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New Drug Evaluation: Risdiplam (Evrysdi™) oral solution

Date of Review: December 2020
Generic Name: Risdiplam

End Date of Literature Search: 9/30/2020
Brand Name (Manufacturer): Evrysdi™ (Genentech, Inc.)
Dossier Received: yes

Research Questions:

1. What is the efficacy and effectiveness of risdiplam in reducing symptoms, improving functional outcomes and reducing mortality in patients with spinal muscular atrophy (SMA)?
2. What are the harms of risdiplam in patients with SMA?

Conclusions:

- The efficacy of risdiplam was evaluated in two unpublished trials: one double blind, randomized, placebo-controlled trial in children and adults with Type 2 and 3 SMA (SUNFISH) and one open-label trial with historical controls in infants with Type 1 SMA (FIREFISH).[1,2] In SUNFISH, the primary outcome was the mean change from baseline in the total Motor Function Measure 32 (MFM-32) score at Month 12 compared to placebo.[1,2] A statistically significant difference was reported in mean MFM32 score with risdiplam-treated patients compared to placebo (least squares [LS] mean difference: 1.55 (95% CI, 0.30 to 2.81; p-value = 0.016).[1,2] In FIREFISH, the primary outcome was the proportion of infants able to sit without support for at least 5 seconds as measured by item 22 (gross motor skills) of the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) after 12 months post treatment initiation.[1,2] Compared to historical controls, 33% (7/21) of all risdiplam patients and 41% (7/17) of patients given the higher risdiplam dose, were able to sit without support for at least 5 seconds after 12 months of therapy.[1,2]
- There is insufficient evidence to evaluate risdiplam long-term safety or effects on survival, the clinical course of SMA disease, and ventilator dependency.
- In Type 2 and Type 3 SMA patients, risdiplam had increased rates of adverse effects compared to placebo: pyrexia (22% risdiplam vs 17% placebo), diarrhea (17% vs 8%), rash (17% vs 2%), mouth ulcers (7% vs 0%), arthralgia (5% vs 0%), and urinary tract infection (5% vs 0%).[1,2,3] In Type 1 SMA patients, there was increased incidence of upper respiratory tract infection (32%), pyrexia (27%), pneumonia (21%), constipation (16%), diarrhea (13%), vomiting (13%), nasopharyngitis (10%).[1,2,3]
- Trials were unpublished, therefore the quality, risk of bias, applicability, and influence of financial support on the studies were unclear.

Recommendations:

- Add risdiplam to the Preferred Drug List (PDL) class for Spinal Muscular Atrophy agents.
- Implement prior authorization (PA) criteria for risdiplam to ensure appropriate use (**Appendix 2**).
- Designate risdiplam as non-preferred.

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Background:
SMA is a heterogeneous autosomal recessive neuromuscular disease characterized by degeneration of motor neurons in the spinal cord which results in progressive weakness, atrophy, and dysfunction of skeletal and respiratory muscles. Severity of disease ranges from progressive infantile paralysis, respiratory failure, and premature death to limited motor neuron loss, ambulation, and normal life expectancy.[4] The incidence of SMA is estimated to range from 1 to 10 individuals per 100,000 live births.[4] Although SMA is rare, it is the leading genetic cause of infantile death due to respiratory insufficiency.[4]

SMA is caused by deletions, rearrangements, or mutations of the survival motor neuron (SMN1) gene on chromosome 5q13 which reduces the overall production of SMN protein.[5] In the human genome, the SMN gene region contains a single SMN1 gene and multiple copies of closely related SMN2 gene.[5,6] Although both genes make SMN protein, a large portion of the SMN2 gene codes for non-functional protein.[5,6] Since SMA patients must rely on the SMN2 pathway to compensate for the loss of SMN1, higher numbers of SMN2 copies tend to positively correlate with functional status.[6] SMA patients with 3 or more copies of SMN2 and a later age of disease onset typically have milder symptoms, are able to ambulate, and have a normal life expectancy.[6] Those with two or fewer SMN2 copies and SMA onset before 6 months of age usually have a poorer prognosis and a median survival of less than 2 years.[6]

There is a wide spectrum of SMA clinical severity, and 5 main subtypes based on age of onset and motor function status. The most common SMA cases are Types 1 through 3 which make up roughly 95% of all cases. [6] SMA Types 0 and 4 are very rare. SMA type 1 is the most frequent (45%) type of SMA and occurs primarily in infants under 6 months of age.[5,6] SMA type 1 infants rarely achieve improvements in motor function or acquire motor developmental milestones.[6] These infants cannot sit unsupported and usually die within the first 2 years of life due to respiratory failure or infection.[5,6] Children with SMA type 2 display muscle weakness that is more conspicuous in the lower extremities. They may sit unassisted but are never able to walk independently. Respiratory failure is not as severe and manifests later in life compared to children with SMA type 1.[6] Children with SMA type 3 develop variable muscle weakness after 18 months of age and are generally able to walk.[5,6] However, as the disease progresses, they may become wheelchair bound.[5,6] Respiratory muscles are rarely affected and life expectancy is normal in type 3 SMA patients.[6] SMA type 4 generally occurs in the second or third decade of life and is the mildest form of the disease characterized by slight muscle weakness and normal life expectancy.[6] The characteristics of each SMA type are described in **Table 1**.

Table 1. SMA classification and characteristics[6]

SMA Type	SMN2 copy numbers	Age of Onset	Motor Function	Median Survival *	Incidence (per 100,000 live births)
0	1	Prenatal	Respiratory failure at birth	Less than 6 months	< 1%
I	2	1 - 6 months	Never able to sit unassisted	<2 years	3.2–7.1 (45% of cases)
II	2-4	7 - 18 months	Able to sit, but unable to independently walk	>2 years (~70% still alive at age 25)	1– 5.3 (20% of cases)
III	3-4	>18 months	Able to independently stand and walk, which may decline with disease progression	Normal	1.5–4.6 (30 % of cases)
IV	4-8	10 - 30 years	Ambulatory	Normal	5% of cases

*Natural history may vary depending on supportive interventions

Diagnosis of SMA is confirmed via genetic testing to assess for homozygous deletions or mutations in the SMN1 gene.[7] Carrier testing is available and carrier frequency is estimated as 1:40 to 1:60.[7] There is no known cure for SMA. Medical care for SMA symptoms typically involves respiratory support, motor function assistance and rehabilitation, as well as optimization of nutritional needs. Swallowing and feeding challenges often result in increased respiratory tract infections, gastrointestinal problems and malnourishment. SMA type 1 patients may require full time noninvasive ventilation greater than 16 hours per day in many cases.[8] Food and Drug Administration (FDA)-approved pharmacotherapy has been developed for the treatment of SMA. Nusinersen targets the modification of the SMN2 gene through the use of antisense oligonucleotides to help produce more functional SMN protein.[9] Other therapies such as onasemnogene abeparvovec have focused on gene-replacement therapy through the use of non-replicating adeno-associated virus (AAV) capsid to deliver fully functional SMN1 gene to motor neurons.[10] Nusinersen must be administered intrathecally every 4 months and onasemnogene abeparvovec is a one-time intravenous infusion.[9,10]

Several scales and tools have been developed to assess functional status in children with SMA. The Motor Function Measure 32 (MFM32) is an ordinal scale used to assess patients with neuromuscular diseases.[2] It is comprised of 32 items to evaluate physical function.[2] Scores are tallied and converted to a 0-100 point scale to be expressed as a percentage of the maximum.[2] A lower score indicates more severe impairment.[2] There is no established minimal clinically important difference between point values on the MFM32.

The Upper Limb Module (ULM) is used in non-ambulatory patients greater than 2 years of age.[11] This assessment was designed to assist in evaluation of young children's ability to perform specific tasks such as lifting small objects, pushing buttons, or using a pencil.[11] It has been validated for use in SMA assessments in a variety of settings. A revised version of the ULM (RULM) was designed to address a wider range of patient cohorts at the extreme ends of the SMA spectrum including ambulatory and non-ambulatory patients.[11] The RULM has 19 scorable items which range from 0 to 2 (0=unable; 1=able, with modification; 2=able, no difficulty) with a maximum possible score of 37.[11]

The Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) is an assessment tool used to measure major clinical development issues in the early childhood years. Although not specific to SMA, the tool measures 5 standardized developmental domains: cognitive, language, motor, social-emotional, and adaptive behavior.[12] The social-emotional and adaptive behavior portions are completed by parental questionnaire while the other 3 areas are administered with child interaction.[12] This tool has not been validated in SMA patients.

The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) was developed by physical therapists to provide a standardized method for motor skill evaluation of neck, trunk, and limb strength of SMA patients. [13] The assessment includes the restricted abilities of SMA patients to sit and roll over and focuses on motor assessment in the prone position. It is a 16-item assessment of functional muscle strength and is scored on a 0–4 scale: no response (0), minimal (1), partial (2), nearly full (3) and complete (4) level of response; with a maximum score of 64 points. It was validated in a small population of children (n = 27) with SMA aged 3 to 260 months (mean age = 49 months).[14] The relationship between CHOP INTEND scores correlated with subject age ($r = -0.51$, $p = 0.007$) and BiPAP utilization ($r = -0.74$, $P < .0001$).[14]

Pediatric neurologists developed the Hammersmith Infant Neurological Exam (HINE) to assist in assessment of neurologic function of infants between 2 and 24 months of age.[15] It includes three sections which measure neurologic signs (section 1), motor function development (section 2), and behavior (section 3). Each section may be assigned a score based on descriptive ratings and tallied. The HINE-section 2 score can be used to evaluate 8 motor milestones in patients with SMA, including voluntary grasp, ability to kick in supine, head control, rolling, sitting, crawling, standing, or walking.[16] A score increase in each category indicates improved function with a minimum score of 0 (inability to perform task) up to a maximum score between 2 to 4 points (full milestone development, depending

upon task).[9] Referenced within the tool are descriptors of each milestone and the age expected to reach based on healthy infants. Although each milestone category varies in value and maximum score, the highest score achievable for HINE-section 2 is 26.

The Hammersmith Functional Motor Scale (HFMS) motor assessment includes upper and lower limb activities as well as head and trunk control.[17] Specific motor functions include rolling, sitting, lifting the head from prone to supine, propping on arms, 4-point kneeling, crawling and standing. Each item is scored on a 3-point scoring system: inability (0), assistance (1), and unaided (2). The total score ranges from 0 (all activities are failed) to 40 (all activities are achieved). Inter-rater reliability was tested on 35 children with an inter-observer agreement greater than 99%.[17] For ambulatory patients with SMA type 3, the HFMS was extended with 13 items to assess walking, running, and jumping which resulted in the HFMSE (HFMS Extended) score.[18] It is scored on a 3-point scale similar to the HFSME, but scores range from 0 to 66.

Spirometry measures Forced Vital Capacity (FVC) which is the volume of air forcibly exhaled from the point of maximal inspiration.[19] FVC has been used to track changes in lung function in SMA type 2 patients.[20] FVC and lung volumes tend to decrease over time in SMA patients and non-invasive ventilation (NIV) support is typically used when FVC is <80% predicted.[20,21] For patients with bulbar dysfunction or with high secretion burden, invasive/tracheostomy ventilation may be necessary due to risk of aspiration.[21] Use of a mask interface for <16 hours per day or nocturnal use is life-sustaining for a number of respiratory and neuromuscular diseases.[21] Patients dependent upon ventilators for life-support usually require a tracheotomy or mask interface for >16 hours per day to prevent life-threatening respiratory complications.[21]

In the past year, approximately 83 patients within the Oregon Health Plan had a SMA-related diagnosis, 22 in the Fee-for-Service (FFS) population and the remaining individuals were enrolled in a coordinated care organization (CCO). The Health Evidence Review Commission (HERC) has included SMA as a funded condition on lines 71, 292, 345, and 377.[22] In addition, SMA carrier screening for pregnant women is addressed in HERC Guideline Note D17.[22] Genetic screening for SMA (CPT 81239) is funded once in a lifetime.[22]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Risdiplam is a new orally administered small molecule SMN2 splicing modifier designed to promote the inclusion of exon 7 to produce full-length SMN2 mRNA, which results in an increased production of functional SMN protein from the SMN2 gene.[1,2] Risdiplam is indicated for the treatment of SMA in patients 2 months of age and older.[3] Dosing for risdiplam is weight-based and age-dependent given once daily after a meal (see **Appendix 1**). Risdiplam was evaluated by the FDA using data from two unpublished trials: one double blind, randomized, placebo-controlled trial in children and adults with Type 2 and 3 SMA (SUNFISH) and one open-label trial with historical controls in infants with Type 1 SMA (FIREFISH).[1,2] Both studies were unpublished as of September 2020. Details of the study were accessed from the summary report posted on the FDA website.[1,2] Due to its orphan drug status, risdiplam had a Fast Track designation by the FDA.[1,2] Prior to approval, FDA Guidance for Industry was released for the use of historical controls in clinical studies of rare diseases. In the document, the FDA stated that historical controls are appropriate when "(1) there is an unmet medical need; (2) there is a well-documented, highly predictable disease course that can be objectively measured and verified, such as high and temporally predictable mortality; and (3) there is an expected drug effect that is large, self-evident, and temporally closely associated with the intervention."[24] Efficacy was established based on improvements MFM total score compared to placebo, as well as

attainment of motor milestones and survival beyond what would be expected in the normal disease course.[1,2] The FDA noted that efficacy data for the more severe Type 1 SMA patients in the open-label FIREFISH study was originally designated as exploratory.

SUNFISH was multicenter study that consisted of 2 parts.[1,2] Part 1 was a 12-week exploratory dose-finding study in 51 patients with Type 2 and Type 3 (ambulant and non-ambulant) SMA patients.[1,2] Motor and respiratory function findings from the open-label patient assessments were used by an Independent Monitoring Committee to select the dose for part 2.[1,2] Patients from Part 1 were not included in Part 2.[1,2] Part 2 included 180 Type 2 and non-ambulant Type 3 SMA patients.[1,2] Patients were randomized 2:1 to receive a once-daily, weight-based risdiplam oral solution (n=120) or placebo (n=60) for 12 months.[1,2] The primary outcome was the change from baseline in the total MFM32 score at Month 12.[1,2] Relevant secondary endpoints included proportion patients with $\geq$ 3-point change from baseline MFM32 total score at Month 12 with the investigators citing that the medical literature suggests the mean annual decline in untreated patients would be < 1 point per year. Other secondary endpoints assessed at 12 months included change from baseline in mean RULM total score, HFMSE total score, FVC and SMAIS.[1,2] After the 12-month assessment, all placebo patients were switched to risdiplam until month 24.[1,2]

At the time of treatment, there were 71% Type 2 and 29% Type 3 SMA patients, the mean patient age was 9 years (range: 2-25), 51% were female, 67% were white/Caucasian and 19% were Asian.[1,2] Most (87%) of patients were reported to have 3 copies of SMN2, and 67% of patients had scoliosis at screening (10% higher in placebo group).[1,2,23] All patients except one were non-ambulatory.[1,2] Treatment compliance was roughly 98% for placebo and 100% for the risdiplam arm as recorded in a subject diary for all drug administration doses throughout the study at each site.[1,2] There was a statistically significant difference reported in MFM32 score with risdiplam-treated patients compared to placebo (LS mean difference: 1.55 (95% CI, 0.30 to 2.81; p-value = 0.016).[1,2] The clinical importance of a 1.55-point difference on a 100-point scale is unclear. For secondary outcomes, there was a statistically significant difference in proportion patients with $\geq$3-point change from baseline MFM32 score in the risdiplam group compared to placebo (38.3% vs 23.7%, respectively; ARR 14.6%/NNT 7).[1,2] Once again, the clinical significance of even a 3-pont change on a 100-point physical function scale is unclear. A modest but statistically significant difference was also observed in the mean RULM total score for risdiplam compared to placebo patients (mean difference +1.59 points [95% CI, 0.55 to 2.62]; p-value = 0.0469).[1,2] There was not a statistically significant difference between risdiplam and placebo of change from baseline in HFMSE score or FVC measurements.[1,2]

FIREFISH was an open label study in pediatric patients with infantile-onset Type-1 SMA.[1,2] The original protocol had divided the study into 2 parts, Part 1 (dose finding) and part 2 (motor milestone efficacy and safety at 12 and 24 months).[1,2] A total of 21 subjects were enrolled in Part 1 of the trial each with a confirmed diagnosis of 5q-autosomal recessive SMA with two SMN gene copies or SMA Type 1 symptoms.[2,3] Median patient ages were almost 5 months (range 1 to 7 months) at screening.[1,2] The primary outcome to be measured in part 2 was the proportion of infants able to sit without support for at least 5 seconds as measured by item 22 (gross motor skills) of the BSID-III after 12 months post treatment initiation.[1,2] Assessment was via video recording and centrally reviewed by two independent clinical evaluators.[1,2] The FDA statistical review noted that a statistically significant result would be achieved when a minimum of 6 out of 41 infants are sitting without support for 5 seconds after 12 months of treatment, based on an exact binomial test with a one-sided 5% significance level.[20] Secondary endpoint measures included a mixture of motor assessments (CHOP-INTEND scale), motor milestone achievements (BSID-III and HINE-2 scale), survival and ventilator-free survival, respiratory and feeding assessments, as well as hospitalizations (see Table 3).[1,2] Many of the secondary endpoints were considered exploratory since scales such as CHOP-INTEND and HINE have not been well characterized in the infantile-onset SMA population.[1,2] None of the SMA Type 1 patients were sitting without support at baseline.[1,2] Median baseline scores for the motor assessment tests were as follows: CHOP-INTEND = 24.0, BSID-III = 2.0, HINE-2 = 1.0.[1,2,20] Efficacy was compared to historical controls of motor milestones typically expected for the age group. After the sponsor presented what was considered promising information during Part 1, the FDA allowed the investigators to change protocol.[2] Therefore, Part 1 patients served as the primary intent to treat population for efficacy analysis.[2] Part 2 data were not submitted for FDA review.[2]

Based on only 21 patients observed, results from FIREFISH showed that, compared to historical controls, 33% (7/21) of the risdiplam-treated patients, and 41% (7/17) of patients given the higher dose, were able to sit without support for at least 5 seconds as assessed by Item 22 of the BSID-III gross motor scale after treatment with for 12 months.[1,2] For motor function and developmental milestone secondary endpoints assessed at 12 months via the CHOP-INTEND tool, 52% (11/21) of patients achieved a total score of 40 or higher, 86% (18/21) achieved an increase from baseline of 4 or more points, and 52% (11/21) of patients achieved head control (as defined by score $\geq$3 for item 12).[1,2] HINE-2 12-month assessments also were reported to increase as 43% (9/21) of patients maintained upright head control and 67% (14/21) were considered motor milestone responders.[1,2] There were 91% of patients alive without permanent ventilation at 12 months as well as 86% (18/21) with the ability to feed orally.[1,2] The proportion of patients with no hospitalizations at 12-months was 38% (8/21).[1,2] The FDA noted the potential for observer bias in the open-label study design and recognized that other sources of bias were possible due to the small sample size, lack of concurrent control group, study population differences, and changes in standards of care.[2] Even with the highly predictable clinical course of Type 1 SMA, it was unclear what prognostic variables may have been unidentified in the historical data. Although many of the secondary endpoints in FIREFISH were designed to be assessed at both 12 and 24 months, efficacy data was only submitted for 12 months, so efficacy beyond 12 months is unclear. In addition, FDA statistical reviewers noted that FIREFISH had a multiplicity issue because although Part A was initially designated as exploratory, the sponsor submitted uncontrolled open label data as confirmatory evidence once favorable outcomes were observed.[23] Nonetheless, in the final review, the FDA lead clinical reviewer concluded that the study was rigorously conducted and the study endpoints of sitting unsupported and ventilator-free survival were well-defined with a low potential for bias.[2]

Clinical Safety:

The safety profile for risdiplam is based on observational data in 242 patients from the Phase 2/3 RCT ("SUNFISH") and open label ("FIREFISH") studies in pediatric and adult patients with SMA.[1,2] Also included was supportive safety data obtained from 12 subjects in the open-label phase 2 JEWELFISH study in infantile- and later-onset SMA patients provided to the FDA.[1,2]

In the SUNFISH study, 117/120 patients in the risdiplam group and 59/60 patients in the placebo group completed the study.[1,2] Three patients in the risdiplam group and one patient in the placebo group switched to an alternative treatment (3 - nusinersen and 1 – unspecified). Significant adverse events which lead to dose interruption occurred in 3.3% of patients in both risdiplam and placebo arms.[1,2] Nine patients in the risdiplam group developed a serious pneumonia, with 2 reported as life threatening.[1,2] The most common adverse events in risdiplam-treated patients with an incidence at least 5% greater than placebo was pyrexia (22% risdiplam vs 17% placebo), diarrhea (17% vs 8%), rash (17% vs 2%), mouth ulcers (7% vs 0%), arthralgia (5% vs 0%), and urinary tract infection (5% vs 0%)(see **Table 2**).[1,2,3] There were no reported patient withdrawals due to adverse events.[1,2]

Treatment-emergent adverse events in the FIREFISH study (N=62) that occurred in at least 10% of the patients on risdiplam treatment included upper respiratory tract infection (32%), pyrexia (27%), pneumonia (21%), constipation (16%), diarrhea (13%), vomiting (13%), nasopharyngitis (10%).[1,2] The study recorded 44% of subjects with Grade 3-5 adverse events (Grade 3 = severe; Grade 4 = life threatening; Grade 5= death).[1,2] Most patients (95%) received concomitant medications for an adverse event after risdiplam administration.[1,2,23] Six deaths occurred in the FIREFISH study all due to SMA-related respiratory complications, but the FDA reviewer concluded these were unlikely a cause of risdiplam treatment.[1,2] FDA analysis of TEAEs in the JEWELFISH study were reported to be generally similar to FIREFISH.[1,2] Safety concerns from the non-clinical trials included retinal toxicity as well as epithelial tissue reactions (skin, larynx, eyelid, and gastrointestinal tract), but no such finding was evident in the clinical review.[1,2] FDA reviewers analyzed safety data by demographic subgroups and were unable to find differences in adverse event rates based on age, sex, or race.[1,2] Due to the relatively small number of patients included in the clinical trials and limited duration of exposure, the safety of risdiplam is largely unknown.

Table 2. Adverse Reactions Reported in ≥ 5% of Patients Treated with EVRYSDI and with an Incidence ≥ 5% Greater Than on Placebo in Study 2 Part 2[3]

Adverse Reaction	Risdiplam (N=120) %	Placebo (N=60) %
Fever (pyrexia and hyperpyrexia)	22	17
Diarrhea	17	8
Rash (erythema; maculo-papular, erythematous, or popular rash; dermatitis allergic, and folliculitis)	17	2
Mouth and aphthous ulcers	7	0
Arthralgia	5	0
Urinary tract infection (urinary tract infection and cystitis)	5	0

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Survival
2) Respiratory Support (need for ventilation)
3) Functional improvement (independently sit, stand, walk)
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Motor function improvement from baseline as assessed by the total MFM-32 score at 12 months
2) Proportion of patients with ability to sit unsupported ≥5 seconds at 12 months

Table 3. Pharmacology and Pharmacokinetic Properties.[1-3]

Parameter	
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.
Oral Bioavailability	81%; Tmax, oral: 1 to 4 hours
Distribution and Protein Binding	Vd: 6.3 L/kg; Protein binding, albumin: Predominant
Elimination	Renal excretion: 28%, 8% unchanged; Fecal excretion: 53%, 14% unchanged
Half-Life	50 hours
Metabolism	Substrate of flavin monooxygenase 1 and 3 (FMO1 and FMO3); Substrate of CYP1A1, CYP2J2, CYP3A4, and CYP3A7

Abbreviations: CYP=cytochrome-P; L=liters; kg=kilograms; Vd=volume of distribution

Table 4. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
BP39055[1,2,20] ("SUNFISH") Phase 2/3 DB RCT	1. Risdiplam 5 mg once daily for patients with a BW ≥ 20 kg and 0.25 mg/kg once daily for	Demographics (Part 2): -Mean Age: 10 years -Male/Female: 49%/51% -Race: -White 67% -Asian 19%	ITT: 1. 120 2. 60 Attrition:	Primary Endpoint: Change from baseline in total Motor Function Measure 32 (MFM32) score assessed at 12 months 1. +1.36 points 2. -0.19 points		TEAEs: 1. 93% 2. 92% SAEs 1. 20%	NA for all	Study completed but unpublished so risk of bias and applicability of study unclear.

	patients with a BW <20 kg (part 2 dosing) 2. Placebo Part 1: -Dose finding 12 week (N=51) Part 2: -Efficacy 12 months -Safety 24 months (N=180)	-Black/African American 1% -Multiple 1% -Unknown 12% -Type 2 SMA: 71% -Type 3 SMA: 29% -Patients with 3 copies of SMN2: 87% -scoliosis: 67% -risdiplam: 63% (28% severe) -placebo: 73% (38% severe) <u>Key Inclusion Criteria</u>: - 2 to 25 years of age at screening -Part 1 Type 2 ambulatory and non-ambulatory Type 3 SMA -Part 2 only non-ambulant patients <u>Key Exclusion Criteria</u>: -No current/prior study participation in past 90 days -Concomitant/ previous administration of a SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier -History of gene or cell therapy - Hospitalization for a pulmonary event -Invasive ventilation or tracheostomy -Surgery for scoliosis or hip fixation -Clinically significant abnormalities in laboratory tests -Any major illness within one month before screening	1. 3 (2.5%) 2. 1 (1.7%)	LS mean difference: 1.55 (95% CI, 0.30 to 2.81) p-value = 0.016 <u>Secondary Endpoints</u>: Proportion patients with change from baseline MFM32 total score of 3 or more at month 12 1. 38.3% 2. 23.7% OR 2.35 (95% CI, 1.01 to 5.44) p-value = 0.0469 Mean Revised Upper Limb Module (RULM) score change at Month 12 compared to baseline 1. 1.61 2. 0.02 Mean increase difference 1.59 points (95% CI, 0.55 to 2.62) p-value = 0.0469	NA ARR 14.6 NNT 7 NA	2. 18% <u>AE leading to dose modification or interruption:</u> 1. 7% 2. 3% <u>Most common AEs:</u> -pyrexia 1. 22% 2. 17% -diarrhea 1. 17% 2. 8% -rash 1. 17% 2. 2% -mouth ulcers 1. 7% 2. 0% -arthralgia 1. 5% 2. 0% -urinary tract infection 1. 5% 2. 0%).		
BP39056 [1,2,20] ("FIREFISH") Phase 2/3, multicenter, multinational, open-label, single arm, two-part study	Risdiplam dose: 1. Variable dosing between 0.0106, 0.04, 0.08, 0.2, and 0.25 mg/kg once daily (Cohort 1) 2. 0.2 mg/kg once daily (Cohort 2):	<u>Demographics</u>: -Female: 71% -Caucasian: 81% -Asian: 19% (Median ages and baseline scores reported) -Sx onset: 2 mo. (range 0.9 to 3.0) -screening: 4.9 mo. (range 1.5 to 6.7) -12-month analysis: 16.9 months (range 13.5-18.7 months)	<u>ITT</u>: 1. 4 2. 17 <u>Attrition</u>: 1. 0 2. 0	<u>Primary Endpoint</u>: Proportion of patients sitting without support for > 5 sec (as assessed in Item 22 of the Bayley Scales of Infant and Toddler Development – Third Edition (BSID-III) gross motor scale) at 12 months: 1. (cohort 1): 0 2. (cohort 2): 7 Overall: 7/21 (33%) <u>Secondary Endpoint</u>:	NA for all	<u>Most common AEs - part 1 and 2 data:</u> (N=62) -upper respiratory tract infection (32%) -pyrexia (27%) -pneumonia (21%) -constipation (16%) -diarrhea (13%) -vomiting (13%)	NA for all	Study completed but unpublished so risk of bias and applicability of study unclear.

	Part 1: open-label dose escalation (exploratory) N=21 Part 2: active treatment N=41 (efficacy results for Part 2 not reported)	-No pulmonary care at baseline: 76% -non-invasive BiPAP <16 hrs daily: 14% Baseline scores: -CHOP-INTEND: 24.0 -BSID-III: 2.0 -HINE-2: 1.0 -Able to sit without support: none Country of origin: Italy: 52% France:4% United States: 14% <u>Key Inclusion Criteria</u>: - Age 1-7 months at enrollment -Confirmed diagnosis of 5q-autosomal recessive SMA -two SMN2 gene copies <u>Key Exclusion Criteria</u>: -Same as SUNFISH (sans surgery, abnormal labs) -PLUS- - Non-invasive ventilation or with awake hypoxemia (SaO2 <95%) with or without ventilator support -History of respiratory failure/ severe pneumonia not fully recovered -Recent history (less than <u>6 months</u>) of ophthalmic diseases -Recent therapy of CYP3A4 inhibitor or inducer, OCT-2 or MATE substrate - Presence of non-SMA-related concurrent syndromes or diseases		*Motor Function and Development Milestones* CHOP-INTEND: -score increase of 40 or higher: 1. 1 2. 10 Overall: 11/21 (52%) -increase of 4 or more points from baseline: 1. 3 2. 15 Overall: 18/21 (86%) -achieve head control per score 3 or more on item 12: 1. 2 2. 9 Overall: 11/21 (52%) HINE-2: -head control maintained upright: 1. 0 2. 9 Overall: 9/21 (43%) -motor milestone responders: 1. 1 2. 13 Overall: 14/21 (67%) *Survival and Ventilation-free survival* -Patients alive with or w/o permanent ventilation at month 12: 1. 3 2. 16 Overall: 19/21 (91%) *Respiratory* -Patients not requiring respiratory support at month 12: 1. 1 2. 3 Overall: 4/21 (19%) *Feeding Assessments* -Patients able to feed orally at month 12: 1. 3 2. 15 Overall: 18/21 (86%)		-nasopharyngitis (10%) <u>Deaths:</u> 6 Part 1: 3 Part 2: 3		

				Hospitalizations -Patients with no hospitalizations at month 12: 1. 0 2. 8 Overall: 8/21 (38%)				

Abbreviations [alphabetical order]: ARR = absolute risk reduction; BW = body weight; CGIC = Clinical Global Impression of Change; CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI = confidence interval; FVC = forced vital capacity; HINE-2 = Hammersmith Infant Neurological Exam 2; HFMS = Hammersmith Functional Motor Scale; ITT = intention to treat; mo = months; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; PP = per protocol; RCT = randomized controlled trial; SMA = spinal muscular atrophy; SMN = survival motor neuron; Sx = symptom; Tx = treatment; ULM = Upper Limb Module

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Appendix 1: Prescribing Information Highlights

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
Initial U.S. Approval: 2020

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

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

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

EVRYSDI must be constituted by a pharmacist prior to dispensing.

Administer orally once daily after a meal using the provided oral syringe. (2.1, 2.4)

Age and Body Weight	Recommended Daily Dosage
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

See Full Prescribing Information for important preparation and administration instructions. (2.1, 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)

---------- **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, pneumonia, constipation, and vomiting. (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)

Hepatic Impairment: Avoid use in patients with hepatic impairment. (8.6)

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

Revised: 8/2020

Risdiplam

Goal(s):
Approve risdiplam for funded OHP conditions supported by evidence of benefit (e.g. Spinal Muscular Atrophy)

Length of Authorization:
6 months

Requires PA:
- Risdiplam

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1:

Age and Body Weight	Recommended Daily Dosage
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

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this a request for continuation of therapy approved by the FFS program?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #3

Approval Criteria		
3. Are the patient's age and the prescribed dose within the limits defined in Table 1?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness. Recommended FDA-approved dosage is determined by age and body weight.
4. Does the patient have a diagnosis of spinal muscular atrophy (SMA), confirmed by SMN1 (chromosome 5q) gene mutation or deletion AND at least 2 copies of the SMN2 gene as documented by genetic testing?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; not funded by the OHP.
5. Is the patient experiencing symptoms of SMA?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness**.**
6. Does the patient have advanced SMA disease (ventilator dependence >16 hours/day or tracheostomy)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #7
7. Has the patient had previous administration of onasemnogene either in a clinical study or as part of medical care?	**Yes:** Pass to RPh. Deny; medical appropriateness**.**	**No:** Go to #8
8. Is the patient on concomitant therapy with a SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier or gene therapy?	**Yes:** Pass to RPh. Deny; medical appropriateness**.**	**No:** Go to #9
9. Is the drug being prescribed by a pediatric neurologist or a provider with experience treating spinal muscular atrophy?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness**.**

Approval Criteria		
10. Is a baseline motor assessment available such as one of the following assessments? • Hammersmith Infant Neurological Examination (HINE-2) • The Motor Function Measure 32 (MFM32) • Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) • Upper Limb Module (ULM) or Revised Upper Limb Module (RULM) • Current status on motor milestones: ability to sit or ambulate	**Yes:** Document baseline results. Go to #11	**No:** Pass to RPh. Deny; medical appropriateness**.**
11. For able patients, is there baseline documentation of pulmonary function measured by spirometry (FEV1, FVC, etc) or other validated pulmonary function test?	**Yes:** Document baseline results. Approve for 6 months. If approved, a referral will be made to case management by the Oregon Health Authority.	**No:** Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Is there evidence of adherence and tolerance to therapy through pharmacy claims/refill history and provider assessment?	**Yes:** Go to #2	**No:** Pass to RPh; Deny medical appropriateness

Renewal Criteria		
2. Has the patient shown a positive treatment response in one of the following areas? • Within one month of renewal request, documented improvement from the baseline motor function assessment score with more areas of motor function improved than worsened -OR- • Documentation of clinically meaningful stabilization, delayed progression, or decreased decline in SMA-associated signs and symptoms compared to the predicted natural history trajectory of disease -OR- • Documentation of an improvement or lack of decline in pulmonary function compared to baseline	**Yes:** Approve for additional 6 months.	**No:** Pass to RPh. Deny; medical appropriateness.

P&T/DUR Review: 12/20 (DE)
Implementation: 1/1/2021