receiving disease-modifying treatments (DMTs)^{13*}

Natural history of motor function in SMA by phenotype¹⁴

A schematic depiction of the anticipated clinical course of SMA Types 1, 2, and 3



✓ Treatment can change the course of SMA⁸

Patients receiving DMTs have reported improvements, such as¹⁵:

- Hitting more motor milestones
- Slowing down symptom progression
- Using fewer healthcare resources

The **2024 Cure SMA Recommendations for Treatment Considerations** emphasize the **use of DMTs as early as possible for SMA¹⁶**

*Approximately 30%-40% of individuals with SMA are not receiving an FDA-approved treatment.¹³

Important Safety Information (continued)

Pregnancy & Breastfeeding (continued)

- There is a pregnancy exposure registry that monitors pregnancy and fetal/neonatal/infant outcomes in women exposed to Evrysdi during pregnancy. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-833-760-1098 or visiting <https://www.evrysdipregnancyregistry.com>.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.



EVERYWHERE

Evrysdi is formulated to address the underlying cause of SMA^{1,2}

SMN2 splice-modifying technology increases the production of functional SMN protein in the blood¹



In SMA, a deletion or mutation in the *SMN1* gene leads to a deficit in SMN protein²



The *SMN2* gene also produces SMN protein, but not enough to compensate for the mutation²

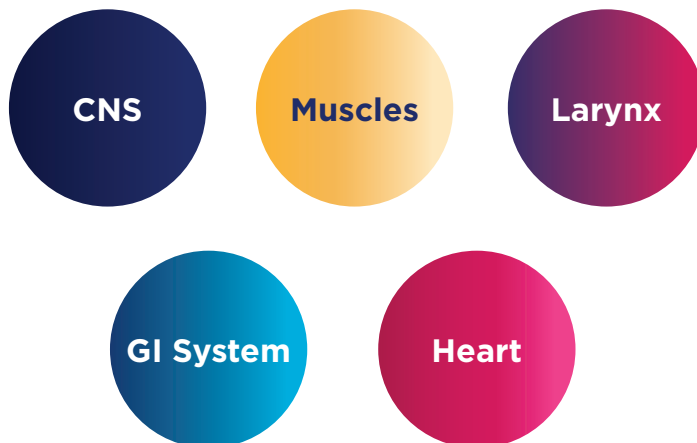


Evrysdi is a *SMN2*-splicing modifier that increases the production of full-length SMN protein in the blood^{1*}

*Proposed mechanism of action. In preclinical studies, risdiplam was shown to increase exon 7 inclusion in *SMN2* messenger ribonucleic acid transcripts and production of full-length SMN protein in the brain. SMN= survival motor neuron.¹

Designed to go everywhere²

Evrysdi is formulated as a small molecule that can cross the blood-brain barrier, allowing it to reach tissues and organs throughout the body that need SMN protein, such as^{2†}:



[†]As observed in animal models.²

CNS=central nervous system; GI=gastrointestinal.

Important Safety Information (continued)

Pregnancy & Breastfeeding (continued)

- The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Evrysdi and any potential adverse effects on the breastfed infant

Potential Effects on Male Fertility

- Counsel male patients that fertility may be compromised by treatment with Evrysdi. Male patients may consider sperm preservation prior to treatment

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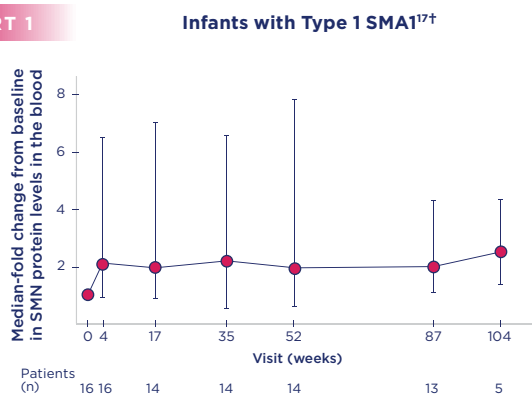


EVERYWHERE

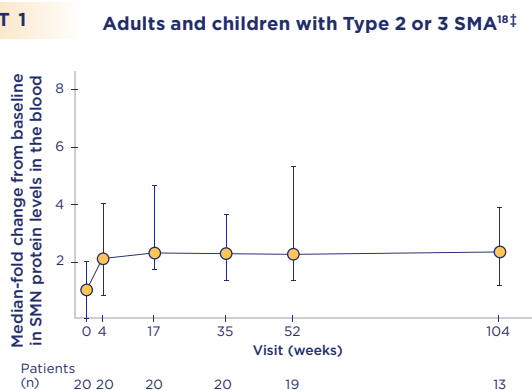
Evrysdi works daily to sustain increased SMN protein levels in the blood¹

Treatment with Evrysdi **approximately doubled and sustained SMN protein levels** throughout the 2-year treatment period^{1*}

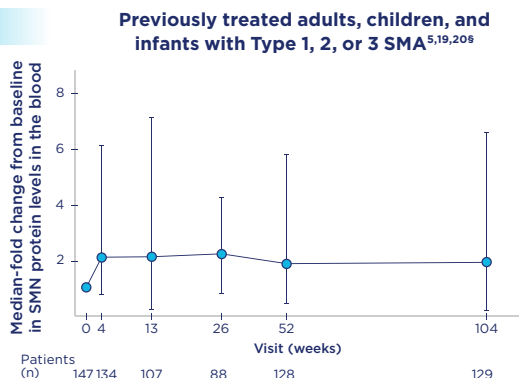
FIREFISH PART 1



SUNFISH PART 1



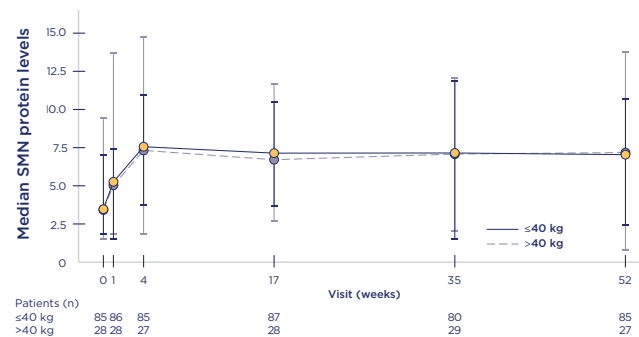
JEWELFISH



SMN protein levels were consistent, regardless of weight^{1,19}

SUNFISH PART 2

Adults and children with Type 2 or 3 SMA weighing ≤ 40 kg and > 40 kg^{5,19‡}



*Types 1, 2, and 3 SMA. No data available in presymptomatic SMA. Ages include 16 days to 60 years.^{1,20}

†Final doses at 12 months. Infants had their dose adjusted to the recommended dose of 0.2 mg/kg/day before 12 months of treatment. The approved dose of Evrysdi in infants aged 2 months to < 2 years is 0.2 mg/kg/day.^{1,21}

‡Final doses at 12 months. Patients had their dose adjusted to the recommended dose of 5 mg/day before 12 months of treatment. The approved dose of Evrysdi in patients ≥ 2 years of age and weighing ≥ 20 kg is 5 mg/day.^{1,22}

§The approved dose of Evrysdi in infants aged 2 months to < 2 years is 0.2 mg/kg/day. The approved dose of Evrysdi in infants aged ≥ 2 years and weighing < 20 kg is 0.25 mg/kg/day. The approved dose of Evrysdi in patients aged ≥ 2 years and weighing ≥ 20 kg is 5 mg/day.¹ SMN=survival motor neuron.

Important Safety Information (continued)

Most Common Adverse Reactions

- The most common adverse reactions in later-onset SMA (incidence in at least 10% of patients treated with Evrysdi and more frequent than control) were fever, diarrhea, and rash
- The most common adverse reactions in infantile-onset SMA were similar to those observed in later-onset SMA patients. Additionally, adverse reactions with an incidence of at least 10% were upper respiratory tract infection (including nasopharyngitis, rhinitis), lower respiratory tract infection (including pneumonia, bronchitis), constipation, vomiting, and cough

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.



EVERYWHERE

The most inclusive clinical trial program in SMA^{1,20}

Participants reflective of the real-world SMA population^{11,20,23,24}

490+

individuals with presymptomatic, infantile-onset, and later-onset SMA^{1,20,25++}

Aged

16

days^{1,24}

Aged

60

years^{1,20}

- Both ambulatory and nonambulatory^{1,20†}
- With different levels of disease severity and functional ability^{1,20}
- With and without scoliosis (mild to severe)^{1,20}
- With and without prior DMT (evaluated for safety)^{20§}

Efficacy data

in participants aged
16 days to 25 years^{1,24}

Safety data

in participants aged
16 days to 60 years^{1,20}

*Enrollment across 4 clinical trials.^{1,20}

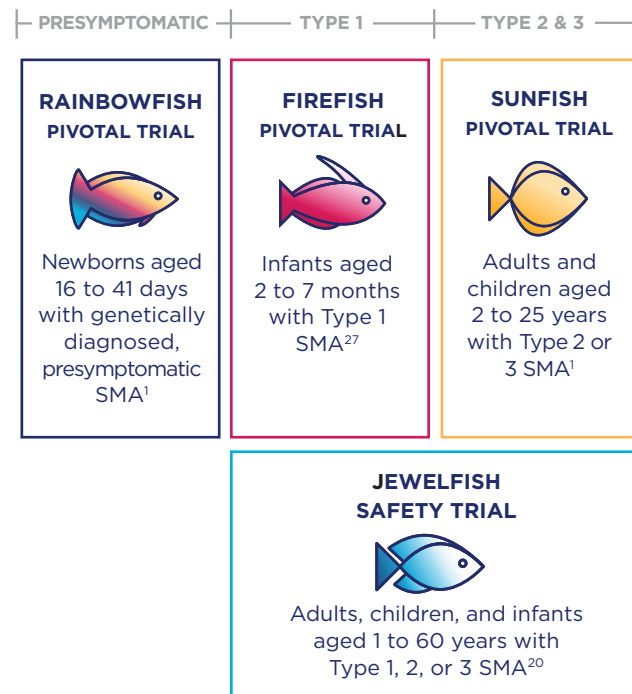
†Presymptomatic SMA defined as genetically diagnosed SMA in infants aged <6 weeks at time of first Evrysdi dose who had not yet presented with symptoms; infantile-onset SMA defined as Type 1 SMA; later-onset SMA defined as Type 2 or 3 SMA.^{1,20}

‡9 ambulatory patients included in SUNFISH Part 1; no ambulatory patients included in Part 2. There are 15 patients included in JEWELFISH who are ambulatory.^{1,20,26}

§Approved and investigational therapies including an *SMN2*-splicing modifier or gene-replacement therapy.²⁰
DMT=disease-modifying treatment; FDA=Food and Drug Administration; *SMN2*=survival motor neuron 2.

Proven results in a broad range of patient types^{1,20}

The Evrysdi clinical trial program consists of 4 trials^{1,20}



The first trial program of an FDA-approved SMA treatment to include patients **older than 18 years**, some of whom had severe scoliosis^{20,28}

Important Safety Information (continued)

Most Common Adverse Reactions (continued)

- The safety profile for presymptomatic patients is consistent with the safety profile for symptomatic SMA patients treated with Evrysdi in clinical trials

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

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EVERYWHERE

Evrysdi was studied in adults, children, and infants with SMA¹



SUNFISH

A 2-part, randomized, placebo-controlled trial in later-onset SMA (Type 2 and Type 3 SMA)¹

- Part 1 (N=51) was the exploratory, dose-finding portion¹
- In Part 2 (N=180)^{1,22}:
 - Adults and children were randomized 2:1 to receive either the recommended dose of Evrysdi or the placebo. After 1 year, adults and children receiving the placebo were switched to Evrysdi
 - The primary endpoint was mean change from baseline in MFM-32 at 1 year



FIREFISH

A 2-part, open-label trial in infantile-onset SMA (Type 1 SMA)¹

- Part 1 (N=21) determined the recommended dose¹
- In Part 2 (N=41), the primary endpoint was the ability to sit without support for at least 5 seconds, as measured by Item 22 of the BSID-III gross motor scale¹
- In Parts 1 and 2 (pooled analysis), key efficacy endpoints were¹:
 - The ability to sit without support for at least 5 seconds, as measured by Item 22 of the BSID-III gross motor scale (recommended-dose cohort; n=58)
 - Survival without permanent ventilation (all-patients cohort; N=62)

BSID-III=Bayley Scales of Infant and Toddler Development-Third Edition;
MFM-32=Motor Function Measure-32 Items.

Evrysdi was also studied in newborns with presymptomatic SMA and people with previously treated SMA^{1,20}



RAINBOWFISH

An open-label, single-arm trial in newborns with genetically diagnosed, presymptomatic SMA¹

- Infants (N=26) were <6 weeks of age at the time of their first Evrysdi dose, had a genetic diagnosis of SMA, but had not yet presented with symptoms¹
- The primary endpoint was the ability to sit without support for at least 5 seconds at 1 year, as measured by Item 22 of the BSID-III gross motor scale¹



JEWELFISH

An open-label safety trial in 174 individuals with Type 1, 2, or 3 SMA²⁰

- This trial is investigating the safety, tolerability, pharmacokinetics, and pharmacodynamics of Evrysdi in both ambulatory and nonambulatory patients²⁰
 - Ambulatory and nonambulatory patients: 9% (n=16) walkers, 57% (n=100) sitters, and 34% (n=59) nonsitters²⁰
- Participants have received previous treatment with approved or investigational therapies,* including an SMN2-splicing modifier (≥90 days prior to screening) or gene-replacement therapy (≥12 months prior to screening)²⁰

*Investigational at the start of JEWELFISH. All but 3 patients enrolled in JEWELFISH received previous treatment; these 3 patients were previously enrolled in the MOONFISH trial and received placebo and were never switched to RG7800.²⁰
SMN2=survival motor neuron 2.

Important Safety Information

Interactions with Substrates of MATE Transporters

- Based on in vitro data, Evrysdi may increase plasma concentrations of drugs eliminated via MATE1 or MATE2-K, such as metformin
- Avoid coadministration of Evrysdi with MATE (multidrug and toxin extrusion) substrates. If coadministration cannot be avoided, monitor for drug-related toxicities and consider dosage reduction of the coadministered drug if needed

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EVERYWHERE

SUNFISH included a broad range of participants^{1,23}

Designed to reflect the real-world SMA population^{11,23,24}

SUNFISH PART 2

Patient characteristics ^{1,5,23}	Evrysdi (n=120)	Placebo (n=60)
SMA Type, % (n)		
Type 2	70.0% (84)	73.3% (44)
Type 3	30.0% (36)	26.7% (16)
Median weight at baseline, kg (range)	27 (10-100)	27 (11-112)
Disease severity²⁹		
Mean age at onset, months (SD)	14.1 (8.4)	18.5 (21.1)
Scoliosis, % (n)		
Yes	63.3% (76)	73.3% (44)
>40° curvature	28.3% (34)	38.3% (23)
Surgery for scoliosis before screening, % (n)		
Yes	24.2% (29)	28.3% (17)
No	52.5% (63)	55.0% (33)
Motor function assessment scores at baseline⁵		
MFM-32 total score, median (range)	46.9 (16.7-71.9)	47.9 (17.7-71.9)
n	115	59
RULM total score, median (range)	19.0 (3.0-36.0)	20.0 (9.0-38.0)
n	119	58
HFMSE total score, median (range)	14.0 (0.0-48.0)	13.0 (2.0-43.0)
n	120	60

SUNFISH was **purposely designed to include adults and children with complications**, such as contractures and severe scoliosis^{23*}

Established safety at 1 year¹

SUNFISH PART 2

Adverse reactions occurring in $\geq 5\%$ of adults and children receiving Evrysdi and with an incidence of $\geq 5\%$ compared with placebo (N=180)

Adverse reaction	Evrysdi (n=120)	Placebo (n=60)
Fever [†]	22%	17%
Diarrhea	17%	8%
Rash [‡]	17%	2%
Mouth and aphthous ulcers	7%	0%
Arthralgia	5%	0%
Urinary tract infection [§]	5%	0%

As of clinical cut-off date: September 6, 2019.

- The most common adverse reactions reported in $\geq 10\%$ of adults and children receiving Evrysdi and at an incidence greater than placebo were fever, diarrhea, and rash

*The overall baseline demographic characteristics were well balanced between Evrysdi and placebo groups, with the exception of an imbalance of patients with scoliosis (63% in the Evrysdi arm and 73% in the placebo arm).¹

[†]Includes pyrexia and hyperpyrexia.¹

[‡]Includes rash, erythema, rash maculopapular, rash erythematous, rash papular, dermatitis allergic, and folliculitis.¹

[§]Includes urinary tract infection and cystitis.¹

HFMSE=Hammersmith Functional Motor Scale Expanded; MFM-32=Motor Function Measure-32 Items; RULM=Revised Upper Limb Module; SD=standard deviation.

Important Safety Information (continued)

Pregnancy & Breastfeeding

- Evrysdi may cause embryofetal harm when administered to a pregnant woman. In animal studies, administration of Evrysdi during pregnancy and/or lactation resulted in adverse effects on development. Advise pregnant women of the potential risk to the fetus

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.



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Proven long-term safety over 4 years^{5,23}

SUNFISH PART 2

	Placebo 0-12 months (n=60)*	Evrysdi 0-12 months (n=120)	Evrysdi 12-24 months (n=117)	Evrysdi 24-36 months (n=116)	Evrysdi 36-48 months (n=112)
Most common adverse events,[†] % (n)					
Upper respiratory tract infection	30.0% (18)	31.7% (38)	16.2% (19)	8.6% (10)	17.9% (20)
Cold	25.0% (15)	25.8% (31)	22.2% (26)	9.5% (11)	5.4% (6)
Fever	16.7% (10)	20.8% (25)	13.7% (16)	9.5% (11)	8.0% (9)
Headache	16.7% (10)	20.0% (24)	10.3% (12)	7.8% (9)	3.6% (4)
Diarrhea	8.3% (5)	16.7% (20)	8.5% (10)	6.0% (7)	3.6% (4)
Vomiting	23.3% (14)	14.2% (17)	13.7% (16)	6.9% (8)	7.1% (8)
Cough	20.0% (12)	14.2% (17)	10.3% (12)	4.3% (5)	2.7% (3)
Most common serious adverse events, % (n)					
Pneumonia	3.3% (2)	8.3% (10)	6.8% (8)	1.7% (2)	2.7% (3)
Influenza	0% (0)	0.8% (1)	0.9% (1)	0.9% (1)	0.9% (1)

Clinical cut-off date for Evrysdi 0-12 months and placebo 0-12 months: September 6, 2019.^{5,23}

Clinical cut-off date for Evrysdi 12-24 months: September 30, 2020.^{5,23}

Clinical cut-off date for Evrysdi 24-36 months: September 6, 2021.^{5,23}

Clinical cut-off date for Evrysdi 36-48 months: September 6, 2022.^{5,23}

*Patients in the placebo arm received placebo for 12 months, followed by Evrysdi. The patients who started in the placebo group and switched to Evrysdi are not included in the 12- to 24-month, 24- to 36-month, and 36- to 48-month data.³⁰

[†]Adverse reactions have an assumed causality to drug treatment under appropriate use; adverse events include any untoward event associated with the use of a drug, regardless of causality.^{1,31}

[‡]One patient withdrew from the trial after the September 6, 2021 clinical cut-off date because of an adverse event (transaminitis) that was initially reported as related to Evrysdi and then reassessed after discontinuation as unrelated to Evrysdi.³²

No treatment-related adverse events leading to permanent withdrawal or treatment discontinuation over 4 years^{23†}

Important Safety Information (continued)

Pregnancy & Breastfeeding (continued)

- Pregnancy testing is recommended prior to initiating Evrysdi. Advise female patients to use contraception during treatment with Evrysdi and for at least 1 month after the last dose

Please see additional
Important Safety Information
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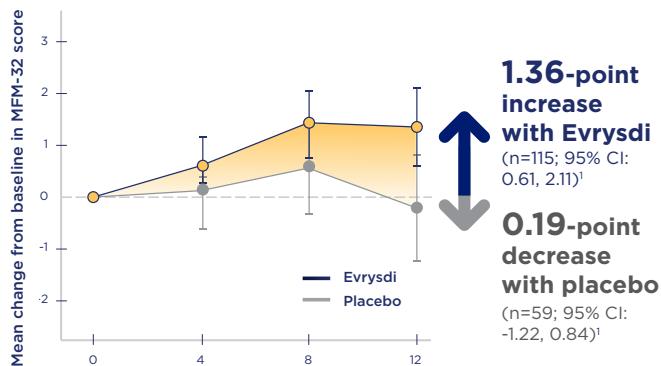
EVERYWHERE

Helping preserve daily function¹

Significantly improved or preserved motor skills vs placebo at 1 year, as measured by MFM-32¹

SUNFISH PART 2

Change in MFM-32 score over 1 year of treatment^{1*†}



- **1.55-point difference** (95% CI: 0.30, 2.81) between the means ($P=0.0156$)¹
- The MFM-32 is a 32-item scale designed to assess various motor functions in people with neuromuscular disorders. The scale measures motor function abilities that relate to important daily functions³³

These results demonstrated a **clinically meaningful difference for patients treated with Evrysdi** compared with placebo^{1†}

*The least squares (LS) mean difference for change from baseline in MFM-32 score (95% CI).¹

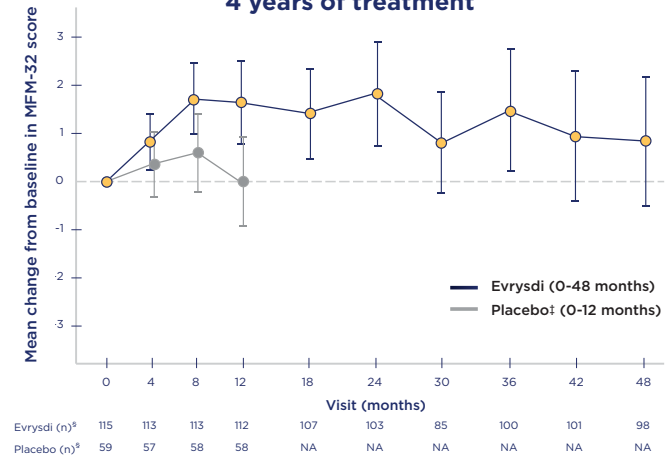
[†]Based on the missing-data rule for MFM-32, 6 patients (n=5 for Evrysdi; n=1 for placebo) were excluded from the analysis.¹ CI=confidence interval; MFM-32=Motor Function Measure-32 Items.

EXPLORATORY ASSESSMENTS SUGGEST

Increase in motor function at 1 year was maintained at 4 years³⁴

SUNFISH PART 2

Change in MFM-32 score over 4 years of treatment



These 4-year data should be interpreted with caution, as they are from a non-placebo-controlled follow-up period of the Evrysdi arm.

¹Patients in the placebo arm received placebo for 1 year, followed by Evrysdi for 3 years. Evrysdi period not shown. After 2 years, participants had the opportunity to enter the open-label extension portion of the study.^{23,34}

³⁴Number of patients with an available total score (result) at respective time points. Intent-to-treat patients.³⁴ NA=not applicable.

Important Safety Information (continued) Pregnancy & Breastfeeding (continued)

- There is a pregnancy exposure registry that monitors pregnancy and fetal/neonatal/infant outcomes in women exposed to Evrysdi during pregnancy. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-833-760-1098 or visiting <https://www.evrysdipregnancyregistry.com>.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.



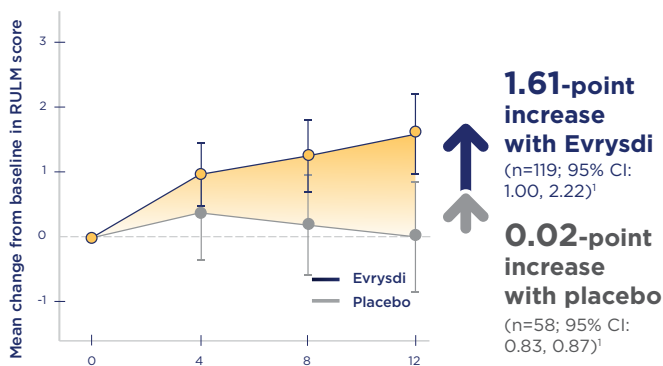
EVERYWHERE

Meaningful improvement in upper limb function^{1,22}

Greater strength in hand and arm movements vs placebo at 1 year, as measured by RULM^{1,22}

SUNFISH PART 2

Change in RULM score over 1 year of treatment^{1,22*†}



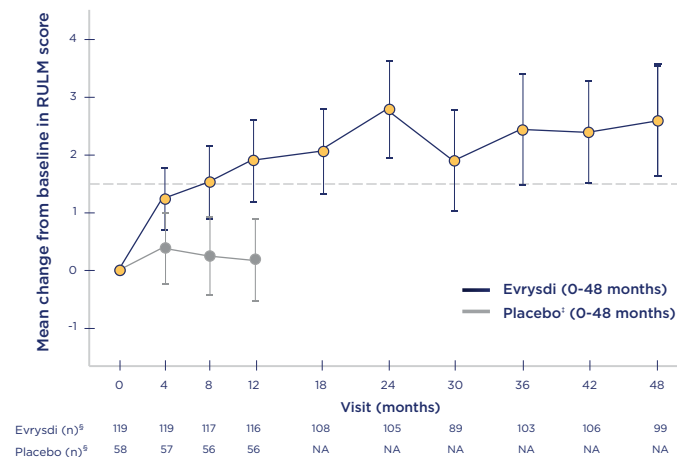
- **1.59-point difference** (95% CI: 0.55, 2.62) between the means ($P=0.0469$)¹

These results demonstrated a **clinically meaningful difference for patients treated with Evrysdi** compared with placebo¹

EXPLORATORY ASSESSMENTS SUGGEST Improvement in upper limb function at 1 year was maintained at 4 years³⁴

SUNFISH PART 2

Change in RULM score over 4 years of treatment



2.58-point mean change from baseline with Evrysdi at 4 years (95% CI: 1.62, 3.55)

These 4-year data should be interpreted with caution, as they are from a non-placebo-controlled follow-up period of the Evrysdi arm.

[†]Patients in the placebo arm received placebo for 1 year, followed by Evrysdi for 3 years. Evrysdi period not shown. After 2 years, participants had the opportunity to enter the open-label extension portion of the study.³⁴

[§]Number of patients with an available total score (result) at respective time points. Intent-to-treat patients.³⁴ NA=not applicable.

Important Safety Information (continued)

Pregnancy & Breastfeeding (continued)

- The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Evrysdi and any potential adverse effects on the breastfed infant

Potential Effects on Male Fertility

- Counsel male patients that fertility may be compromised by treatment with Evrysdi. Male patients may consider sperm preservation prior to treatment

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

[†]Based on the missing-data rule for RULM, 3 patients (n=1 for Evrysdi; n=2 for placebo) were excluded from the analysis.¹

CI=confidence interval; RULM=Revised Upper Limb Module.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.



EVERYWHERE

Characteristics reflective of real-world patients^{1,11,35}

Infants had varying levels of disease severity²⁷

FIREFISH PART 1 AND 2

Baseline demographics

Recommended-dose cohort (n=58)^{5,27}

Patient characteristics	
Median age at onset, months (range)	1.5 (0.9-3.0)
Median age at enrollment, months (range)	5.5 (2.2-6.9)
Median weight, kg (range)	6.6 (4.1-10.6)
Motor function assessment scores	
CHOP INTEND, median (range)	23.0 (8.0-37.0)
HINE-2, median (range)	1.0 (0.0-5.0)

Ages, disease progression rate, and baseline motor function reflect those seen in a real-world setting^{1,11,35}

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

Important Safety Information (continued)

Most Common Adverse Reactions

- The most common adverse reactions in later-onset SMA (incidence in at least 10% of patients treated with Evrysdi and more frequent than control) were fever, diarrhea, and rash

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

Proven safety in infantile-onset SMA³⁶

The most common adverse reactions* to Evrysdi in infantile-onset SMA with an incidence of at least 10% were fever, diarrhea, rash, upper respiratory tract infection (including nasopharyngitis, rhinitis), lower respiratory tract infection (including pneumonia, bronchitis), constipation, vomiting, and cough.¹

FIREFISH PART 1 AND 2

Adverse events* occurring in ≥10 infants receiving Evrysdi over 5 years³⁶

Adverse event	Evrysdi (n=58)
Upper respiratory tract infection	64%
Pyrexia	64%
Pneumonia	50%
Nasopharyngitis	28%
Diarrhea	28%
Constipation	26%
Vomiting	21%
Cough	21%
COVID-19	21%
Rhinitis	21%
Bronchitis	19%
Respiratory tract infection	19%
Influenza	17%
Urinary tract infection	17%

As of clinical cut-off date: December 22, 2023.

No treatment-related adverse events leading to permanent withdrawal or treatment discontinuation over 5 years³⁶

As of clinical cut-off date: December 22, 2023.³⁶

The safety findings from JEWELFISH have been consistent with the safety findings in FIREFISH²⁰

* Adverse reactions have an assumed causality to drug treatment under appropriate use; adverse events include any untoward event associated with the use of a drug, regardless of causality.³¹



EVERYWHERE

Meaningful improvements with Evrysdi¹

Infants exceeded expectations for development vs those not on treatment

FIREFISH PART 1 AND 2

Sitting ability as measured by BSID-III, Item 22

Recommended-dose cohort



PART 2 (PRIMARY ENDPOINT)
AFTER 1 YEAR OF TREATMENT

29% of infants (12/41)
were sitting without support for at least 5 seconds

PARTS 1 AND 2 (POOLED ANALYSIS)
AFTER 1 YEAR OF TREATMENT

33% of infants (19/58)
were sitting without support for at least 5 seconds

AFTER 2 YEARS OF TREATMENT

60% of infants (35/58)
were sitting without support for at least 5 seconds

These results indicate a clinically meaningful difference. Based on the natural history of untreated infantile-onset SMA, patients would not be expected to attain the ability to sit independently¹

BSID-III=Bayley Scales of Infant and Toddler Development-Third Edition.

Infants saw remarkable achievement of key milestones¹

FIREFISH PART 1 AND 2 (POOLED ANALYSIS)

Motor milestones after 2 years of treatment¹

Recommended-dose cohort



40% of infants (23/58)
were sitting without support for 30 seconds
As measured by BSID-III, Item 26



28% of infants (16/58)
were able to stand
As measured by HINE-2

- 9/58 could stand supporting weight
- 7/58 could stand with support
- 0/58 could stand unaided⁵

These results indicate a clinically meaningful difference. Based on the natural history of untreated infantile-onset SMA, patients would not be expected to achieve motor milestones, such as independent sitting, standing, or walking³⁶

HINE-2=Hammersmith Infant Neurological Examination-Module 2.

Important Safety Information (continued)

Most Common Adverse Reactions (continued)

- The most common adverse reactions in infantile-onset SMA were similar to those observed in later-onset SMA patients. Additionally, adverse reactions with an incidence of at least 10% were upper respiratory tract infection (including nasopharyngitis, rhinitis), lower respiratory tract infection (including pneumonia, bronchitis), constipation, vomiting, and cough

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.



EVERYWHERE

Defying natural history with prolonged survival¹

FIREFISH PART 1 AND 2 (POOLED ANALYSIS)

All-patients cohort (N=62)*



AFTER 1 YEAR OF TREATMENT

87% of infants (54/62) were alive without permanent ventilation[†]

AFTER 2 YEARS OF TREATMENT

84% of infants (52/62) were alive without permanent ventilation[†]

Based on the natural history of untreated infantile-onset SMA, **no more than 25% of these infants would be expected to reach ≥14 months of age** without permanent ventilation¹

*All-patients cohort, dose adjusted per protocol. Intent-to-treat population.¹

[†]Permanent ventilation was defined as a tracheostomy or >21 consecutive days of either non-invasive ventilation (≥16 hours per day) or intubation, in the absence of an acute reversible event.¹

Important Safety Information (continued)

Most Common Adverse Reactions (continued)

- The safety profile for presymptomatic patients is consistent with the safety profile for symptomatic SMA patients treated with Evrysdi in clinical trials

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

EXPLORATORY ASSESSMENTS SUGGEST Infants taking Evrysdi for 5 years achieved key milestones³⁶

FIREFISH PART 1 AND 2 (POOLED ANALYSIS)

Motor milestones after 5 years of treatment

Recommended-dose cohort³⁶



62% of infants (36/58)[†] were sitting without support for at least 5 seconds
As measured by BSID-III, Item 22



59% of infants (34/58)[†] were sitting without support for 30 seconds
As measured by BSID-III, Item 26



21% of infants (12/58)[†] were able to stand
As measured by HINE-2

- 5/58 could stand supporting weight
- 3/58 could stand with support
- 4/58 could stand unaided⁵

The above results should be interpreted with caution, as these are exploratory data.

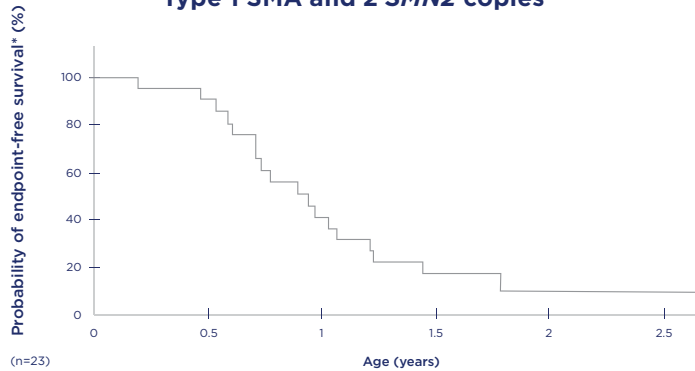
[†]The analyses at Year 1 and Year 5 include the pooled population with children from Part 1 (high-dose cohort, n=17) and all children from Part 2 (n=41). Results at Year 1 (data cutoff: November 14, 2019) are based on the assessment of 2 independent central readers, and those at Year 5 (data cutoff: December 22, 2023) are based on the assessment of the site clinical evaluator. Any children not assessed were included as non-responders (BSID-III, n=11; HINE-2, n=10).^{5,36} BSID-III=Bayley Scales of Infant and Toddler Development-Third Edition; HINE-2=Hammersmith Infant Neurological Examination-Module 2.



EVERYWHERE

Survival without permanent ventilation: natural history vs Evrysdi³⁶

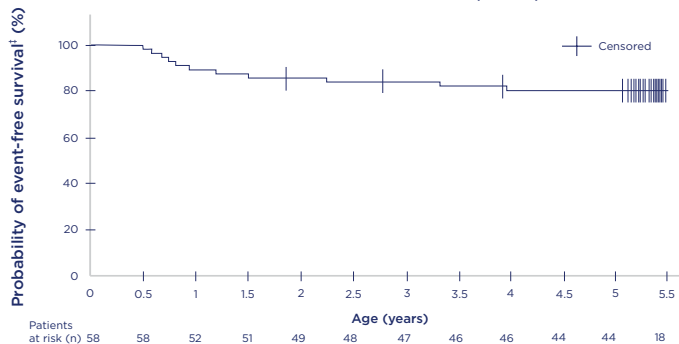
Natural history data for infants with Type 1 SMA and 2 *SMN2* copies



EXPLORATORY ASSESSMENTS SUGGEST[†]

FIREFISH PART 1 AND 2 (POOLED ANALYSIS)

81% of infants were estimated event-free after 5 years of treatment^{†§}
Recommended-dose cohort (n=58)



Event-free survival results should be interpreted with caution, as these are exploratory data.

* Defined as alive and not requiring ≥ 16 hours/day non-invasive ventilation support for ≥ 2 weeks.³⁶

[†] Data is exploratory so interpret with caution.³⁶

[‡] Defined as alive with no permanent ventilation. Permanent ventilation was defined as a tracheostomy or >21 consecutive days of either non-invasive ventilation (≥ 16 hours per day) or intubation, in the absence of an acute reversible event.³⁶

[§] Of the 11 children who were not deemed 'event free', 6 children met the definition of permanent ventilation and 5 had died. One additional child died 3.5 months after withdrawing from treatment and was censored at 22.9 months of age. Additionally, 3 children withdrew from the study, censored at 34.1 months of age, 48.2 months of age, and 63.6 months of age. Another 25 children were censored on completing 5 years of risdiplam treatment before 5.5 years of age.³⁶

As of clinical cut-off date: December 22, 2023.

EXPLORATORY ASSESSMENTS SUGGEST Infants taking Evrysdi had better feeding and swallowing abilities compared with natural history^{27||}

FIREFISH PART 1 AND 2 (POOLED ANALYSIS)

AFTER 5 YEARS OF TREATMENT

91%
of infants (42/46)
were able to feed orally^{36¶}

96%
of infants (46/48)
were able to swallow^{36¶}

As of clinical cut-off date: December 22, 2023³⁶

Based on the natural history of untreated infantile-onset SMA, **87% of infants typically require feeding support by 18 months old^{1,11}**

Feeding and swallowing assessments should be interpreted with caution, as these are exploratory data.

^{||} Assessed using nutritional status interview of the parent/caregiver and a standard swallowing assessment based on local practice and performed by a qualified individual. Swallowing assessment was completed at baseline and during follow-up visits. Ability of the patient to swallow age appropriate foods was assessed.^{21,27}

[¶] These calculations are based on the number of patients assessed for feeding or swallowing at 5 years.³⁶

Important Safety Information

Interactions with Substrates of MATE Transporters

- Based on in vitro data, Evrysdi may increase plasma concentrations of drugs eliminated via MATE1 or MATE2-K, such as metformin
- Avoid coadministration of Evrysdi with MATE (multidrug and toxin extrusion) substrates. If coadministration cannot be avoided, monitor for drug-related toxicities and consider dosage reduction of the coadministered drug if needed

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.



EVERYWHERE

Representing a range of disease severity in presymptomatic SMA^{1,5}

Infants had varied numbers of *SMN2* copies and CMAP amplitudes^{1,5}

RAINBOWFISH			
	Primary analysis population (n=5)	More severe disease (n=8)	ITT (N=26)
Patient characteristics⁵			
Age at first dose (days), median (range)	24.0 (22.0-35.0)	23.5 (16.0-35.0)	25.0 (16.0-41.0)
<i>SMN2</i> copy number, % (n)			
2	100.0% (5)	100.0% (8)	30.8% (8)
3	0.0% (0)	0.0% (0)	50.0% (13)
≥4	0.0% (0)	0.0% (0)	19.2% (5)
Gender, % (n)			
Female	60.0% (3)	50.0% (4)	61.5% (16)
Male	40.0% (2)	50.0% (4)	38.5% (10)
Weight (g), median (range)	4045.0 (3865-4270)	3999.0 (3076-4270)	4015.0 (3076-5726)
Baseline CMAP amplitude (mV), median (range)	2.6 (1.6-3.8)	2.0 (0.5-3.8)	3.6 (0.5-6.7)
Baseline value <1.5 mV, % (n)	0.0% (0)	37.5% (3)	11.5% (3)
Baseline value ≥1.5 mV, % (n)	100.0% (5)	62.5% (5)	88.5% (23)

As of clinical cut-off date: February 20, 2023.

The only trial of an FDA-approved DMT that studied infants with presymptomatic SMA who had CMAP <1 mV^{1,5,37,38}

CMAP=compound muscle action potential; DMT=disease-modifying treatment; FDA=Food and Drug Administration; ITT=intent-to-treat; mV=millivolt; SMN2=survival motor neuron 2.

Important Safety Information (continued)

Pregnancy & Breastfeeding

- Evrysdi may cause embryofetal harm when administered to a pregnant woman. In animal studies, administration of Evrysdi during pregnancy and/or lactation resulted in adverse effects on development. Advise pregnant women of the potential risk to the fetus

Established safety in presymptomatic SMA^{1,24,39}

No infants from the ITT population discontinued due to adverse events^{1,24,39}

- Adverse events observed in presymptomatic SMA were consistent with those observed in infantile-onset and later-onset SMA¹

Adverse events* occurring in ≥5 infants receiving Evrysdi over 2 years³⁹

Evrysdi (N=26)	
Adverse events	
Teething	42%
Gastroenteritis	39%
COVID-19	35%
Diarrhea	35%
Eczema	31%
Pyrexia	31%
Constipation	23%
Upper respiratory tract infection	23%
Vomiting	23%
Nasal congestion	19%
Nasopharyngitis	19%
Respiratory tract infection viral	19%
Rhinitis	19%
Viral infection	19%

As of clinical cut-off date: March 27, 2024.

- Multiple occurrences of the same adverse event in an individual are counted only once³⁹
- Includes adverse events with onset from first dose to the cut-off date³⁹

RAINBOWFISH

No treatment-related adverse events leading to permanent discontinuation^{1,24,39}

As of clinical cut-off date: March 27, 2024.

*Adverse reactions have an assumed causality to drug treatment under appropriate use; adverse events include any untoward event associated with the use of a drug, regardless of causality.³¹
ITT=intent-to-treat.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.



EVERYWHERE



Early treatment with Evrysdi helped infants sit without support^{1,40}

Results were clinically meaningful across populations, including the group with the more severe disease^{1,40}

RAINBOWFISH

AFTER 1 YEAR OF TREATMENT^{1,5,40}

INFANTS IN PRIMARY ANALYSIS POPULATION (n=5)



80%

of infants (4/5)

were able to sit without support for at least 5 seconds

As measured by BSID-III, Item 22



INFANTS WITH MORE SEVERE DISEASE (n=8)

88%

of infants (4/5)

were able to sit without support for at least 5 seconds

As measured by BSID-III, Item 22



INFANTS IN ITT POPULATION (n=26)

96%

of infants (25/26)

were able to sit without support for at least 5 seconds

As measured by BSID-III, Item 22

- 81% of infants (21/26) were able to sit without support for 30 seconds¹

As measured by BSID-III, Item 26

Based on the natural history of infantile-onset Type 1 SMA, **untreated infants never acquire the ability to sit without support^{41*}**

*According to a study of SMA patients, approximately 79% of patients with 2 *SMN2* copies develop Type 1 SMA.⁴¹

As of clinical cut-off date: February 20, 2023.⁵

BSID-III=Bayley Scales of Infant and Toddler Development-Third Edition; ITT=intent-to-treat.

EXPLORATORY ASSESSMENTS SUGGEST Infants achieved a key sitting milestone after 2 years of taking Evrysdi³⁹

RAINBOWFISH

AFTER 2 YEARS OF TREATMENT

INFANTS IN PRIMARY ANALYSIS POPULATION (n=4)[†]



100%

of infants (4/4)

were able to sit without support for at least 5 seconds

As measured by BSID-III, Item 22



INFANTS WITH MORE SEVERE DISEASE (n=5)[‡]

100%

of infants (5/5)

were able to sit without support for at least 5 seconds

As measured by BSID-III, Item 22



INFANTS IN ITT POPULATION (n=23)

100%

of infants (23/23)

were able to sit without support for at least 5 seconds

As measured by BSID-III, Item 22

These data reflect the impact of Evrysdi in conjunction with the natural development toward achieving these milestones. Two-year assessments should be interpreted with caution, as these are exploratory data.

As of clinical cut-off date: March 27, 2024.

[†]Excludes 1 infant who withdrew before the Year 2 assessment to receive a one-time disease-modifying treatment.³⁹

[‡]Excludes 3 infants who withdrew before the Year 2 assessment to receive a one-time disease-modifying treatment.³⁹

Important Safety Information (continued)

Pregnancy & Breastfeeding (continued)

- Pregnancy testing is recommended prior to initiating Evrysdi. Advise female patients to use contraception during treatment with Evrysdi and for at least 1 month after the last dose

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.



EVERYWHERE

IN INFANTS FROM THE ITT POPULATION

Evrysdi helped infants sit, stand, or walk independently¹

RAINBOWFISH

AFTER 1 YEAR OF TREATMENT (N=26)¹



96% of infants (24/25)*
were able to sit without support
As measured by HINE-2



84% of infants (21/25)*
were able to stand with and without support
As measured by HINE-2

- 13/25 could stand unaided
- 8/25 could stand with support



48% of infants (12/25)*
were able to walk independently
As measured by HINE-2

As of clinical cut-off date: February 20, 2023.⁵

EXPLORATORY ASSESSMENTS IN ITT POPULATION SUGGEST

Two years of treatment helped infants hit motor milestones³⁹

RAINBOWFISH

AFTER 2 YEARS OF TREATMENT (N=23)[†]



100% of infants (23/23)
were able to sit without support
As measured by HINE-2



96% of infants (22/23)
were able to stand with and without support
As measured by HINE-2

- 21/23 could stand unaided
- 1/23 could stand with support



87% of infants (20/23)[‡]
were able to walk independently
As measured by HINE-2

As of clinical cut-off date: March 27, 2024.

These data reflect the impact of Evrysdi in conjunction with the natural development toward achieving these milestones. HINE-2 assessments should be interpreted with caution, as these are exploratory data.

*One infant with ≥ 4 SMN2 copies could not be assessed.⁵
HINE-2=Hammersmith Infant Neurological Examination-Module 2;
ITT=intent-to-treat; mV=millivolt; SMN2=survival motor neuron 2.

Important Safety Information (continued)

Pregnancy & Breastfeeding (continued)

- There is a pregnancy exposure registry that monitors pregnancy and fetal/neonatal/infant outcomes in women exposed to Evrysdi during pregnancy. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-833-760-1098 or visiting <https://www.evrysidipregnancyregistry.com>.

[†]Excludes 3 infants who withdrew before the Year 2 assessment to receive a one-time disease-modifying treatment.³⁹

[‡]One child could not be assessed at Year 2.³⁹

Please see additional
Important Safety Information
throughout and accompanying
full Prescribing Information.



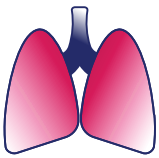
EVERYWHERE

IN INFANTS FROM THE ITT POPULATION

All infants taking Evrysdi survived without permanent ventilation after 1 and 2 years^{1,24,39*}

RAINBOWFISH

AFTER 1 YEAR OF TREATMENT (N=26)^{1,24†}



100% of infants (26/26)[†] were alive without permanent ventilation

As of clinical cut-off date: February 20, 2023.

EXPLORATORY ASSESSMENTS SUGGEST AFTER 2 YEARS OF TREATMENT (N=23)^{39‡}

100% of infants (23/23) were alive without permanent ventilation

Alive without permanent ventilation data should be interpreted with caution, as these are exploratory data.

As of clinical cut-off date: March 27, 2024.

EXPLORATORY ASSESSMENTS IN ITT POPULATION SUGGEST

All infants taking Evrysdi were able to feed exclusively by mouth and swallow^{39§}

RAINBOWFISH

AFTER 2 YEARS OF TREATMENT (N=23)^{39||}

100% of infants (23/23) were able to feed exclusively by mouth

100% of infants (23/23) were able to swallow

As of clinical cut-off date: March 27, 2024.³⁹

Feeding and swallowing assessments should be interpreted with caution, as these are exploratory data.

[§]Assessed using nutritional status interview of the parent/caregiver and a standard swallowing assessment based on local practice and performed by a qualified individual. Swallowing assessment was completed at baseline and during follow-up visits. Ability of the patient to swallow age-appropriate foods was assessed.⁵

^{||}Excludes 3 infants who withdrew before the Year 2 assessment to receive a one-time disease-modifying treatment. The 3 infants were able to swallow and feed orally at their last assessments.³⁹

Important Safety Information (continued)

Pregnancy & Breastfeeding (continued)

- The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Evrysdi and any potential adverse effects on the breastfed infant

Potential Effects on Male Fertility

- Counsel male patients that fertility may be compromised by treatment with Evrysdi. Male patients may consider sperm preservation prior to treatment

*Permanent ventilation was defined as a tracheostomy or >21 consecutive days of either non-invasive ventilation (≥16 hours per day) or intubation, in the absence of an acute reversible event.⁵

†8 patients had 2 *SMN2* copies, 13 patients had 3 *SMN2* copies, and 5 patients had ≥4 *SMN2* copies.⁵

‡Excludes 3 infants who withdrew before the Year 2 assessment to receive a one-time disease-modifying treatment.³⁹
ITT=intent-to-treat.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.



EVERYWHERE

JEWELFISH adverse events and serious adverse events at 2 years²⁰

Previous treatment	RG7800* (MOONFISH) (n=13) [†]	Nusinersen (n=76)	Olesoxime* (n=70)	Onasemnogene abeparvovec (n=14)	All patients (N=173) [‡]
Most common adverse events (reported in ≥12% of all patients), % (n)					
Pyrexia	15% (2)	30% (23)	16% (11)	43% (6)	24% (42)
Upper respiratory tract infection	0	22% (17)	23% (16)	29% (4)	21% (37)
Headache	8% (1)	22% (17)	19% (13)	0	18% (31)
Nasopharyngitis	15% (2)	16% (12)	11% (8)	36% (5)	16% (27)
Diarrhea	0	22% (17)	9% (6)	7% (1)	14% (24)
Nausea	0	18% (14)	10% (7)	7% (1)	13% (22)
Cough	0	16% (12)	9% (6)	21% (3)	12% (21)
Most common serious adverse events (reported in >2% of all patients),[§] % (n)					
Pneumonia	0	4% (3)	1% (1)	7% (1)	3% (5)
Respiratory failure	0	4% (3)	1% (1)	0	2% (4)
Respiratory distress	0	3% (2)	0	7% (1)	2% (3)
Lower respiratory tract infection	0	1% (1)	3% (2)	0	2% (3)
Upper respiratory tract infection	0	4% (3)	0	0	2% (3)

As of clinical cut-off date: January 31, 2022.

Evrysdi treatment duration in months, median (range): 26.8 (0.9-59.0)

- As follow-up duration is different between groups, the overall rate of adverse events and serious adverse events cannot be compared
- The safety findings from JEWELFISH have been consistent with the safety findings from FIREFISH and SUNFISH

Important Safety Information (continued)

Most Common Adverse Reactions

- The most common adverse reactions in later-onset SMA (incidence in at least 10% of patients treated with Evrysdi and more frequent than control) were fever, diarrhea, and rash
- The most common adverse reactions in infantile-onset SMA were similar to those observed in later-onset SMA patients. Additionally, adverse reactions with an incidence of at least 10% were upper respiratory tract infection (including nasopharyngitis, rhinitis), lower respiratory tract infection (including pneumonia, bronchitis), constipation, vomiting, and cough

*Investigational therapies; not approved by FDA for any use.⁴²

[†]In the MOONFISH trial, 3 patients were treated with placebo and were not switched to RG7800.²⁰

[‡]One patient withdrew from the study at baseline; therefore, 173 patients received Evrysdi.²⁰

[§]Multiple occurrences of the same adverse events in one individual are counted only once.²⁰

FDA=Food and Drug Administration.

Please see additional
Important Safety Information
throughout and accompanying
full Prescribing Information.



EVERYWHERE

Splice-modifying technology in 2 oral formulations^{1,6}



Evrydsi tablets deliver the same demonstrated efficacy and safety as the liquid^{1,6}

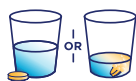
- Studied in 48 participants
- Both formulations provided **comparable Evrydsi exposure** over the course of 6 days
- **The safety profile of Evrydsi tablets was consistent with the safety profile of the liquid formulation**

TABLET BENEFITS



Refrigeration-free storage¹:

offering more freedom in how and where patients take it



Flexible oral administration¹:

option to swallow whole with water or disperse with non-chlorinated drinking water (eg, filtered water, bottled water)



Simplified dosing¹:

which may help patients stay consistent

Important Safety Information (continued)

Most Common Adverse Reactions (continued)

- The safety profile for presymptomatic patients is consistent with the safety profile for symptomatic SMA patients treated with Evrydsi in clinical trials

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

One daily dose tailored for your patients¹

Optimized dosing was studied across several types of SMA*

Age and body weight	Recommended once-daily dose	Dosage form
Less than 2 months of age	0.15 mg/kg	Evrydsi liquid
2 months to less than 2 years of age	0.2 mg/kg	
2 years of age and older weighing less than 20 kg	0.25 mg/kg	
2 years of age and older weighing 20 kg or more	5 mg	Evrydsi liquid or Evrydsi tablet

Since the liquid form of Evrydsi is administered as a solution, the calculated recommended daily dose needs to be converted from mg to a dosing volume in mL. Using the concentration of the 0.75 mg/mL constituted solution, the calculation would be:

Recommended daily dose (mg) ÷ 0.75 mg/mL = dosing volume (mL)

- Evrydsi powder must be constituted to the oral solution by a pharmacist or other healthcare provider prior to dispensing
- The specialty pharmacist will provide the patient with 1 or 2 reusable syringe(s)
- They will select the appropriate oral syringe (1 mL, 6 mL, or 12 mL) based on the patient's dose
- They will remove the other oral syringes from the carton
- Modify dose to reflect changes in the weight of children <2 years of age or in individuals <20 kg
- The maximum recommended dose of Evrydsi is 5 mg once daily

Before prescribing, review the dosing and administration instructions for Evrydsi with your patients or their caregivers



EVERYWHERE

*Types 1, 2, 3, and presymptomatic SMA.¹

Giving patients more non-invasive treatment options¹

Liquid and tablet formulations offer options that fit individual patient needs

	 Liquid	 Tablet
 Eligibility	Patients of any age or weight	Patients must be ≥2 years of age and weigh ≥20 kg (44 lb)
 Administration	Taken via oral syringe	Can be swallowed whole with water or dispersed with non-chlorinated drinking water (eg, filtered water, bottled water)
 Storage	Refrigerate 36°F to 46°F (2°C to 8°C)	Store at room temperature 68°F to 77°F (20°C to 25°C)
 Use with G- or NG-tube	Yes	No
 Obtaining Evrysdi	Shipped directly to	your patient's door through a specialty pharmacy

OTHER CONSIDERATIONS

- If refrigeration is not available, Evrysdi liquid can be kept at room temperature up to 104°F (40°C) for a combined total of 5 days
- Store Evrysdi tablets at room temperature, between 68°F to 77°F (20°C to 25°C). Excursions permitted between 59°F to 86°F (15°C to 30°C). Keep the bottle tightly closed in order to protect from moisture
- In infants who are breastfed, Evrysdi liquid can be administered before or after breastfeeding. Evrysdi liquid cannot be mixed with formula or milk
- Evrysdi liquid must be taken immediately after it is drawn up into the oral syringe. If Evrysdi is not taken within 5 minutes, Evrysdi should be discarded from the oral syringe and a new dose should be prepared
- Advise patients to not chew, crush, or cut the Evrysdi tablet, or dissolve it on the tongue. Evrysdi tablets cannot be dispersed with anything other than room temperature bottled water
- For patients who have difficulty swallowing the tablet whole, it can be dispersed with bottled water or the liquid formulation can be prescribed

For complete information on how to take and administer Evrysdi, please refer your patients to the Instructions for Use for **liquid** and the Dosage and Administration section of the Prescribing Information for **tablets**

Important Safety Information

Interactions with Substrates of MATE Transporters

- Based on in vitro data, Evrysdi may increase plasma concentrations of drugs eliminated via MATE1 or MATE2-K, such as metformin
- Avoid coadministration of Evrysdi with MATE (multidrug and toxin extrusion) substrates. If coadministration cannot be avoided, monitor for drug-related toxicities and consider dosage reduction of the coadministered drug if needed

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.



EVERYWHERE

Help patients get started on Evrysdi

Evrysdi Start Program*

Program overview:

The Evrysdi Starter Program may help people with SMA begin treatment as soon as possible by providing short-term, free medication. The Evrysdi Starter Program is available for insured people with SMA who have been prescribed Evrysdi and are experiencing a delay in insurance approval. Eligible people with SMA may receive up to 2 shipments of Evrysdi at treatment initiation.

How it works:

If you believe your patient qualifies for the Evrysdi Starter Program, please submit the completed Evrysdi Start Form and check the Starter section (Step 6) of the Prescriber Service Form. A valid Patient Consent Form is also required to enroll a patient into the Evrysdi Starter Program. For more information, please contact your Evrysdi representative.

*The Evrysdi Starter Program ("Program") provides eligible patients who are experiencing an insurance coverage delay with one free -30-day supply of Evrysdi. Eligible patients include newborns with an insured parent or an insured legal guardian. Such insured parent or insured legal guardian must attest that the newborn will be added to the insurance policy within the timeframe specified by the insurer. In addition, it must be confirmed that the insurance policy will require prior authorization for Evrysdi. If the patient experiences a persistent coverage delay, the patient may be eligible for one -30-day refill of Evrysdi. There is no obligation to purchase any future product and receipt of free product is not contingent on any past or future purchase. Requests for the Evrysdi Starter Program cannot be processed without a completed and signed 1) Evrysdi Prescriber Service Form and 2) Patient Consent Form. Patients must be prescribed Evrysdi for a valid FDA-approved indication. Neither the prescriber, the pharmacy, nor any patient receiving free medicine via the Evrysdi Starter Program may seek reimbursement or credit for any part of the benefit received by the patient through this offer from any insurer, health plan, or government program. The Program cannot be counted towards any out-of-pocket costs under any plan (such as true out-of-pocket cost under a Medicare Part D prescription drug plan). The Evrysdi Starter Program Enrollment Team may notify the patient's insurer that the patient is receiving a free supply of medicine from the Program. Prescribers may not advertise or otherwise use the Program as a means of promoting their services or Genentech's medicines to patients. This Program is void where prohibited by law and may not be used in or by residents of restricted states, where applicable. The free supply may not be sold, purchased or traded or offered for sale, purchase or trade. This Program is not a health insurance or benefit plan. Submission of true and accurate information is a requirement for eligibility and Genentech reserves the right to disqualify patients who do not comply with Genentech Program Terms and Conditions. Genentech reserves the right to rescind, revoke or amend the program without notice at any time. FDA=Food and Drug Administration.

Evrysdi Bridge Program†

Program overview:

The Evrysdi Bridge Program may help eligible patients who experience a delay in obtaining a coverage determination from their insurance by providing a short-term supply of free product.

How it works:

If your patient is eligible, they may be able to receive up to 2 shipments (containing the equivalent of approximately 2 months of product) of Evrysdi. The second shipment will only be sent if the patient is still experiencing a delay in obtaining a coverage determination from their payer.

If you believe your patient qualifies for the Evrysdi Bridge Program, you must complete no. 6 of the Evrysdi Prescriber Bridge Form. A prescriber's signature is required.

Genentech will determine eligibility for the Evrysdi Bridge Program and make the final decision on program approval.

Your patient must also have completed and signed a valid Evrysdi Patient Bridge Form on file and meet the Evrysdi Bridge Program eligibility requirements.

†Subject to eligibility requirements and terms and conditions. This program is void where prohibited by law and may not be used in or by residents of restricted states, if applicable.

Important Safety Information (continued) Pregnancy & Breastfeeding

- Evrysdi may cause embryofetal harm when administered to a pregnant woman. In animal studies, administration of Evrysdi during pregnancy and/or lactation resulted in adverse effects on development. Advise pregnant women of the potential risk to the fetus
- Pregnancy testing is recommended prior to initiating Evrysdi. Advise female patients to use contraception during treatment with Evrysdi and for at least 1 month after the last dose

Please see additional
Important Safety Information
throughout and accompanying
full Prescribing Information.



EVERYWHERE

MySMA™ Support is here for your patients

Financial assistance offerings



Evrysdi Co-pay Program*

The Evrysdi Co-pay Program provides financial assistance to eligible commercially insured patients to help with their co-pays, co-insurance, or other out-of-pocket maximum. Patients who qualify can receive up to \$25,000 in assistance per calendar year. They pay as little as \$0 per prescription co-pay or co-insurance until the annual limit is reached.



Referrals to independent co-pay foundations†

If eligible publicly or commercially insured patients have difficulty paying for their co-pay, co-insurance, or other out-of-pocket maximum, a Case Manager can refer them to an independent co-pay assistance foundation supporting SMA.



Genentech Patient Foundation

The Genentech Patient Foundation gives free Genentech medicine to people who don't have insurance coverage or who have financial concerns and meet eligibility criteria. The Genentech Patient Foundation helps:

- Uninsured patients with incomes under \$150,000[‡]
- Insured patients without coverage for a Genentech medicine with incomes under \$150,000[‡]
- Insured patients with coverage for a Genentech medicine[§]:
 - With out-of-pocket maximum more than 7.5% of their yearly income
 - With household size and income within certain guidelines outlined below

Household size	Annual income
1	Less than \$75,000
2	Less than \$100,000
3	Less than \$125,000
4	Less than \$150,000 [‡]

*The Co-pay Program ("Program") is valid ONLY for patients with commercial (private or non-governmental) insurance who have a valid prescription for a Food and Drug Administration (FDA)-approved indication of a Genentech medicine. The Program is not available to patients whose prescriptions are reimbursed under any federal, state, or government-funded insurance programs (included but not limited to Medicare, Medicare Advantage, Medigap, Medicaid, TRICARE, Department of Defense, or Veterans Affairs Programs) or where prohibited by law or by the patient's health insurance provider. If at any time a patient begins receiving prescription drug coverage under any such federal, state or government-funded healthcare programs, the patient will no longer be eligible for the Program. Under the Program, the patient may be required to pay a co-pay. The final amount owed by a patient may be as little as \$0 for the Genentech medicine (see Program specific details available at the Program website). The total patient out-of-pocket cost is dependent on the patient's health insurance plan. The Program assists with the cost of the Genentech medicine only. It does not assist with the cost of other medicines, procedures or office visit fees. After reaching the maximum annual Program benefit amount, the patient will be responsible for all remaining out-of-pocket expenses. The Program benefit amount cannot exceed the patient's out-of-pocket expenses for the Genentech medicine. All participants are responsible for reporting the receipt of all Program benefits as required by any insurer or by law. The Program is only valid in the United States and U.S. Territories, is void where prohibited by law and shall follow state restrictions in relation to AB-rated generic equivalents (e.g., MA, CA) where applicable. No party may seek reimbursement for all or any part of the benefit received through the Program. The value of the Program is intended exclusively for the benefit of the patient. The funds made available through the Program may only be used to reduce the out-of-pocket costs for the patient enrolled in the Program. The Program is not intended for the benefit of third parties, including without limitation third party payers, pharmacy benefit managers, or their agents. If Genentech determines that a third party has implemented a program that adjusts patient cost-sharing obligations based on the availability of support under the Program and/or excludes the assistance provided under the Program from counting towards the patient's deductible or out-of-pocket cost limitations, Genentech may impose a per fill cap on the cost-sharing assistance available under the Program. Submission of true and accurate information is a requirement for eligibility and Genentech reserves the right to disqualify patients who do not comply with Genentech Program Terms and Conditions. Genentech reserves the right to rescind, revoke or amend the Program without notice at any time. Additional terms and conditions apply. Please visit the Co-pay Program website for the full list of Terms and Conditions.

†Independent co-pay assistance foundations have their own rules for eligibility. Genentech has no involvement or influence in independent foundation decision-making or eligibility criteria and does not know if a foundation will be able to help your patient. We can only refer your patient to a foundation that supports their disease state. Genentech does not endorse or show preference for any particular foundation. The foundations to which we refer your patient may not be the only ones that might be able to help.

‡For all patient types, add \$25,000 for each extra person in households larger than 4 people.

§We encourage insured patients to pursue other financial assistance options prior to applying for help from the Genentech Patient Foundation, if possible. Genentech reserves the right to modify or discontinue the program at any time and to verify the accuracy of information submitted. FDA=Food and Drug Administration.

Important Safety Information (continued)

Pregnancy & Breastfeeding (continued)

- There is a pregnancy exposure registry that monitors pregnancy and fetal/neonatal/infant outcomes in women exposed to Evrysdi during pregnancy. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-833-760-1098 or visiting <https://www.evrysdipregnancyregistry.com>.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.



EVERYWHERE

Important Safety Information

Indication

EVRYSDI is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

Important Safety Information

Interactions with Substrates of MATE Transporters

- Based on in vitro data, Evrysdi may increase plasma concentrations of drugs eliminated via MATE1 or MATE2-K, such as metformin
- Avoid coadministration of Evrysdi with MATE (multidrug and toxin extrusion) substrates. If coadministration cannot be avoided, monitor for drug-related toxicities and consider dosage reduction of the coadministered drug if needed

Pregnancy & Breastfeeding

- Evrysdi may cause embryofetal harm when administered to a pregnant woman. In animal studies, administration of Evrysdi during pregnancy and/or lactation resulted in adverse effects on development. Advise pregnant women of the potential risk to the fetus
- Pregnancy testing is recommended prior to initiating Evrysdi. Advise female patients to use contraception during treatment with Evrysdi and for at least 1 month after the last dose
- There is a pregnancy exposure registry that monitors pregnancy and fetal/neonatal/infant outcomes in women exposed to Evrysdi during pregnancy. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-833-760-1098 or visiting <https://www.evrysdipregnancyregistry.com>.
- The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Evrysdi and any potential adverse effects on the breastfed infant

Potential Effects on Male Fertility

- Counsel male patients that fertility may be compromised by treatment with Evrysdi. Male patients may consider sperm preservation prior to treatment

Most Common Adverse Reactions

- The most common adverse reactions in later-onset SMA (incidence in at least 10% of patients treated with Evrysdi and more frequent than control) were fever, diarrhea, and rash
- The most common adverse reactions in infantile-onset SMA were similar to those observed in later-onset SMA patients. Additionally, adverse reactions with an incidence of at least 10% were upper respiratory tract infection (including nasopharyngitis, rhinitis), lower respiratory tract infection (including pneumonia, bronchitis), constipation, vomiting, and cough
- The safety profile for presymptomatic patients is consistent with the safety profile for symptomatic SMA patients treated with Evrysdi in clinical trials

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Genentech at 1-888-835-2555.

Please see additional
Important Safety Information
throughout and accompanying
full Prescribing Information.



EVERYWHERE

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Please see Important Safety Information throughout and accompanying full Prescribing Information.



EVERYWHERE

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Please see Important Safety Information throughout and accompanying full Prescribing Information.



EVERYWHERE

CONSIDER EVRYSDI:

Designed to go everywhere*

so your patients have the
flexibility to do the same^{1,2†}

*In animal models, Evrydsi was distributed
throughout the body.²

- ✓ Approved for **all ages and types** of SMA^{1†}
- ✓ **No required monitoring** or lab testing^{1,4}
- ✓ Small molecule designed to reach both the **CNS and peripheral tissues**²
- ✓ **Works daily** to increase and sustain SMN protein levels in the blood¹



Two **oral, non-invasive**
formulations: liquid and tablet¹

¹If refrigeration is not available, Evrydsi liquid can be kept at room temperature up to 104°F (40°C) for a combined total of 5 days. Store Evrydsi tablets at room temperature, between 68°F to 77°F (20°C to 25°C). Excursions permitted between 59°F to 86°F (15°C to 30°C). Keep the bottle tightly closed in order to protect from moisture. Please refer to the Storage and Handling section of the Prescribing Information for additional information about storage.¹

[†]Excluding Type 0.¹

CNS=central nervous system; SMN=survival motor neuron.

Important Safety Information (continued)

Pregnancy & Breastfeeding (continued)

- The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Evrydsi and any potential adverse effects on the breastfed infant

Please see additional Important Safety Information throughout and accompanying full Prescribing Information.

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M-US-00009360(v7.0) 03/25



EVERYWHERE

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EVRYSDI safely and effectively. See full prescribing information for EVRYSDI.

EVRYSDI® (risdiplam) for oral solution

EVRYSDI® (risdiplam) tablets, for oral use

Initial U.S. Approval: 2020

-----RECENT MAJOR CHANGES-----

Dosage and Administration (2.1, 2.2, 2.4) 2/2025

-----INDICATIONS AND USAGE-----

EVRYSDI is a survival of motor neuron 2 (SMN2) splicing modifier indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients. (1)

-----DOSAGE AND ADMINISTRATION-----

- Administer once daily with or without food per the table below (2.1):

Age and Body Weight	Recommended Daily Dosage	Dosage Form
Less than 2 months of age	0.15 mg/kg	EVRYSDI for Oral Solution
2 months to less than 2 years of age	0.2 mg/kg	
2 years of age and older weighing less than 20 kg	0.25 mg/kg	
2 years of age and older weighing 20 kg or more	5 mg	EVRYSDI for Oral Solution or EVRYSDI Tablet

- Swallow EVRYSDI tablet whole with water or dispersed in non-chlorinated drinking water (e.g., filtered water). (2.2)
- Administer EVRYSDI for oral solution with the provided oral syringe. (2.2)

- EVRYSDI for oral solution must be constituted by a healthcare provider prior to dispensing. (2.4)
 - See Full Prescribing Information for important preparation and administration instructions. (2.2, 2.4)
- DOSAGE FORMS AND STRENGTHS-----
- For Oral Solution: 60 mg of risdiplam as a powder for constitution to provide 0.75 mg/mL solution. (3)
 - Tablets: 5 mg

-----CONTRAINDICATIONS-----

None. (4)

-----ADVERSE REACTIONS-----

The most common adverse reactions in later-onset SMA (incidence at least 10% of patients treated with EVRYSDI and more frequent than control) were fever, diarrhea, and rash. (6.1)

The most common adverse reactions in infantile-onset SMA were similar to those observed in later-onset SMA patients. Additionally, adverse reactions with an incidence of at least 10% were upper respiratory tract infection, lower respiratory tract infection, constipation, vomiting, and cough. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

Avoid coadministration with drugs that are substrates of multidrug and toxin extrusion (MATE) transporters. (7.1)

-----USE IN SPECIFIC POPULATIONS-----

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 2/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

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- 2 DOSAGE AND ADMINISTRATION**
 - 2.1 Dosing Information
 - 2.2 Important Administration Instructions
 - 2.3 Missed Dose
 - 2.4 Preparation of Powder for Oral Solution by Healthcare Provider
- 3 DOSAGE FORMS AND STRENGTHS**
- 4 CONTRAINDICATIONS**
- 6 ADVERSE REACTIONS**
 - 6.1 Clinical Trials Experience
- 7 DRUG INTERACTIONS**
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* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

EVERYSDI is indicated for the treatment of spinal muscular atrophy (SMA) in pediatric and adult patients.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

EVERYSDI is administered orally once daily with or without food. The recommended dosage is determined by age and body weight (see Table 1). EVERYSDI tablets are available for patients prescribed the 5 mg dose.

Table 1 Adult and Pediatric Dosing Regimen by Age and Body Weight

Age and Body Weight	Recommended Daily Dosage	Dosage Form
Less than 2 months of age	0.15 mg/kg	EVERYSDI for Oral Solution
2 months to less than 2 years of age	0.2 mg/kg	
2 years of age and older weighing less than 20 kg	0.25 mg/kg	
2 years of age and older weighing 20 kg or more	5 mg	EVERYSDI for Oral Solution or EVERYSDI Tablet

2.2 Important Administration Instructions

It is recommended that a healthcare provider discuss with the patient or caregiver how to prepare the prescribed daily dose prior to administration of the first dose [*see Instructions for Use for EVERYSDI for Oral Solution and Patient Information*].

EVERYSDI is taken orally once daily with or without food at approximately the same time each day.

EVERYSDI for Oral Solution

In infants who are breastfed, EVERYSDI for oral solution can be administered before or after breastfeeding. EVERYSDI cannot be mixed with formula or milk.

Instruct patients or caregivers to administer the dose using the reusable oral syringe provided.

EVERYSDI for oral solution must be taken immediately after it is drawn up into the oral syringe. If EVERYSDI is not taken within 5 minutes, EVERYSDI should be discarded from the oral syringe, and a new dose should be prepared.

Instruct patients to drink water after taking EVERYSDI for oral solution to ensure the drug has been completely swallowed.

If the patient is unable to swallow and has a nasogastric or gastrostomy tube, EVERYSDI for oral solution can be administered via the tube. The tube should be flushed with water after delivering EVERYSDI for oral solution [*see Instructions for Use*].

EVERYSDI Tablets

Swallow EVERYSDI tablets whole with water. Do not chew, cut, or crush the tablets.

The EVERYSDI tablet can also be dispersed in one teaspoon (5 mL) of room temperature non-chlorinated drinking water (e.g., filtered water). EVERYSDI tablets must not be dispersed in any liquid other than non-chlorinated drinking water. Do not expose the prepared dispersion to sunlight. Swirl the small cup gently for up to 3 minutes until fully mixed (though some particles

will remain). Administer the dispersed tablet immediately. To ensure no particles are left in the small cup, refill it with at least one tablespoon (15 mL) of non-chlorinated drinking water, swirl, and administer immediately again.

EVERYSDI must be taken immediately after it is dispersed in non-chlorinated drinking water. Discard the prepared dispersion if it is not used within 10 minutes of adding non-chlorinated drinking water.

Do not administer the prepared dispersion via a nasogastric or gastrostomy tube. If administration through a nasogastric or gastrostomy tube is required, EVERYSDI for oral solution should be used.

2.3 Missed Dose

If a dose of EVERYSDI is missed, EVERYSDI should be administered as soon as possible if still within 6 hours of the missed dose, and the usual dosing schedule can be resumed on the next day. Otherwise, the missed dose should be skipped, and the next dose should be taken at the regularly scheduled time on the next day.

If a dose is not fully swallowed or vomiting occurs after taking a dose of EVERYSDI, another dose should not be administered to make up for the lost dose. The patient should wait until the next day to take the next dose at the regularly scheduled time.

2.4 Preparation of Powder for Oral Solution by Healthcare Provider

EVERYSDI powder must be constituted to the oral solution by a pharmacist or other healthcare provider prior to dispensing to the patient.

Preparation of the EVERYSDI Oral Solution 0.75 mg/mL

The EVERYSDI “Instructions for Constitution” booklet contains more detailed instructions on the preparation of the oral solution [*see Instructions for Constitution*].

Caution should be exercised when handling EVERYSDI powder for oral solution. Avoid inhalation and direct contact with skin or mucous membranes with the dry powder and the constituted solution. If such contact occurs, wash thoroughly with soap and water; rinse eyes with water. Wear disposable gloves during the preparation and cleanup procedure.

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 into the EVERYSDI bottle to yield the 0.75 mg/mL oral solution. Do not mix EVERYSDI with formula or milk.
4. Insert the press-in bottle adapter into the bottle opening by pushing it down against the bottle lip. Ensure it is completely pressed against the bottle lip.
5. Re-cap the bottle tightly and shake well for 15 seconds. Wait for 10 minutes. You should have obtained a clear solution. If not, shake well again for another 15 seconds or until you have obtained a clear solution.
6. Write the date of expiration of the constituted oral solution (calculated as 64 days after constitution) and the lot number on the bottle label. Peel off the part of the bottle label that has the expiration date of the powder.
7. Put the bottle back in its original carton.
8. Select the appropriate oral syringes (1 mL, 6 mL, or 12 mL) based on the patient’s dosage and remove the other oral syringes from the carton.

9. Dispense with the “Instructions for Use” and FDA-approved patient labeling. Alert patients to read the important handling information described in the Instructions for Use.

Storage

Keep the constituted oral solution of EVRYSDI in the original amber bottle to protect from light. Store in a refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze. Discard any unused portion 64 days after constitution. Keep the bottle in an upright position with the cap tightly closed. If refrigeration is not available, EVRYSDI can be kept at room temperature up to 40°C (up to 104°F) for a combined total of 5 days. EVRYSDI can be removed from, and returned to, a refrigerator. The total combined time out of refrigeration should not exceed 5 days.

3 DOSAGE FORMS AND STRENGTHS

EVRYSDI for oral solution: 60 mg as a light yellow, pale 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.

EVRYSDI tablet: 5 mg as a pale yellow film-coated tablet, round and curved, with EVR debossed on one side.

4 CONTRAINDICATIONS

None.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials including patients with infantile-onset SMA, later-onset SMA, and pre-symptomatic SMA, a total of 491 patients (51% female, 74% Caucasian) were exposed to EVRYSDI for up to a median duration of 48.1 months (range: 0.6 to 63.4 months), with 231 patients receiving treatment for more than 24 months. At the time of first EVRYSDI dose, 90 (18%) patients were 18 years and older, 119 (24%) were 12 years to less than 18 years, 189 (39%) were 2 years to less than 12 years, 67 (14%) 2 months to less than 2 years, and 26 (5%) were less than 2 months.

Clinical Trial in Later-Onset SMA

The safety of EVRYSDI for later-onset SMA is based on data from a randomized, double-blinded, placebo-controlled study (Study 2 Part 2) in patients with SMA Type 2 or 3 (n = 180) [see *Clinical Studies (14.2)*]. The patient population in Study 2 Part 2 ranged in age from 2 to 25 years at the time of the first dose.

The most common adverse reactions (reported in at least 10% of patients treated with EVRYSDI and at an incidence greater than on placebo) in Study 2 Part 2 were fever, diarrhea, and rash. Table 2 lists the adverse reactions that occurred in at least 5% of patients treated with EVRYSDI and at an incidence \geq 5% greater than on placebo in Study 2 Part 2.

Table 2 Adverse Reactions Reported in \geq 5% of Patients Treated with EVRYSDI and with an Incidence \geq 5% Greater Than on Placebo in Study 2 Part 2

Adverse Reaction	EVRYSDI (N = 120) %	Placebo (N = 60) %
Fever ¹	22	17
Diarrhea	17	8
Rash ²	17	2
Mouth and aphthous ulcers	7	0
Arthralgia	5	0
Urinary tract infection ³	5	0

¹ Includes pyrexia and hyperpyrexia.

² Includes rash, erythema, rash maculo-papular, rash erythematous, rash papular, dermatitis allergic, and folliculitis.

³ Includes urinary tract infection and cystitis.

Clinical Trial in Infantile-Onset SMA

The safety of EVRYSDI therapy for infantile-onset SMA is based on data from an open-label study in 62 patients (Study 1) [see *Clinical Studies (14.1)*]. The patient population ranged in age from 2 to 7 months at the time of the first EVRYSDI dose (weight range: 4.1 to 10.6 kg).

The most frequent adverse reactions reported in infantile-onset SMA patients treated with EVRYSDI in Study 1 were similar to those observed in later-onset SMA patients in Study 2. Additionally, the following adverse reactions reported in $\geq 10\%$ of patients were: upper respiratory tract infection (including nasopharyngitis, rhinitis), lower respiratory tract infection (including pneumonia, bronchitis), constipation, vomiting, and cough.

Clinical Trial in Pre-Symptomatic SMA

The safety of EVRYSDI therapy for pre-symptomatic SMA is based on data from an open-label, single-arm study in 26 patients (Study 3) [see *Clinical Studies (14.3)*]. The patient population ranged in age from 16 to 41 days at the time of the first dose (weight range: 3.1 to 5.7 kg). The safety profile of EVRYSDI in pre-symptomatic patients in Study 3 is consistent with the safety profile for symptomatic SMA patients treated with EVRYSDI in clinical trials.

7 DRUG INTERACTIONS

7.1 Effect of EVRYSDI on Substrates of Multidrug and Toxin Extrusion (MATE) Protein Transporters

Based on in vitro data, EVRYSDI may increase plasma concentrations of drugs eliminated via MATE1 or MATE2-K [see *Clinical Pharmacology (12.3)*], such as metformin. Avoid coadministration of EVRYSDI with MATE substrates. If coadministration cannot be avoided, monitor for drug-related toxicities and consider dosage reduction of the coadministered drug (based on the labeling of that drug) if needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy and fetal/neonatal/infant outcomes in women exposed to EVRYSDI during pregnancy. Physicians are encouraged to

register patients and pregnant women are encouraged to register themselves by calling 1-833-760-1098 or visiting <https://www.evrysdipregnancyregistry.com>.

Risk Summary

There are no adequate data on the developmental risk associated with the use of EVRYSDI in pregnant women. In animal studies, administration of risdiplam during pregnancy or throughout pregnancy and lactation resulted in adverse effects on development (embryofetal mortality, malformations, decreased fetal body weights, and reproductive impairment in offspring) at or above clinically relevant drug exposures [see *Data*].

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defect and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Based on animal data, advise pregnant women of the potential risk to the fetus.

Data

Animal Data

Oral administration of risdiplam (0, 1, 3, or 7.5 mg/kg/day) to pregnant rats throughout organogenesis resulted in decreased fetal body weights and increased incidences of fetal structural variations at the highest dose tested, which was not associated with maternal toxicity. The no-effect level for adverse effects on embryofetal development (3 mg/kg/day) was associated with maternal plasma exposure (AUC) approximately 2 times that in humans at the maximum recommended human dose (MRHD) of 5 mg.

Oral administration of risdiplam (0, 1, 4, or 12 mg/kg/day) to pregnant rabbits throughout organogenesis resulted in embryofetal mortality, fetal malformations (hydrocephaly), and structural variations at the highest dose tested, which was associated with maternal toxicity. The no-effect dose for adverse effects on embryofetal development (4 mg/kg/day) was associated with maternal plasma exposure (AUC) approximately 4 times that in humans at the MRHD.

When risdiplam (0, 0.75, 1.5, or 3 mg/kg/day) was orally administered to rats throughout pregnancy and lactation, gestation was prolonged in the dams, and delayed sexual maturation (vaginal opening) and impaired reproductive function (decreased numbers of corpora lutea, implantation sites, and live embryos) were observed in female offspring at the highest dose. The no-effect dose for adverse effects on pre- and postnatal development in rats (1.5 mg/kg/day) was associated with maternal plasma exposure (AUC) similar to that in humans at the MRHD.

8.2 Lactation

Risk Summary

There are no data on the presence of risdiplam in human milk, the effects on the breastfed infant, or the effects on milk production. Risdiplam was excreted in the milk of lactating rats orally administered risdiplam.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EVRYSDI and any potential adverse effects on the breastfed infant from EVRYSDI or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Studies of risdiplam in juvenile and adult rats and in monkeys demonstrated adverse effects on the reproductive organs, including germ cells, in males at clinically relevant plasma exposures [*see Use in Specific Populations (8.4) and Nonclinical Toxicology (13.1)*].

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating EVRYSDI [*see Use in Specific Populations (8.1)*].

Contraception

EVRYSDI may cause embryofetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*].

Female Patients

Advise female patients of reproductive potential to use effective contraception during treatment with EVRYSDI and for at least 1 month after her last dose.

Infertility

Male Patients

Male fertility may be compromised by treatment with EVRYSDI [*see Nonclinical Toxicology (13.1)*].

Counsel male patients of reproductive potential receiving EVRYSDI about the potential effects on fertility. Male patients may consider sperm preservation prior to treatment.

8.4 Pediatric Use

The safety and effectiveness of EVRYSDI in pediatric patients (neonates and older) have been established. Use of EVRYSDI for SMA is supported by evidence from adequate and well-controlled studies of EVRYSDI in patients 2 months of age and older with SMA. Use of EVRYSDI for SMA in patients 2 months of age and younger is supported by pharmacokinetic and safety data from pediatric patients 16 days and older, and pharmacokinetic modeling and simulation to identify the dosing regimen [*see Clinical Pharmacology (12.3) and Clinical Studies (14)*].

Juvenile Animal Toxicity Data

Oral administration of risdiplam (0, 0.75, 1.5, 2.5 mg/kg/day) to young rats from postnatal day (PND) 4 through PND 31 resulted in decreased growth (body weight, tibia length) and delayed sexual maturation in males at the mid and high dose. The skeletal and body weight deficits persisted after cessation of dosing. Ophthalmic changes consisting of vacuoles in the anterior vitreous were seen at the high dose. Decreases in absolute B lymphocyte counts were observed at all doses after cessation of dosing. Decreases in testis and epididymis weights, which correlated with degeneration of the seminiferous epithelium in the testis, occurred at the mid and high doses; the histopathology findings were reversible, but organ weight persisted after cessation of dosing. Impaired female reproductive performance (decreased mating index, fertility index, and conception rate) was observed at the high dose. A no-effect dose for adverse developmental effects on preweaning rats was not identified. The lowest dose tested (0.75 mg/kg/day) was associated with plasma exposures (AUC) lower than that in humans at the maximum recommended human dose (MRHD) of 5 mg/day.

Oral administration of risdiplam (0, 1, 3, or 7.5 mg/kg/day) to young rats from PND 22 through PND 112 produced a marked increase in micronuclei in the bone marrow, male reproductive organ histopathology (degeneration/necrosis of the seminiferous tubule epithelium,

oligo/aspermia in the epididymis, spermatic granulomas), and adverse effects on sperm parameters (decreased sperm concentration and motility, increased sperm morphology abnormalities) at the highest dose tested. Increases in T lymphocytes (total, helper, and cytotoxic) were observed at the mid and high doses. The reproductive and immune effects persisted after cessation of dosing. The no-effect dose (1 mg/kg/day) for adverse effects on postweaning juvenile rats was associated with plasma exposures (AUC) lower than that in humans at the MRHD.

8.5 Geriatric Use

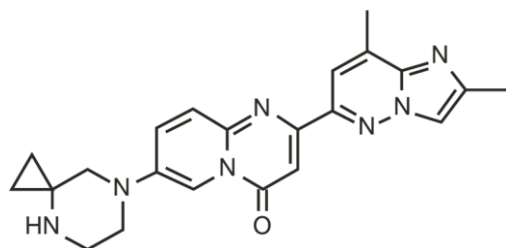
Clinical studies of EVERYSDI did not include patients aged 65 years and older to determine whether they respond differently from younger adult patients.

11 DESCRIPTION

EVERYSDI for oral solution and EVERYSDI tablets for oral use contain risdiplam, which is a survival of motor neuron 2 (SMN2)-directed RNA splicing modifier.

The chemical name of risdiplam is 7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2,8-dimethylimidazo[1,2-b]pyridazin-6-yl)pyrido-4H-[1,2-a]pyrimidin-4-one. Risdiplam has a molecular weight of 401.46 g/mol. Risdiplam demonstrates pH-dependent aqueous solubility; the greatest solubility is at low pH, and solubility decreases with increasing pH. Risdiplam has a pKa₁ of 3.78 (base) and pKa₂ of 6.62 (base).

The molecular formula of risdiplam is C₂₂H₂₃N₇O and the chemical structure is shown below.



EVERYSDI for oral solution is supplied as a powder in an amber glass bottle. Each bottle contains 60 mg of risdiplam. The inactive ingredients of EVERYSDI are: ascorbic acid, disodium edetate dihydrate, isomalt, mannitol, polyethylene glycol 6000, sodium benzoate, strawberry flavor, sucralose, and tartaric acid.

The powder is constituted with purified water to yield 60 mg/80 mL (0.75 mg/mL) of risdiplam after constitution [*see Dosage and Administration (2.4)*].

Each EVERYSDI tablet contains 5 mg of risdiplam. The inactive ingredients of EVERYSDI tablet are colloidal silicon dioxide, crospovidone, mannitol, microcrystalline cellulose, polyethylene glycol 3350, polyvinyl alcohol, sodium stearyl fumarate, strawberry flavor, talc, tartaric acid, titanium dioxide, and yellow iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Risdiplam is a survival of motor neuron 2 (SMN2) splicing modifier designed to treat patients with spinal muscular atrophy (SMA) caused by mutations in chromosome 5q that lead to SMN protein deficiency. Using in vitro assays and studies in transgenic animal models of SMA, risdiplam was shown to increase exon 7 inclusion in SMN2 messenger ribonucleic acid (mRNA) transcripts and production of full-length SMN protein in the brain.

In vitro and in vivo data indicate that risdiplam may cause alternative splicing of additional genes, including FOXM1 and MADD. FOXM1 and MADD are thought to be involved in cell

cycle regulation and apoptosis, respectively, and have been identified as possible contributors to adverse effects seen in animals.

12.2 Pharmacodynamics

In clinical trials for infantile-onset SMA and later-onset SMA patients, EVRYSDI led to an increase in SMN protein with a greater than 2-fold median change from baseline within 4 weeks of treatment initiation across all SMA types studied. The increase was sustained throughout the treatment period (of at least 24 months).

Cardiac Electrophysiology

At the maximum recommended dose, clinically significant QTc interval prolongation was not observed.

12.3 Pharmacokinetics

Pharmacokinetics of EVRYSDI have been characterized in healthy adult subjects and in patients with SMA.

After administration of EVRYSDI as an oral solution, pharmacokinetics of risdiplam were approximately linear between 0.6 and 18 mg in a single-ascending-dose study in healthy adult subjects, and between 0.02 and 0.25 mg/kg once daily in a multiple-ascending-dose study in patients with SMA. Following once-daily oral administration of risdiplam in healthy subjects, approximately 3-fold accumulation of peak plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC_{0-24h}) was observed. Risdiplam exposures reach steady state 7 to 14 days after once daily administration. EVRYSDI tablet (swallowed whole or dispersed in water) demonstrated comparable bioavailability to EVRYSDI for oral solution in adult healthy volunteers under fasted and fed states.

Absorption

Following oral administration of risdiplam in fasted state, the median time to reach maximum plasma concentration (T_{max}) was 3.26 to 4 hours. The T_{max} was delayed by up to 1 hour in fed state compared to that under fasted state.

Effect of Food

Food (high-fat, high calorie breakfast) had no relevant effect on the exposure of risdiplam. In the clinical efficacy studies (Study 1 and Study 2), risdiplam was administered with a morning meal or after breastfeeding.

Distribution

The apparent volume of distribution at steady state is 190.4 L for a 31.3 kg patient.

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

Elimination

The apparent clearance (CL/F) of risdiplam is 2.45 L/h for a 31.3 kg patient. The terminal elimination half-life of risdiplam was approximately 50 hours in healthy adults.

Metabolism

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

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.

Excretion

Following a dose of 18 mg, approximately 53% of the dose (14% unchanged risdiplam) was excreted in the feces and 28% in urine (8% unchanged risdiplam).

Specific Populations

There were no clinically significant differences in the pharmacokinetics of EVRYSDI based on race or gender. Renal impairment is not expected to alter the exposures to risdiplam.

The impact of geriatric age on the pharmacokinetics of EVRYSDI has not been studied.

Hepatic Impairment

The pharmacokinetics and safety of risdiplam have been studied in subjects with mild or moderate hepatic impairment (as defined by Child-Pugh class A and B, respectively, n = 8 each) compared to subjects with normal hepatic function (n = 10). Following the administration of 5 mg EVRYSDI, the AUC_{inf} and C_{max} of risdiplam were approximately 20% and 5% lower, respectively, in subjects with mild hepatic impairment and were approximately 8% and 20% higher, respectively, in subjects with moderate hepatic impairment, versus matched healthy control subjects. The magnitude of these changes is not considered to be clinically meaningful. The pharmacokinetics and safety in patients with severe hepatic impairment (Child-Pugh class C) have not been studied.

Pediatric Patients

Body weight and age were found to have significant effect on the pharmacokinetics of risdiplam. The estimated exposure (mean AUC_{0-24h}) in pre-symptomatic infants at the age of 1 to 2 months was 2090 ng.h/mL at the recommended dose of 0.15 mg/kg once daily. The estimated exposure for infantile-onset SMA patients (age 2 to 7 months at enrollment) at the recommended dose of 0.2 mg/kg once daily was 1930 ng.h/mL. The estimated exposure for later-onset SMA patients (2 to 25 years old at enrollment) at the recommended dose was 2070 ng.h/mL (0.25 mg/kg once daily for patients with a body weight < 20 kg and 5 mg once daily for patients with a body weight ≥ 20 kg).

No data on risdiplam pharmacokinetics are available in patients less than 16 days of age [*see Use in Specific Populations (8.4)*].

Drug Interaction Studies

Effect of Other Drugs on EVRYSDI

Coadministration of 200 mg itraconazole (a strong CYP3A inhibitor) twice daily with a single 6 mg oral dose of risdiplam did not have a clinically relevant effect on the pharmacokinetics of risdiplam (11% increase in AUC and 9% decrease in C_{max}).

Risdiplam is a weak substrate of human MDR-1 and breast cancer resistant protein (BCRP) transporters in vitro. Human MDR-1 or BCRP inhibitors are not expected to result in a clinically significant increase of risdiplam concentrations.

Effect of EVRYSDI on Other Drugs

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 in vitro.

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%); this increase is not considered clinically relevant. Based on

physiologically-based pharmacokinetic (PBPK) modeling, a similar increase is expected in children and infants as young as 2 months of age.

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) transporters, and human organic cation transporter 2 (OCT2), at clinically relevant concentrations. Risdiplam and its metabolite are, however, in vitro inhibitors of the multidrug and toxin extrusion (MATE) 1 and MATE2-K transporters [*see Drug Interactions (7.1)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Risdiplam was not carcinogenic in Tg.rasH2 mice when administered at oral doses of up to 9 mg/kg/day for 26 weeks.

In a 2-year carcinogenicity study in rats, oral administration of risdiplam (0, 0.3, 1, or 3 mg/kg/day) resulted in increased incidences of preputial gland squamous cell carcinomas in males and combined thyroid follicular cell adenomas and carcinomas in females at the highest dose tested. The higher dose not associated with an increase in tumors (1 mg/kg/day) was associated with plasma drug exposures (AUC) similar to that in humans at the maximum recommended human dose (MRHD) of 5 mg/day.

Mutagenesis

Risdiplam was negative in an in vitro Ames assay. In an in vivo combined bone marrow micronucleus and comet assay in rat, risdiplam was clastogenic, as evidenced by an increase in micronuclei in bone marrow, but was negative in the comet assay. A pronounced increase in bone marrow micronuclei was also observed in toxicity studies in adult and juvenile rats [*see Use in Specific Populations (8.4)*].

Impairment of Fertility

Oral administration of risdiplam to rats for 4 (0, 1, 3, or 9 mg/kg/day) or 26 (0, 1, 3, or 7.5 mg/kg/day) weeks resulted in histopathological effects in the testis (degenerated spermatocytes, degeneration/atrophy of the seminiferous tubules) and epididymis (degeneration/necrosis of ductular epithelium) at the mid and/or high doses. At the high dose in the 26-week study, the testicular lesions persisted to the end of the recovery period, which corresponds, in rat, to approximately one spermatogenic cycle. The no-effect dose for adverse reproductive system effects in adult male rats (1 mg/kg/day) was associated with plasma drug exposures (AUC) similar to that in humans at the maximum recommended human dose (MRHD) of 5 mg/day.

Adverse effects of risdiplam on the testis could not be fully evaluated in the monkey because the majority of monkeys tested were sexually immature. However, oral administration of risdiplam (0, 2, 4, or 6 mg/kg/day) for 2 weeks resulted in histopathological changes in the testis (increases in multinucleate cells, germ cell degeneration) at the highest dose. At the no-effect dose for testicular toxicity in monkeys, plasma exposures were approximately 3 times that in humans at the MRHD.

Oral administration of risdiplam to postweaning juvenile rats resulted in male reproductive toxicity (degeneration/necrosis of the testis seminiferous epithelium with associated oligo/azospermia in the epididymis and abnormal sperm parameters). The no-effect dose for adverse reproductive effects in postweaning male juvenile rats was associated with plasma

exposures approximately 4 times that in humans at the MRHD [see *Use in Specific Populations* (8.4)].

13.2 Animal Toxicology and/or Pharmacology

Retinal toxicity

Risdiplam-induced functional and structural retinal abnormalities were seen in animal studies. In a 39-week toxicity study in monkeys, oral administration of risdiplam (0, 1.5, 3, or 7.5/5 mg/kg/day; high dose lowered after 4 weeks) produced functional abnormalities on the electroretinogram (ERG) in all mid- and high-dose animals at the earliest examination time (Week 20). These findings were associated with retinal degeneration, detected by optical coherence tomography (OCT), on Week 22, the first examination time. The retinal degeneration, with peripheral photoreceptor loss, was irreversible. A no-effect dose for the retinal findings (1.5 mg/kg/day) was associated with plasma exposures (AUC) similar to that in humans at the maximum recommended human dose (MRHD) of 5 mg.

Effect on Epithelial Tissues

Oral administration of risdiplam to rats and monkeys resulted in histopathological changes in epithelium of the gastrointestinal (GI) tract (apoptosis/single cell necrosis), lamina propria (vacuolation), the exocrine pancreas (single cell necrosis), the skin, tongue, and larynx (parakeratosis/hyperplasia/degeneration) with associated inflammation. The skin and GI epithelial effects were reversible. The no-effect doses for effects on epithelial tissues in rats and monkeys were associated with plasma exposures (AUC) similar to that in humans at the MRHD.

14 CLINICAL STUDIES

The efficacy of EVRYSDI for the treatment of patients with infantile-onset, later-onset, and pre-symptomatic SMA was evaluated in three clinical studies, Study 1 (NCT02913482) and Study 2 (NCT02908685), and Study 3 (NCT03779334), respectively.

The overall findings of these studies support the effectiveness of EVRYSDI in SMA pediatric and adult patients and appear to support the early initiation of treatment with EVRYSDI.

14.1 Infantile-Onset SMA

Study 1 was an open-label, 2-part study to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of EVRYSDI for oral solution in patients with Type 1 SMA (symptom onset between 28 days and 3 months of age). All patients had genetic confirmation of homozygous deletion or compound heterozygosity predictive of loss of function of the SMN1 gene, and two SMN2 gene copies.

Part 1 of Study 1 was designed as a dose-finding study. Part 2 of Study 1 assessed the safety and efficacy of EVRYSDI at 0.20 mg/kg, the recommended dose determined in Part 1 [see *Dosage and Administration* (2.4)]. 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 recommended dosage [see *Dosage and Administration* (2.1)]. The median age of onset of clinical signs and symptoms was 1.5 months (range: 0.9 to 3.0 months). The median age at enrollment 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. The demographics and baseline disease characteristics were comparable between Part 1 and Part 2 of the study.

Effectiveness was established based on 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) and on the basis of survival without permanent ventilation. 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.

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) achieved this milestone.

Other efficacy endpoints of EVRYSDI-treated patients in Study 1 (pooled Part 1 and Part 2) are shown in Table 3.

Table 3 Key Efficacy Results at Month 12 and Month 24 (Study 1, Parts 1 and Part 2)

Efficacy Endpoints	Proportion of Patients Parts 1 & 2 at Month 12	Proportion of Patients Parts 1 & 2 at Month 24
Motor Function and Development Milestones	N = 58 ^a	
BSID-III, Item 22: sitting without support for at least 5 seconds	32.8%	60.3%
Survival and Event-Free Survival	N = 62 ^b	
Alive without Permanent Ventilation	87.1%	83.8%

^a Results were pooled from all patients who received the recommended dose of risdiplam (all patients in Part 2 and those in the high-dose cohort of Part 1; n = 58).

^b Results were pooled from all patients who received any dose of risdiplam in Part 1 and Part 2 (n = 62).

At Month 24, 40% (23/58) of patients who received the recommended dose achieved sitting without support for 30 seconds (BSID-III, Item 26). In addition at Month 24, patients continued to achieve additional motor milestones; 28% (16/58) of patients achieved a standing measure (16% [9/58] supporting weight and 12% [7/58] standing with support), as measured by Section 2 of the Hammersmith Infant Neurological Examination (HINE-2) which assesses motor milestones.

The proportion of patients alive without permanent ventilation (event-free survival) was 84% for all patients at Month 24 (Table 3). Out of 62 patients, 6 infants died (4 within the first 3 months following study enrollment) 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. As described in the natural history of untreated infantile-onset SMA, patients would not be expected to attain the ability to sit independently, and no more than 25% of these patients would be expected to survive without permanent ventilation beyond 14 months of age.

14.2 Later-Onset SMA

Study 2 was a 2-part, multicenter trial to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of EVRYSDI for oral solution in patients diagnosed with SMA Type 2 or Type 3. Part 1 of Study 2 was dose-finding and exploratory in 51 patients (14% ambulatory). Part 2 was randomized, double-blind, placebo-controlled, and is described below.

The primary endpoint in Study 2 Part 2 was the change from baseline to Month 12 in the Motor Function Measure 32 (MFM32) score. A key secondary endpoint was the proportion of patients

with a 3-point or greater change from baseline to Month 12 in the MFM32 total score. The MFM32 measures motor function abilities that relate to daily functions. 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. Another key secondary endpoint was the Revised Upper Limb Module (RULM). The RULM is a tool used to assess motor performance of the upper limb in SMA patients. It tests proximal and distal motor functions of the arm. The total score ranges from 0 (all the items cannot be performed) to 37 (all the activities are achieved fully without any compensatory maneuvers).

Study 2 Part 2 enrolled 180 non-ambulatory patients with Type 2 (71%) or Type 3 (29%) SMA. Patients were randomized 2:1 to receive EVRYSDI at the recommended dosage [*see Dosage and Administration (2.1)*] or placebo. Randomization was stratified by age group (2 to 5, 6 to 11, 12 to 17, or 18 to 25 years of age).

The median age of patients at the start of treatment was 9.0 years (range: 2 to 25), and the median time between onset of initial SMA symptoms and first treatment was 102.6 months (range: 1 to 275). Of the 180 patients included in the trial, 51% were female, 67% were Caucasian, and 19% were Asian. At baseline, 67% of patients had scoliosis (32% of them with severe scoliosis). Patients had a mean baseline MFM32 score of 46.1, and RULM score of 20.1. Overall baseline demographic characteristics were reasonably balanced between the treatment groups (EVRYSDI and placebo), with the exception of scoliosis (63% in the EVRYSDI arm vs. 73% in the placebo group).

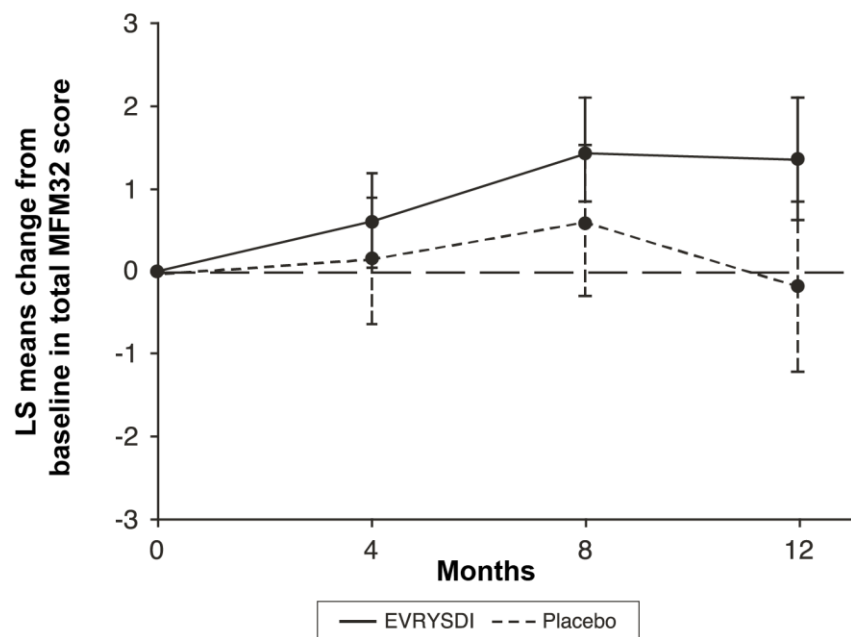
The primary analysis on the change from baseline in MFM32 total score at Month 12 showed a clinically meaningful and statistically significant difference between patients treated with EVRYSDI and placebo. The results of the primary analysis and key secondary endpoints are shown in Table 4 and Figure 1.

Table 4 Summary of Efficacy in Patients with Later-Onset SMA at Month 12 of Treatment (Study 2 Part 2)

Endpoint	EVRYSDI (N = 120)	Placebo (N = 60)
Primary Endpoint:		
Change from baseline in total MFM32 score at Month 12, LS means (95% CI) ^{1,2,3}	1.36 (0.61, 2.11)	-0.19 (-1.22, 0.84)
Difference from Placebo, Estimate (95% CI) ¹ p-value	1.55 (0.30, 2.81) 0.0156	
Secondary Endpoints:		
Proportion of patients with a change from baseline MFM32 total score of 3 or more at Month 12 (95% CI) ^{2,3}	38.3% (28.9, 47.6)	23.7% (12.0, 35.4)
Odds ratio for overall response (95% CI) adjusted ⁴ (unadjusted) p-value ⁵	2.35 (1.01, 5.44) 0.0469 (0.0469)	
Change from baseline in total score of RULM at Month 12, LS means (95% CI) ^{1, 6}	1.61 (1.00, 2.22)	0.02 (-0.83, 0.87)
Difference from Placebo, Estimate (95% CI) adjusted ⁴ (unadjusted) p-value ¹	1.59 (0.55, 2.62) 0.0469 (0.0028)	

- ¹. The Mixed Model Repeated Measure (MMRM) analysis included the change from baseline total score as the dependent variable and as independent variables the baseline total score, treatment group, time, treatment-by-time interaction, and the randomization stratification variable of age group (2 to 5, 6 to 11, 12 to 17, 18 to 25).
- ². The MFM total score was calculated according to the user manual, expressed as a percentage of the maximum score possible for the scale (i.e., sum of the 32 item scores divided by 96 and multiplied by 100).
- ³. Based on the missing data rule for MFM32, 6 patients were excluded from the analysis (EVRYSDI n = 115; placebo control n = 59).
- ⁴. The adjusted p-value was obtained for the endpoints included in the hierarchical testing and was derived based on all the p-values from endpoints in order of the hierarchy up to the current endpoint.
- ⁵. The logistic regression analysis included the baseline total score, treatment and age group as independent variables.
- ⁶. Based on the missing data rule for RULM, 3 patients were excluded from the analysis (EVRYSDI n = 119; placebo control n = 58).

Figure 1 Mean Change from Baseline in Total MFM32 Score Over 12 Months (Study 2 Part 2)^{1,2}



¹ Error bars denote the 95% confidence interval.

² The MFM total score was calculated according to the user manual, expressed as a percentage of the maximum score possible for the scale (i.e., sum of the 32 item scores divided by 96 and multiplied by 100).

14.3 Pre-Symptomatic SMA

Study 3 was an open-label, single-arm, multicenter clinical study to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of EVRYSDI in infants up to 6 weeks of age (at first dose) who have been genetically diagnosed with SMA but do not yet present with symptoms.

The efficacy in pre-symptomatic SMA patients was evaluated at Month 12 in 26 patients treated with EVRYSDI in Study 3: 8 patients had 2 copies of the *SMN2* gene, 13 patients had 3 copies, and 5 patients had 4 or more copies. The median age of these patients at first dose was 25 days (range: 16 to 41), 62% were female, and 85% were Caucasian. The primary efficacy population (N = 5) included patients with 2 *SMN2* copies and a baseline CMAP amplitude ≥ 1.5 mV.

The primary efficacy 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) at Month 12. This milestone was achieved by 80% (4/5) of patients in the primary efficacy population. This milestone was also achieved by 87.5% (7/8) of all patients with 2 copies of *SMN2* and 96.2% (25/26) of patients in the full treated population.

At Month 12, 80.8% (21/26) of patients in the full treated population achieved sitting without support for 30 seconds (BSID-III, Item 26). Of the 26 patients treated with EVRYSDI, 25 patients had motor milestones measured by the HINE-2 at Month 12. Of these, 24 (96%) achieved sitting (23 patients could pivot/rotate and 1 achieved stable sit); 21 (84%) could stand (13 patients could stand unaided and 8 could stand with support); and 12 (48%) could walk independently. Seven patients were not tested for walking at Month 12. All 26 patients were alive at 12 months without permanent ventilation.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 EVRYSDI for Oral Solution

How Supplied

Each amber glass bottle of EVRYSDI for oral solution is packaged with a bottle adapter, two 1 mL reusable oral syringes, two 6 mL reusable oral syringes, and one 12 mL reusable oral syringe. EVRYSDI for oral solution is a light yellow, pale yellow, yellow, greyish yellow, greenish yellow, or light green powder. Each bottle contains 60 mg of risdiplam (NDC 50242-175-07).

Storage and Handling

Store the dry powder at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C to 30°C (59°F to 86°F) [*see USP controlled room temperature*]. Keep in the original carton.

Keep the constituted oral solution of EVRYSDI in the original amber bottle to protect from light. Store in a refrigerator at 2°C to 8°C (36°F to 46°F) [*see Dosage and Administration (2.4)*].

16.2 EVRYSDI Tablets

How Supplied

Pale yellow film-coated tablet, round and curved, with EVR debossed on one side; available in HDPE bottles of 30 tablets with a child-resistant cap (NDC 50242-202-01).

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [*see USP Controlled Room Temperature*]. Keep the bottle tightly closed in order to protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Pregnancy and Fetal Risk

Inform pregnant women and women of reproductive potential that, based on animal studies, EVRYSDI may cause fetal harm [*see Use in Specific Populations (8.1)*].

Discuss with women of childbearing age whether they are pregnant, might be pregnant, or are trying to become pregnant.

Advise women of childbearing potential to use effective contraception during treatment with EVRYSDI and for at least 1 month after stopping EVRYSDI.

Advise a female patient to immediately inform the prescriber if she is pregnant or planning to become pregnant [*see Use in Specific Populations (8.3)*].

Pregnancy Registry

Encourage patients to enroll in the EVRYSDI Pregnancy Registry if they become pregnant while taking EVRYSDI [*see Use in Specific Populations (8.1)*].

Potential Effects on Male Fertility

Advise male patients that their fertility may be compromised while on treatment with EVRYSDI [*see Use in Specific Populations (8.3)*].

Instructions for Preparation of Oral Solution

Advise patients/caregivers to ensure that EVRYSDI oral solution is in liquid form when received from the pharmacy.

Instruct patients/caregivers to take EVRYSDI oral solution with or without food or before or after breastfeeding at approximately the same time each day. However, instruct caregivers not to mix EVRYSDI with formula or milk.

Instruct patients/caregivers to take EVRYSDI oral solution immediately after it is drawn up into the reusable oral syringe [*see Dosage and Administration (2.1)*].

Instructions for EVRYSDI Tablets

Advise patients/caregivers to swallow EVRYSDI tablets whole with water. Do not chew, cut, or crush the tablets.

Alternatively, the tablet can be dispersed in one teaspoon (5 mL) of room temperature non-chlorinated drinking water (e.g., filtered water) and taken immediately. EVRYSDI tablets must not be dispersed in any liquid other than non-chlorinated drinking water. Instruct the patient/caregivers that the dispersion must be administered within 10 minutes of adding non-chlorinated drinking water, or it must be discarded.

Advise patients/caregivers that the EVRYSDI tablet dispersion is for oral administration only. If administration through a nasogastric/gastrostomy tube is required, EVRYSDI for oral solution should be used.

Advise patients/caregivers to wash their hands before and after preparing or taking EVRYSDI tablets.

Advise patients/caregivers to avoid getting the dispersed tablet on their skin or in their eyes. Advise patients/caregivers to wash the area with soap and water if the dispersed tablet gets on the skin. Advise patients/caregivers to rinse their eyes with water if the dispersed tablet gets in the eyes.

Advise patients/caregivers to use a dry paper towel to dry the area if the dispersion is spilled and then clean with soap and water. Advise patients/caregivers to throw the paper towel away in the trash and wash their hands with soap and water.

EVRYSDI® [risdiplam]

Distributed by:

Genentech, Inc.

A Member of the Roche Group

1 DNA Way

South San Francisco, CA 94080-4990

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Patient Information

**EVERYSDI® [ev-RIZ-dee]
(risdiplam)
for oral solution**

**EVERYSDI® [ev-RIZ-dee]
(risdiplam)
tablets**

What is EVERYSDI?

- EVERYSDI is a prescription medicine used to treat spinal muscular atrophy (SMA) in children and adults.

Before taking EVERYSDI, tell your healthcare provider about all of your medical conditions, including if you:

- are pregnant or plan to become pregnant. If you are pregnant, or are planning to become pregnant, ask your healthcare provider for advice before taking this medicine. EVERYSDI may harm your unborn baby.
- are a woman who can become pregnant:
 - Before you start your treatment with EVERYSDI, your healthcare provider may test you for pregnancy. Because EVERYSDI may harm your unborn baby, you and your healthcare provider will decide if taking EVERYSDI is right for you during this time.
 - Talk to your healthcare provider about birth control methods that may be right for you. Use birth control while on treatment and for at least 1 month after stopping EVERYSDI.
 - **Pregnancy Registry.** There is a pregnancy registry for women who take EVERYSDI during pregnancy. The purpose of this registry is to collect information about the health of the pregnant woman and her baby. If you are pregnant or become pregnant while receiving EVERYSDI, tell your healthcare provider right away. Talk to your healthcare provider about registering with the EVERYSDI Pregnancy Registry. Your healthcare provider can enroll you in this registry or you can enroll by calling 1-833-760-1098 or visiting <https://www.evrysdipregnancyregistry.com>.
- are an adult male planning to have children: EVERYSDI may affect a man's ability to have children (fertility). If this is of concern to you, make sure to ask a healthcare provider for advice.
- are breastfeeding or plan to breastfeed. It is not known if EVERYSDI passes into breast milk and may harm your baby. If you plan to breastfeed, discuss with your healthcare provider about the best way to feed your baby while on treatment with EVERYSDI.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Keep a list of them to show your healthcare provider, including your pharmacist, when you get a new medicine.

How should I take EVERYSDI?

- For infants and children, your healthcare provider will determine the daily dose of EVERYSDI needed based on your child's age and weight. For adults, take 5 mg of EVERYSDI daily.
- Your healthcare provider will either prescribe:
 - EVERYSDI for oral solution
 - Or**
 - EVERYSDI tablet
- Your healthcare provider will tell you how long you or your child needs to take EVERYSDI. Do not stop treatment with EVERYSDI unless your healthcare provider tells you to.
 - Take EVERYSDI exactly as your healthcare provider tells you to take it. Do not change the dose without talking to your healthcare provider.
- Avoid getting EVERYSDI on your skin or in your eyes. If it gets on your skin, wash the area with soap and water. If it gets in your eyes, rinse your eyes with water.

If you are taking EVERYSDI for oral solution:

- **see the detailed Instructions for Use that comes with it for information on how to take or give EVERYSDI for oral solution**
- You should receive EVERYSDI from the pharmacy as a liquid that can be given by mouth or through a feeding tube. The liquid solution is prepared by your pharmacist or other healthcare provider. If the medicine in the bottle is a powder, **do not use it**. Contact your pharmacist for a replacement.
- Take EVERYSDI one time daily with or without a meal at about the same time each day. Drink water afterwards to make sure EVERYSDI has been completely swallowed.
- In infants who are breastfed, EVERYSDI can be given before or after breastfeeding.
- Do not mix EVERYSDI with formula or milk.
- If you are unable to swallow and have a nasogastric (NG-tube) or gastrostomy tube (G-tube), EVERYSDI for oral solution can be given through the tube.

Reusable Oral Syringes for EVRYSDI for Oral Solution

- Your pharmacist will provide you with the reusable oral syringes that are needed for taking your medicine and explain how to use them. You should receive 1 or 2 identical oral syringes depending on your prescribed daily dose.
- From the bottle, draw up (measure) the dose of EVRYSDI with these syringes, as they are made to protect the medicine from light.
- Take EVRYSDI right away after it has been drawn into the syringe. Do not store the EVRYSDI solution in the syringe. If EVRYSDI is not taken within 5 minutes of when it is drawn up, throw away the solution by pressing the plunger and prepare a new dose with the same syringe.
- Do not throw the syringes away because they are reusable.
- Wash the syringes per instructions after use.
- Contact your healthcare provider or pharmacist if your oral syringes are lost or damaged.

If you are taking EVRYSDI Tablets:

- Take EVRYSDI one time daily with or without a meal at about the same time each day.
- Do not chew, cut, or crush the tablet.
- Swallow the EVRYSDI tablet whole with some water.

Or

- You can take an EVRYSDI tablet by mouth after it is mixed with a teaspoon (5 mL) of room temperature non-chlorinated drinking water (e.g., filtered water). See the instructions below for taking EVRYSDI this way.

EVRYSDI Tablets Mixed with Non-chlorinated Drinking Water (e.g., Filtered Water)

- Wash your hands before and after preparing or taking EVRYSDI tablets.
- Put EVRYSDI tablets in a small cup with a teaspoon (5 mL) of room temperature non-chlorinated drinking water (e.g., filtered water).
- Do not mix EVRYSDI tablets with any liquids other than non-chlorinated drinking water.
- Do not expose the EVRYSDI tablet mixture to sunlight.
- Swirl the cup gently until the tablet and non-chlorinated drinking water are fully mixed (though some particles may remain). This may take up to 3 minutes.
- Take EVRYSDI tablet mixture right away after mixing with non-chlorinated drinking water. If you do not take it within 10 minutes of adding non-chlorinated drinking water, throw the mixture away and make a new dose.
- After taking EVRYSDI tablet mixture, to make sure there is no medicine left, refill the small cup with at least a tablespoon (15 mL) of non-chlorinated drinking water, swirl, and take right away.
- If the EVRYSDI tablet mixture is spilled, use a dry paper towel to dry the area and then clean with soap and water. Throw the paper towel away in the trash and wash your hands with soap and water.
- Do not give the EVRYSDI tablet mixture via a nasogastric (NG-tube) or gastrostomy tube (G-tube).

If you miss a dose of EVRYSDI:

- If you remember the missed dose within 6 hours of when you normally take EVRYSDI, then take the dose. Continue taking EVRYSDI at your usual time the next day.
- If you remember the missed dose more than 6 hours after you normally take EVRYSDI, skip the missed dose. Take your next dose at your usual time the next day.
- If you do not fully swallow the dose, or you vomit after taking a dose, **do not take** another dose of EVRYSDI to make up for that dose. Wait until the next day to take the next dose at your usual time.

What are the possible side effects of EVRYSDI?

The most common side effects of EVRYSDI include:

- **For later-onset SMA:**
 - fever
 - diarrhea
 - rash
- **For infantile-onset SMA:**
 - fever
 - runny nose, sneezing, and sore throat (upper respiratory infection)
 - constipation
 - diarrhea
 - lung infection (lower respiratory infection)
 - vomiting
 - rash
 - cough

These are not all of the possible side effects of EVRYSDI. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store EVRYSDI?

EVRYSDI for Oral Solution:

- Store EVRYSDI in the refrigerator between 36°F to 46°F (2°C to 8°C). Do not freeze.
- If necessary, EVRYSDI can be kept at room temperature up to 104°F (up to 40°C) for a combined total of 5 days. EVRYSDI can be removed from, and returned to, a refrigerator. The total combined time out of refrigeration should not be more than 5 days.
- Keep EVRYSDI in an upright position in the original amber bottle to protect from light.
- Throw away (discard) any unused portion of EVRYSDI 64 days after it is mixed by the pharmacist (constitution) or if EVRYSDI has been kept at room temperature (below 104°F [40°C]) for more than a total combined time of 5 days. Discard EVRYSDI if it has been kept above 104°F (40°C). Please see the Discard After date written on the bottle label. (See the **Instructions for Use** that comes with EVRYSDI for oral solution).

EVRYSDI Tablets:

- Store at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep the bottle tightly closed in order to protect from moisture.

Keep EVRYSDI, all medicines and syringes out of the reach of children.

General information about the safe and effective use of EVRYSDI.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use EVRYSDI for a condition for which it was not prescribed. Do not give EVRYSDI to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about EVRYSDI that is written for health professionals.

What are the ingredients in EVRYSDI?

Active ingredient: risdiplam

Inactive ingredients:

EVRYSDI for Oral Solution: ascorbic acid, disodium edetate dihydrate, isomalt, mannitol, polyethylene glycol 6000, sodium benzoate, strawberry flavor, sucralose, and tartaric acid.

EVRYSDI Tablets: colloidal silicon dioxide, crospovidone, mannitol, microcrystalline cellulose, polyethylene glycol 3350, polyvinyl alcohol, sodium stearyl fumarate, strawberry flavor, talc, tartaric acid, titanium dioxide, and yellow iron oxide.

Distributed by: **Genentech, Inc.**, A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990

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For more information, go to www.EVRYSDI.com or call 1-833-387-9734.