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NOVEMBER 2020

RISDIPLAM (EVRYSDI)
FOR
SPINAL MUSCULAR ATROPHY

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Drug Regimen Review Center

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Introduction

Spinal muscular atrophy (SMA) is a rare genetic disorder of survival motor neuron protein (SMNp) deficiency. Deficiency of SMNp leads to neurodegeneration, progressive muscle atrophy, and severely compromised motor function.1,2 Most SMA patients have onset of neuromuscular deficits within 18 months of birth (this includes Type 1 and Type 2 SMA), and of these, at least half—those with Type 1 SMA—usually need permanent ventilatory support or pass away by 2 years of age, if disease modifying treatment is not used.3,4 The natural course of disease in these cases entails that the child will not be able to stand or walk, and those on the more severe end (Type 1 SMA) are unable to ever sit upright independently.5 As muscle strength quickly diminishes, patients suffer from respiratory insufficiency and eventually require gastrostomy tube feeding, ventilation, and orthopedic management.5 Regarding the fewer, less severe cases with onset later in life, key motor abilities such as walking may be gradually lost after attainment, and patients face losing independence in activities of daily living as the disease progresses. Although supportive care can delay the time to death,4,6 it does not target the underlying genetic pathogenesis of SMA nor does it slow the degeneration of motor neurons.

Within the last 4 years, 3 disease-modifying therapies for SMA have been approved: first, Spinraza (nusinersen), approved in 2016, followed by Zolgensma (onasemnogene abeparvovec-xioi) in 2019, and recently, Evrysdi (risdiplam) in August 2020. Risdiplam (Evrysdi) is the first orally administered agent approved for SMA and is the second approved survival motor neuron 2 (SMN2) splicing modifier—the first being the intrathecal injection, nusinersen (Spinraza).7 Onasemnogene (Zolgensma) is a gene therapy, administered as a single life-time, intravenous dose.8

Similar to other medications approved for this rare disorder, risdiplam is a designated orphan drug.9 The sponsor was granted a priority review in November 2019. The clinical development program for risdiplam assesses the safety and efficacy in symptomatic infants, children/adolescents, and adults with Type 1, 2, or 3 SMA in phase 3 studies.10 A phase 2, open-label, single-arm study on safety, tolerability, and pharmacokinetics/dynamics will include patients 6 months to 60 years of age who have previously received treatment with other licensed or experimental drugs for SMA (ie, treatment-experienced patients).10,11 There is also a recruiting, phase 2 study to explore presymptomatic treatment in patients who are identified via SMA genetic newborn screening.12 The approved indication for risdiplam is “…for the treatment of spinal muscular atrophy (SMA) in patients 2 months of age and older,”13 without specification of disease onset age, SMN2 genotype (ie, copy number), or SMA phenotype. FDA approval for risdiplam followed shortly after the sponsor submitted interim data from the phase 3 part of the SUNFISH clinical trial, conducted in patients with Type 2 and 3 SMA.10

This report, prepared prior to the completion and full publication of the phase 3 trials for risdiplam, will present study information available via conference-meeting abstracts and product labeling. Background information will also be provided for other approved SMA treatments. Utah Medicaid prior authorization criteria are currently in place for both Spinraza (nusinersen) and the gene therapy Zolgensma (onasemnogene abeparvovec-xioi). Discussion points will be provided to facilitate the development of prior authorization criteria for risdiplam (see page 21).

Regarding risdiplam utilization in the Medicaid fee-for-service population, there were no pharmacy or medical claims between August to October 2020.
Methods

Background information regarding SMA, and guidance or position statements by key organizations regarding the pharmacological treatment of SMA were sought at the following websites:

I. For treatment guidance we searched websites of the American Academy of Neurology. Additionally, we were already aware of the 2018 practice guidelines published by the International Standard of Care Committee for SMA.

II. For professional prescribing information for SMA medications, we searched drug sponsor websites for up-to-date package inserts and the FDA website (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm).

III. Protocol-related information regarding primary clinical studies was searched in ClinicalTrials.gov.

IV. For background information on the previously approved antisense oligonucleotide, nusinersen, and general orphan-drug information, the previous DUR report was referred to: Updated Overview Of Drugs With Approved Orphan Indications; With Focus on Spinraza, March 2018. Additional background information about orphan-drug approvals from this previous report is included in Appendix A.

Literature searches for reviews and clinical trial information regarding risdiplam were performed in OvidMedline and Embase, searching risdiplam OR RG7916 OR RO7034067 as key words (see Appendix B for search strategies).

Disease Overview

Spinal muscular atrophy results from mutations (deletions or point mutations) in the survival motor neuron 1 (SMN1) gene impairing the production of fully functional survival motor neuron protein (SMNp). The majority of cases are due to autosomal recessive inheritance; however, there have been a few case reports of carriers (with 1 functional copy of the SMN1 gene) becoming symptomatic later in life. Deficiency of SMNp results in loss of alpha-motor neurons in the brainstem and spinal cord; muscle weakness of the limbs, trunk, and respiratory muscles; and profound physical disability. The incidence of SMA is estimated between 1 in 6000 to 11,000 live births and “…is the most common genetic cause of infant death.” This amounts to approximately 400 new SMA cases born per year in the US.

Respiratory complications are the major cause of morbidity and mortality in SMA, which involves impaired clearance of lower airway secretions, hypoventilation, and recurrent infections. Other physiological disturbances include feeding and swallowing difficulties, gastrointestinal dysfunction, cardiac remodeling, autonomic dysfunction, irregular bone remodeling, and immune dysfunction. Pain is a common complaint that may result from constipation, gastrointestinal reflux, fractures, pressure sores, scoliosis/hip subluxation, muscle cramping/spams, or post-surgical intervention. Nutritional, respiratory, and orthopedic therapy and/or surgery are commonly required, especially for infant- and child-onset SMA. Patient and caregiver quality-of-life is greatly affected as physical independence is lost with disease progression.
The age of SMA symptom onset is a predictor of the person’s maximal motor function, with earlier onset distinctive of a more severe disease phenotype.\textsuperscript{1,18} Without therapy to slow disease progression, patients with onset in the first 6 months of life (ie, early-onset SMA) are described as non-sitters, are unable to sit independently, and most do not live past childhood with supportive care alone;\textsuperscript{4} these patients are classified as having Type 1 SMA which accounts for 36% to 60% of SMA cases.\textsuperscript{1,26-28} Patients with slightly delayed onset, occurring between 7 to 18 months, are relatively more mild cases compared to early-onset SMA patients, and are able to achieve unsupported sitting (classified as Type 2 SMA). Nonetheless, as the disease progresses, patients may eventually lose this ability, commonly develop kyphoscoliosis, and are never able to walk independently with the natural course of disease.\textsuperscript{26} Type 2 SMA constitutes around 34% of SMA cases.\textsuperscript{27,29} Though patients with delayed infant-onset SMA can survive into adulthood, aggressive supportive care in adolescent and adulthood is required to address multi-organ complications that develop.\textsuperscript{26}

Few SMA cases have disease onset later in life (eg, during late childhood, adolescent, or adulthood). These individuals are able to walk and generally achieve independence in activities of daily living, but as the disease sets in, motor strength and function gradually decline.\textsuperscript{26} Patients can lose the ability to ambulate independently; lose ability to engage in school, physical activities, or employment; and can lose independence in performing activities of daily living.\textsuperscript{22} Once disease progression begins to impact motor ability, the patient/prescriber may wish to initiate treatment with a disease modifying agent to prevent loss of motor abilities and maintain independence and strength in performing daily activities (eg, self-care, school or work engagement).\textsuperscript{22}

SMA is classified according to the age of onset, disease severity, and, particularly, the motor milestone achievable with the natural course of disease.\textsuperscript{5,16} Table 1 displays the SMA Type classifications. There is variability within Types so additional subtypes have also been proposed, representing a phenotypic continuum of SMA.\textsuperscript{3,18,21}

Humans have 2 genes encoding SMNp, the SMN1 gene and survival motor neuron 2 (SMN2) gene.\textsuperscript{30} In healthy individuals, SMN1 produces the majority of functional SMNp, while SMN2 produces low levels (5-10% of the total normal amount).\textsuperscript{30} Although SMNp production via SMN2 transcription is insufficient to completely compensate for mutated SMN1 in SMA disease, its contribution helps nonetheless. Thus, the severity of SMA is inversely associated with the number of SMN2 copies a person has— the SMN2 copy number varies from person to person.\textsuperscript{18,31} In other words, if patient with SMA has more SMN2 copies, they generally produce more viable SMNp compared to if they had less SMN2 copies. However, there is not tight correlation between the number of SMN2 copies and phenotype, especially in the case of patients with 2 or 3 SMN2 copies;\textsuperscript{3,20} thus, symptom onset and motor milestone achieved are the focus for disease classification (SMA Type) rather than the SMN2 genotype.

In a published cohort study, De Sanctis et al described, “As already reported in previous papers..., two SMN2 copies were not always predictive of a specific phenotype as they were found across [the] spectrum of severity, from severe to moderate and even in one infant with mild phenotype.\textsuperscript{9} Type 1 patients most often have 2 copies (73% with 2 copies; and 7%, 20%, <1%, and <1% were documented with 1, 3, 4, and 5 copies, respectively).\textsuperscript{27,32} About 78% of Type 2 patients have 3 SMN2 copies (<1%, 16%, 5%, and <1% had 1, 2, 4, and 5 copies, respectively). Similar proportions of Type 3 patients have 3
or 4 copies, 51% and 43% respectively (5%, 1%, and <1% had 2, 5, and 6 copies). Less than 2% of SMA cases are with Type 4 diagnosis, usually with 4 copies (81%) or more.  

### Table 1. Classification of Spinal Muscular Atrophy<sup>5, 16-18, 20, 26, 33</sup>

<table>
<thead>
<tr>
<th>Type</th>
<th>Onset</th>
<th>Maximal Motor Milestone&lt;sup&gt;18&lt;/sup&gt;</th>
<th>Prognosis</th>
<th>Select Presentation Features&lt;sup&gt;1, 33-37&lt;/sup&gt;</th>
<th>Other information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 0</td>
<td>Prenatal</td>
<td>None</td>
<td>Death before or shortly after birth</td>
<td>• Severe hypotonia</td>
<td>Patients experience rapid motor function decline&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>None</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>Before 6 months of age</td>
<td>None</td>
<td>Death most likely before age&lt;sup&gt;2&lt;/sup&gt; 17</td>
<td>• Severe muscle weakness/atrophy (ie, 'floppy infant') • Bell shaped chest • Bulbar dysfunction • Has difficulty swallowing, coughing, and breathing • Usually requires ventilator support • Underweight</td>
<td>... median age to death or ventilation (&gt;16 hours per day) is 13.5 months and 10.5 months for patients with 2 copies of SMN2&lt;sup&gt;18&lt;/sup&gt; Patient requires nutritional support, orthotics, bracing, positional supports, and physical therapy to improve function and tolerance to immobility Also known as Werdnig-Hoffmann disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Usually cannot roll, sit, or stand independently&lt;sup&gt;38&lt;/sup&gt;</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Referred to as non-sitters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2</td>
<td>7 to 18 months</td>
<td>Sitting; cannot stand independently</td>
<td>-93% survive to 25 years old&lt;sup&gt;1&lt;/sup&gt; 18</td>
<td>• Weak swallowing/cough • May develop scoliosis • Joint contractures • Frequent pneumonias • Nocturnal hypoventilation • Oxygen desaturations</td>
<td>Patient requires nutritional support, orthotics/bracing/positional supports, and exercise program/physical therapy to promote mobility and stretching. Wheelchairs promote engagement in school, social/work occupation Also known as Dubowitz’s disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Referred to as sitters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 3</td>
<td>Childhood or adolescent years</td>
<td>Walking</td>
<td>Normal expected lifespan</td>
<td>• Obstructive apnea • Proximal muscle strength becomes weaker as patient ages • May experience frequent falls and fatigue • +/- bulbar dysfunction • At risk for scoliosis, lordosis, and joint contractures</td>
<td>May lose ability to walk&lt;sup&gt;17&lt;/sup&gt; Patient can benefit from exercise program/physical therapy and orthotics to promote flexibility and maintain or restore function. Wheelchairs may also be needed for mobility over longer distances Also known as Kugelberg–Welander disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Referred to as walkers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 4</td>
<td>Adulthood</td>
<td>Normal</td>
<td>Normal expected lifespan</td>
<td>• Mild motor impairment • Fatigue • Weakness in legs</td>
<td>Likely to have a delay in diagnosis as presentation is confused with other diseases (this may also happen in other SMA types especially Type 3)</td>
</tr>
</tbody>
</table>

* Percentages were calculated based on reported numbers from Calucho et al data in Table 2 about SMN2 copy number which included Type 4 patients into the Type 3 group for simplicity as described by authors on page 210<sup>27</sup> thus, proportions were re-calculated to get the actual values for Type 3 and Type 4 for the purposes of this report.
Diagnosis

Genetic testing is the standard diagnostic test for SMA, which is supported in the 2007 and 2018 Consensus Statements for Standard of Care in Spinal Muscular Atrophy. Since the majority of patients (96%) have homozygous deletions or interruptions in the SMN1 gene on chromosome 5, the authors describe that the SMN gene deletion test should be the first diagnostic test ordered when SMA is suspected. This test has a 95% sensitivity and close to 100% specificity. The consensus statement states, “A homozygous deletion of SMN1 exon 7 (with or without deletion of exon 8) confirms the diagnosis of SMN-associated spinal muscular atrophy (5q spinal muscular atrophy).” There are also other situations that may lead to SMN1-related SMA such as when a patient has one SMN1 copy but which has subtle mutations, “…rendering homozygous dysfunction of the gene.” Mutations on other genes besides the SMN1 gene can also cause SMA but are not as common (ie, non-5q-SMA).

In Utah, as of 2018, the newborn screening (NBS) panel includes genetic testing for 5q SMA along with at least 40 other disorders, as part of the public health program implemented by the Utah Statute 26-10-6 and Rule R438-15. A positive newborn screening result for SMA has implications for decisions regarding the initiation of disease-modifying therapy for presymptomatic patients versus monitoring for onset; this topic will be discussed further on page 16.

General Disease-Modifying Treatment Information

There are several mechanisms by which pharmaceuticals are designed to increase viable SMNp, by either providing a fully functional SMN1 gene or by increasing production of SMNp via correction or augmentation of SMN2 expression:

- SMN2 splicing modifiers (eg, nusinersen and risdiplam) alter SMN2 transcription so that exon 7 is retained as mRNA (messenger ribonucleic acid) is being transcribed from the SMN2 gene. This leads to production of more stable SMNp. If exon 7 is otherwise excluded, translation of mRNA yields a truncated, less-stable SMN protein. An increase in viable SMNp supports motor neuron function and helps make up for lost SMNp production from mutated SMN1.
- Some experimental drugs augment transcription of SMN2, as is, which can yield higher levels of viable SMNp as well.
- Exogenous supplementation of fully functional SMN1 gene copies (eg, onasemnogene) that can be used by the body’s transcription/translation machinery can increase SMNp levels.
- Other medications in the development pipeline utilize non-SMNp targets that have muscle- or neuro-protective properties.

There is limited guidance regarding when to initiate the SMA-approved therapies for various subsets of SMA patients based on SMA type, disease onset, or according SMN2 copy number. The 2018 Statement for Standard of Care in Spinal Muscular Atrophy by an international committee of SMA experts do not address these aspects regarding criteria for initiation or continuation of SMA approved therapies; however, a treatment algorithm for the presymptomatic SMA subgroup was published in 2018 by another expert panel with overlap of some experts also on the international committee. This guidance document and update will be described further starting on page 16. In the statement by the international committee, authors describe the complexity in clinical decision-making while seeking to
balance the burden-of-care with treatment benefits (or potentially little benefits from treatments), side-effects, and resource limitations.\(^2\) Despite the use of advanced therapies, advancing disease may shift consideration toward favoring palliative care over life-extending treatments.\(^2\) Although treatment can extend life or reduce the need for permanent ventilation in Type 1 disease, there may still be considerable suffering and low quality of life for patients/families; furthermore, ongoing medication may be perceived as not doing enough to reverse the disease, providing minor improvements while prolonging suffering.\(^45\) Specialists note, “The challenge of managing expectations in this fluid context, especially where expectations are shaded by many conflicting opinions, adds further complexity to the task of establishing a standard of care.”\(^2\)

**Risdiplam Place in Therapy**

Risdiplam, like nusinersen, is an antisense oligonucleotide (ASO); both are SMN2-splicing modifiers able to enhance viable SMNp production.\(^46-48\) Nusinersen is a large-molecule ASO that must be administered intrathecally; whereas, risdiplam is a small molecule that is administered orally and distributes to both the periphery and central nervous system (CNS).\(^46-48\) Risdiplam oral solution is administered once daily after a meal and is dosed according to weight:

- 2 months to less than 2 years of age: daily dose of 0.2 mg/kg
- 2 years of age and older weighing < 20 kg: daily dose of 0.25 mg/kg
- 2 years of age and older weighing ≥ 20 kg: daily dose of 5 mg

Contrast this with nusinersen which is provided as 6 intrathecal injections (12 mg per dose) over the first year of initiation, then 3 quarterly intrathecal injections yearly thereafter (12 mg per dose).\(^7\) Risdiplam steady-state concentration is reached between 7 to 14 days with once-daily dosing, and exhibits an elimination half-life of about 50 hours.\(^13\)

Also approved for SMA is Zolgensma, a gene therapy of packaged complimentary DNA (cDNA) of healthy SMN1 gene copies using a non-pathogenic viral vector (adeno-associated virus serotype 9 [AAV9]) for delivery across the blood-brain barrier into the cerebral spinal fluid.\(^49\) The medication is delivered as a single-lifetime dose, administered by intravenous infusion, with pre-and post-treatment corticosteroids (CCS) therapy.\(^8\) Patients must be full-term gestational age before receiving Zolgensma with CCS to avoid potentially negative CCS effects on neurologic development.\(^8,50\)

**Indications for Disease-Modifying Agents**

Both nusinersen and risdiplam are indicated for the treatment of SMA, without specification of disease phenotype or SMN2 genotype. However, an age specification is provided in the indication of risdiplam requiring patients to be 2 months or older.

- The indication for Evrysdi (risdiplam) is worded broadly, approved for the treatment of SMA in patients 2 months of age and older, regardless of SMA type classification (ie, phenotype or age of onset).\(^13\) Ongoing phase 3 studies for risdiplam include symptomatic Type 1, 2, and 3 SMA populations. Further information regarding the clinical trials for risdiplam will be outlined in the next section, *Risdiplam Pivotal Clinical Studies*. 
The indication for Spinraza (nusinersen) is also worded broadly, approved for the treatment of SMA in pediatric and adult patients, regardless of SMA type classification (ie, phenotype or age of onset). In the FDA review for nusinersen, reviewers described that the medication was expected to be effective across the disease spectrum, regardless of disease severity. At that time, there was nusinersen-treatment data in patients with Type 1 SMA, while trials for patients with Type 2 or 3 SMA were ongoing.

Zolgensma is indicated for a narrow age group, approved for pediatric patients less than 2 years of age with bi-allelic mutations of the SMN1 gene. The prescribing information also specifies that the safety and effectiveness of repeat dosing with Zolgensma are not established, nor is use established in patients with advanced disease (eg, complete paralysis of limbs, permanent ventilator dependence).

The FDA-approved indications for these therapies do not specify a requirement regarding symptom presentation; thus, their use can extend to pre-symptomatic treatment which is being further investigated in ongoing studies. With SMA genetic newborn screening now a standard in several states including Utah, an infant with an SMA genotype can be detected early and potentially treated with disease-modifying therapies prior to degeneration of motor neurons or onset of clinical symptoms. Additionally, the indications do not have verbiage to limit use beyond a specific SMN2 copy number—though prescribing information for Zolgensma only discusses efficacy from clinical trials in early-onset SMA patients with 2 copies of the SMN2 gene.

Scenarios That May Preclude Use of Other SMA Therapies

This section reviews scenarios that may preclude the use of nusinersen or onasemnogene, in which case, risdiplam may serve as an option. A later section will address safety concerns with risdiplam.

Serious adverse-event risks with nusinersen include rare but potentially life-threatening thrombocytopenia and renal toxicity observed in clinical trials. Lumbar puncture required for nusinersen administration is generally safe, however, “...side effects such as headache, back pain, and transient or persistent cerebrospinal fluid leakage (post–lumbar puncture syndrome), have been documented.” The procedure may be technically challenging (or may be too risky) if a patient has severe scoliosis. Post-marketing, adverse-event case reports include serious infections, such as meningitis. Other reactions included aseptic meningitis, hydrocephalus, and hypersensitivity. The FDA’s risk assessment notes that prescribers of nusinersen are expected to be pediatric neurologists or other members of the multidisciplinary clinical team. Administration is expected to be carried out by neurologists, radiologists, or pediatric anesthesiologists in a variety of hospital settings such as interventional radiology departments, affiliated outpatient clinics, or the operating room.

Nusinersen is a large molecule drug that has the potential to elicit the development of anti-drug antibodies (ADAs). Although it is not yet clear how these affect treatment response, it is possible that some ADAs are neutralizing antibodies rendering treatment less effective. The prescribing information describes that 4% of patients assessed for antibodies had persistent ADAs. This could be a reason a prescriber wishes to switch to a different medication if response has dwindled, and if ADAs are identified or suspected.
In order to receive onasemnogene, patients must have baseline testing for the presence of anti-AAV9 antibodies. In clinical trials patients were required to have baseline anti-AAV9 antibody titer of ≤ 1:50. Safety and efficacy with a titer above 1:50 have not been evaluated. Patients are more likely to develop anti-AAV9 antibodies as they age, which influences the decision regarding earlier timing of treatment. Nidetz et al describe that “clinical trials have demonstrated that host anti-viral immune responses can prevent the long-term gene expression of AAV vector-encoded genes.”

Tables 2 and 3 of Appendix E provide summary information of the warnings and precautions for nusinersen and onasemnogene.

Risdiplam Pivotal Clinical Studies

There are 2 ongoing phase 2/3 studies assessing the efficacy of risdiplam in patients with SMA, SUNFISH and FIREFISH, each with two parts (exploratory dose finding part and a confirmatory part). JEWELFISH is an active safety/tolerability, phase 2 study in treatment-experienced adults and pediatric patients with SMA. The SUNFISH and FIREFISH studies included patients who have demonstrated SMA physical signs/symptoms upon study entry. There is a recruiting phase 2 study that will investigate the effects of risdiplam in 25 presymptomatic SMA patients who are up to 6 weeks of age, identified via genetic screening, and regardless of SMN2 copy number (RAINBOWFISH). Prior to commercial availability in the US, an expanded access program (EAP) was available so that patients with Type 1 or Type 2 SMA could receive risdiplam treatment if they have been unable to receive other approved agents for SMA or if they have not responded or lost response while on the approved therapies. The FDA decision date regarding approval of risidiplam was extended from May to August 2020 following the drug sponsor’s submission of additional data from Part 2 of the SUNFISH trial. Table 2 contains brief information of the phase 2/3 clinical trials for risdiplam.

<table>
<thead>
<tr>
<th>Table 2. Risdiplam Key Clinical Trials by SMA Type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Presymptomatic SMA</strong></td>
</tr>
<tr>
<td>• Participants from birth to 6 weeks old at the time of first dose of risdiplam</td>
</tr>
<tr>
<td>• With genetic diagnosis of 5q-autosomal recessive SMA (homozygous deletion or compound heterozygosity predictive of loss of function of the SMN1 gene); unspecified SMN2 copy number</td>
</tr>
<tr>
<td><strong>Type 1 SMA (infantile-onset SMA)</strong></td>
</tr>
<tr>
<td>• 5q-autosomal recessive SMA</td>
</tr>
<tr>
<td>• With 2 copies of SMN2</td>
</tr>
<tr>
<td>• Patients 1 to 7 months of age entering the study with symptom onset between 28 days to 3 months of age</td>
</tr>
</tbody>
</table>
SUNFISH is a 2-part study with a phase 2 dose-finding study followed by a phase 3, randomized, placebo-controlled study to confirm efficacy/safety in children and adults with Type 2 or 3 SMA. For study eligibility, patients must have genetic diagnosis of 5q-autosomal recessive SMA and be 2 to 25 years of age at the time of study entry. Part 1, with 51 patients, assessed safety, tolerability, and pharmacokinetics/dynamics over 12 weeks while determining an effective dose. After 12 weeks of risdiplam treatment in Part 1, patients could enter an open-label follow-up study. In a different patient set of non-ambulant, Type 2 or 3 SMA patients, Part 2 (a phase 3 study) randomized patients to risdiplam or to placebo for 12 months (N=180). Placebo patients will cross-over to risdiplam treatment for an additional 12 months. The patients originally randomized to risdiplam will continue treatment out to a total of 24 months.

Of the 180 non-ambulatory patients enrolled in Part 2, 71% were with Type 2 SMA and 29% were with Type 3 SMA. The median time between symptom onset and risdiplam treatment was 103 months. After 1 year of risdiplam treatment, there was a significant change from baseline in the Motor Function Measure 32 (MFM-32) scale compared to placebo (primary endpoint); the treatment difference vs. placebo was considered clinically meaningful (1.55% difference in the MFM32 total score at month 12 [95% confidence interval of 0.30-2.81]). Moreover, there were no major safety signals identified by researchers.

FIREFISH is a 2-part, open-label, non-controlled study in patients with early-onset Type 1 SMA. Infants 1 to 7 months of age were eligible if they had SMA onset occurring between day 28 to 3 months of age. Additionally, patients had genetic diagnosis of 5q-autosomal recessive SMA with 2 copies of SMN2. Part 1 is a dose-finding study with 21 patients while also assessing safety, tolerability, and pharmacokinetics/dynamics. Part 2, with 41 patients, will assesses the safety and efficacy of risdiplam at dosing derived from Part 1 for a duration of 24 months. The pre-specified primary efficacy outcome for Part 2 is the percentage of Infants who are sitting without support for at least 5 seconds at 12-months, assessed by the Gross Motor Scale of the Bayley Scales of Infant and Toddler development Third Edition (BSID-III). Secondary endpoints will include measures of time to death, time to permanent ventilation, quantification of SMN2 mRNA and SMNp, change from baseline in endpoints involving BSID-III, HINE-2, or CHOP-INTEND (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders) scores/domains at various time points. The proportion of patients requiring respiratory support, and proportions able to orally feed, crawl, sit alone, stand alone, and walk alone will also be reported.

### Table 2. Risdiplam Key Clinical Trials by SMA Type

<table>
<thead>
<tr>
<th>Type 2 or 3 SMA (later-onset SMA)</th>
<th>SUNFISH Phase 2/3 (Active study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 5q-autosomal recessive SMA</td>
<td>• Double-blind placebo controlled study; the phase 3 part had randomized allocation with double-blinding</td>
</tr>
<tr>
<td>• Patients 2 to 25 years of age at study entry</td>
<td>• Motor function change from baseline at month 12 as primary endpoint</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment-experienced SMA</th>
<th>JEWELFISH Phase 2 (Active study)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Participants 6 months to 60 years of age previously treated with SMA-targeting therapies</td>
<td>• Open-label, non-controlled study</td>
</tr>
</tbody>
</table>
An interim analysis of Part 1 data showed that 93% of treated infants had ≥4-point improvement in Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) total score from baseline to month 8 (median change, 16 points). Event-free survival rates were also noted as improved in treated infants compared to age-matched SMA infants in natural history studies (2020 meeting abstract). Results reported in the risdiplam package insert for Part 1 of FIREFISH are described below. Part 2 data is not yet available.

- Included patients were with two SMN2 copies and with either SMN1 homozygous deletion or heterozygotes with predictive of loss of SMN1 function. The median treatment duration with risdiplam in Part 1 was 14.8 months. Although inclusion criteria allowed patients as young as 1 month old to enter the study, the enrolled patients of Part 1 and Part 2 received the first risdiplam dose between 2 to 7 months of age.
- At the approved dose used for 17 patients (0.2 mg/kg/day), “…41% (7/17) were able to sit independently for ≥ 5 seconds (BSID-III, Item 22) after 12 months of treatment,” which is a clinically meaningful improvement compared to the natural history of untreated early-onset SMA where none would be expected to sit independently during their lifetime.
- After 12 months and 23 months of risdiplam treatment, 90% (19/21) and 81% (17/21) of patients, respectively, were alive without permanent ventilation (the 21 patient denominator includes 17 patients in the approved-dosage group and 4 patients in the lower-dosage group altogether). This slower disease progress is in contrast to the natural course of disease where less than 25% of early-onset patients are expected to survive beyond 14 months of age without permanent ventilation, as described in the product information.

JEWELFISH, a phase 2 study of patients with any SMA type will evaluate safety, tolerability, and pharmacokinetics/pharmacodynamics of risdiplam in patients 6 months to 60 years of age who either (a) previously participated in early-phase clinical studies with certain experimental drugs, or (b) who previously received treatment with nusinersen or onasemnogene abeparvovec-xioi. Based on interim data from 12 patients with a treatment duration of 57 to 512 days, 9 who previously received RG7800 and 3 who had received nusinersen, there were no withdrawals due to drug-related adverse events. The safety profile and increase in SMNp was thus far comparable to that observed in the SUNFISH Part 1 study (of patients with no history of SMN2-related therapy prior to study entry).

Table 3 is an overview of key phase 3 clinical studies for risdiplam, SUNFISH and FIREFISH, as registered in ClinicalTrials.gov. Table 1 of Appendix C additionally includes exclusion criteria.
Table 3. Registered Phase 3 Studies in ClinicalTrials.gov for Risdiplam

<table>
<thead>
<tr>
<th>Key Eligibility Criteria</th>
<th>62,63</th>
</tr>
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<tbody>
<tr>
<td>Patients ages 2 to 25 years with Type 2 or 3 SMA, with genetic diagnosis of 5q-autosomal recessive SMA</td>
<td></td>
</tr>
<tr>
<td>Ambulation: For Part 2, only non-ambulant patients are included; for Part 1 (phase 2 study) patients could be ambulant or non-ambulant. For Part 2: 1) RULM entry item A of at least 2, and ability to sit independently as assessed by item 9 of the MFM</td>
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<tr>
<td>Negative blood pregnancy test at screening and agreement to comply with measures to prevent pregnancy and restrictions on sperm donation</td>
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<tr>
<td>Signs or symptoms attributable to Type 1 SMA with onset between 28 days to 3 months of age, with genetic diagnosis of 5q-autosomal recessive SMA, and with 2 copies of SMN2 confirmed by central testing</td>
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<tr>
<td>Gestational age of 37 to 42 weeks with body weight at least in the 3rd percentile or higher</td>
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<tr>
<td>Receiving adequate nutrition and hydration (with or without gastrostomy) at the time of screening, in the opinion of the investigator</td>
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<tr>
<td>Adequately recovered from any acute illness at the time of screening and considered well-enough to participate in the opinion of the investigator</td>
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<table>
<thead>
<tr>
<th>Endpoints</th>
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<tbody>
<tr>
<td><strong>Primary endpoint:</strong></td>
<td></td>
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<tr>
<td>Part 2: Change from baseline in the Total Motor Function Measure 32 (MFM-32) score at month 12</td>
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<tr>
<td><strong>Secondary endpoints:</strong></td>
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<tr>
<td>Quantification of SMN2 mRNA</td>
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<tr>
<td>Quantification of SMNp in blood</td>
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<tr>
<td>Change from baseline in HFMSE at month 12</td>
<td></td>
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<tr>
<td>Change from baseline in RULM</td>
<td></td>
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<tr>
<td>Percentage of patients achieving stabilized or improved MFM score; assessment of individual domains of the MFM</td>
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</tr>
<tr>
<td>Percentage of patients by global impression per CGI-C and change from baseline in independence per SMAIS or suicidal ideation per C-SSRS</td>
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<tr>
<td>Respiratory measures (change from baseline) in SNIP, FEV1, FVC, PCF, MIP, MEP</td>
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<tr>
<td>Safety: adverse events and serious adverse events</td>
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<tr>
<td>PK: Cmax, AUC</td>
<td></td>
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<tr>
<td><strong>Primary end point:</strong></td>
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<tr>
<td>Part 2: Percentage of Infants who are sitting without support at 12-months, assessed by the Gross Motor Scale of the Bayley Scales of Infant and Toddler development Third Edition (BSID-III)</td>
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<tr>
<td><strong>Secondary end points</strong></td>
<td></td>
</tr>
<tr>
<td>Time to death, time to permanent ventilation</td>
<td></td>
</tr>
<tr>
<td>Quantification of SMN2 mRNA</td>
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<tr>
<td>Quantification of SMNp in blood</td>
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<tr>
<td>Change from baseline in the raw BSID-III score at month 12 and 24</td>
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<tr>
<td>Percentage of infants achieving highest motor milestone as assessed per HINE-2 and BSID-III</td>
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<tr>
<td>Percentage of infants achieving a CHOP-INTEND score of 40 or higher; head control, or an increase of at least 4 points</td>
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<tr>
<td>Proportion requiring respiratory support, able to orally feed, crawling, sitting, standing alone, or walking alone.</td>
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</tr>
<tr>
<td>Safety: adverse events and serious adverse events</td>
<td></td>
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<tr>
<td>PK: Cmax, AUC</td>
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</table>

* Refer to Appendix D for additional information on motor function scales

Abbreviations: AUC, Area Under the Curve; Cmax, maximum plasma concentration; C-SSRS, Columbia-Suicide Severity Rating Scale; CGI-C, Clinical Global Impression of Change; DB-RCT, double blinded randomized control trial; FEV1, Forced Expiratory Volume in 1 Second; FVC, Forced Vital Capacity; HFMSE, Hammersmith Functional Motor Scale Expanded; HR, hazard ratio; MFM, Total Motor Function Measure; MEP, Maximal Expiratory Pressure; MIP, Maximal Inspiratory Pressure; NUS, nusinersen; PCF, Peak Cough Flow; RULM, Revised Upper Limb Module; SNIP, Sniff Nasal Inspiratory Pressure; SMA, spinal muscular atrophy; SMAIS, SMA Independence Scale; SMN2 mRNA, Survival of Motor Neuron 2 Messenger Ribonucleic Acid; SMNp, Survival of Motor Neuron Protein
Nusinersen (Spinraza) Key Studies

- **Infantile-Onset SMA** (ENDEAR, Phase 3 study): DB-RCT for children up to 7 months old at study screening who had homozygous deletion or mutation of SMN1, with 2 SMN2 copies, and symptom onset by 6 months age (most closely representing SMA Type 1 and few with Type 2; NCT02193074, Published). For most Type 1 SMA patients, nusinersen is expected to provide modest improvement in motor function while the risks of death or use of permanent assisted ventilation are significantly reduced with nusinersen treatment. A quarter to a third of infants with SMA Type 1 were able to sit unsupported after 14 months of treatment with nusinersen which is a milestone usually unachievable with SMA Type 1 without treatment (percentage dependent on the manner of calculation by intention to treat or per protocol).
  - At 6 months, there was a significant difference in the proportion of motor milestone responders favoring the treatment group: 41% (21/51) in the nusinersen group versus 0% (0/27) in the sham-control group, (p<0.001).

- **Later-Onset SMA** (CHERISH, Phase 3 study): DB-RCT in eligible patients between 2 to 12 years of age with SMA onset after 6 months of age; most patients had a diagnosis of Type 2 SMA and some with Type 3, and none were independently ambulating at baseline (NCT02292537, Published). The majority of treated patients had 3 SMN2 copies (88%), and a few with 2 or 4 copies (7% and 2%, respectively).
  - For later-onset pediatric patients (ie, SMA Type 2), nusinersen is expected to increase the Hammersmith Functional Motor Scale Expanded (HFMSE) score: at least half of treated patients (57%) experienced an increase of at least 3 points on the HFMSE score from baseline to month 15 (vs. 26% in the placebo arm, p<0.05).

- **Presymptomatic SMA** (NURTURE, Phase 2 study): non-controlled, open-label, intervention arm only; to assess efficacy for prevention of SMA deficits in patients with 5q SMA homozygous gene deletion or mutation, or compound heterozygous mutation and with 2 or 3 SMN2 copies (mostly reflecting SMA Type 1 and 2, and may include some Type 3 patients); patients included are 6 weeks of age or less at the time of the first nusinersen dose (Active study, NCT02386553).
  - In 2019, an interim assessment reported that the treated group (N=25) was of median age 34.8 month [range 25.7–45.4], all were alive and able to sit without support, none required tracheostomy or permanent ventilation, and 92% and 88% achieved walking with assistance or independently, respectively.

- **Long-term Extension Study** (SHINE, Phase 3): long-term study (up to 5 years) to assess safety and efficacy in patients continuing treatment who were previously enrolled in other nusinersen investigational studies, children and adults; with open-label, intervention arm only (Ongoing study; NCT02594124).

- **High-dose study** (DEVOTE, Phase 2/3): in patients with early-onset, later-onset SMA, and adults already on nusinersen (Recruiting, NCT04089566).
Onasemnogene abeparvovec-xioi (Zolgensma) Key Studies

- **SMA Type 1** (STR1VE and STRIVE-EU, Phase 3): Open-label, single-arm studies in patients with nonfunctional SMN1 gene and 1 or 2 copies of SMN2; enrolled patients less than 6 months of age at the time of the single-dose treatment (Completed, NCT03306277; Active NCT03461289)²⁴⁻⁷⁶
  - Regarding an ongoing study in SMA Type 1 patients, cited in the prescribing information for the medication, at an interim cut-off of March 2019, 47% of infants receiving the FDA-approved dose achieved the ability to sit without support (a milestone usually unattainable in Type 1 SMA) and a higher survival rate than what would be expected with the natural history of disease was observed.⁸
- **SMA Type 1** (Phase 3): Open-label, singe-arm study in patients with nonfunctional SMN1 gene and 1 or 2 copies of SMN2; enrolling patients (at least 6) are less than 6 months of age at the time of the single-dose treatment (Active, NCT03837184)⁷⁶
- **Presymptomatic patients with multiple SMN2 copies** (SPR1NT, Phase 3): for patients with bi-allelic deletion of SMN1 and with 2 or 3 copies of SMN2 (which can span SMA Type 1, 2, and 3)³⁻²⁰; open-label, single-arm study (Active, NCT03505099)⁵³
- **Long-term follow up study** (START, Phase 4): for SMA Type 1 patients who were in a parent clinical study for the gene therapy; will assess durability of effect on developmental milestones and safety for up to 15 years (Active, NCT03421977)⁷⁷
- **Long-term follow up study** (Phase 4): for SMA Type 1, 2, and 3 patients who were in a parent clinical study for the gene therapy; will assess durability of effect on developmental milestones and safety (Enrolling, NCT04042025)⁷⁸
Guidance Regarding Presymptomatic Treatment of SMA

Currently, the position of an SMA expert panel is to treat presymptomatic infants with genetically diagnosed SMA who have 2, 3, or 4 SMN2 copies.\textsuperscript{44,79}

An expert panel was assembled by the SMA Newborn Screening Multidisciplinary Working Group and Cure SMA (a major patient advocacy group) to develop a treatment algorithm for patients who test positive for 5q SMA upon newborn genetic screening.\textsuperscript{44} Their 2018 and 2020 guidance is summarized in Table 4. In the panel’s 2018 publication (by Glascock et al), presymptomatic treatment was recommended for genetically confirmed SMA with 2 or 3 SMN2 copies, which would represent Type 1, 2, and some Type 3 SMA cases in the natural course of disease.\textsuperscript{44} The panel stated that presymptomatic treatment can prevent irreversible loss of motor neurons which, during the natural course of Type 1 and Type 2 SMA, progresses rapidly. In Type 1 patients, “…loss of more than 90\% of motor units [occurs] within six months of age.”\textsuperscript{44} Preclinical studies in animal models suggested better results with earlier treatment. This is supported by the ENDURE study with symptomatic Type 1 patients, as there was a larger percentage of responders to nusinersen when treatment was given within 12 weeks of symptom onset compared to initiation occurring 12 weeks after onset.\textsuperscript{44} Interim data from the NURTURE trial shows positive results with nusinersen-treatment of presymptomatic patients less than 6 weeks of age at first dose who have 2 or 3 SMN2 copies.\textsuperscript{44,71}

The 2018 guidance document by Glascock et al was drafted when nusinersen was the only disease-modifying option available. In February 2020, the panel updated their recommendation which is now in favor of presymptomatic treatment for patients with 4 SMN2 copies.\textsuperscript{79} Previously, the 2018 guidance described the option of a wait-to-treat approach with regular monitoring to detect the first sign of SMA symptom onset for patients with 4 SMN2 copies.\textsuperscript{44} The updated recommendation followed the market entry of onasemnogene (approved in 2019), a drug with a lower administration burden (single lifetime IV dosage) compared to ongoing intrathecal nusinersen treatment; this gene therapy must be administered before 2 years of age.\textsuperscript{8} Approval of risdiplam, also with low administration burden vs. intrathecal injections, was in the workings in early 2020.

The panel expects that benefits shown in presymptomatic patients with 3 SMN copies, where nusinersen treatment has prevented onset of SMA symptoms in the NURTURE trial, will be similarly beneficial for patients with 4 SMN2 copies treated presymptomatically.\textsuperscript{79} The projected benefits of presymptomatic treatment are generally expected regardless of the agent used, whether an approved ASOs or gene therapy. Glascock et al also notes the following as part of their rationale: “…the loss of even a small number of motor neurons is unacceptable when effective treatment is available, as this loss cannot be reversed after onset but can be prevented with earlier treatment.”\textsuperscript{79} It must also be considered that the older the patient, the more likely they will have anti-AAV antibodies which precludes receiving onasemnogene.
Revised guidance, released in February 2020, for patients with 4 SMN2 copies (in the context of nusinersen and onasemnogene approved, and risdiplam in FDA review status)\textsuperscript{79}

- The panel recommended treatment for infants with a genetic diagnosis of SMA upon newborn screening who have 4 copies of SMN2

2018 guidance (in the context of nusinersen approved)\textsuperscript{44}

- For patients testing positive for SMA upon newborn screening who are pre-symptomatic and who have 2 or 3 SMN2 copies, early treatment was recommended according to the panel’s treatment algorithm.\textsuperscript{44}
- For SMA patients with a single SMN2 copy, these patients are usually symptomatic at birth. Treatment would be at the digression of the physician and parents considering the severity of the disease. In the rare case of a pre-symptomatic patient with a single SMN2 copy, the panel generally recommended early treatment.\textsuperscript{44}
- Patients who test positive for SMA upon newborn screening who are pre-symptomatic and have 4 or more SMN2 copies should not necessarily receive early treatment (potentially years prior to the development of symptoms). A shared decision-making approach between the patient’s caregiver and provider should be used to decide when to initiate therapy in these patients. Instead of presymptomatic treatment, such patient may instead be followed closely, ideally by a neuromuscular specialist, if available to the patient, to detect disease onset when it occurs. Routine follow-up care was recommended for these patients every 3 to 6 months until 2 years of age, then every 6 to 12 months thereafter to monitor for the first sign of disease onset.\textsuperscript{44}
- Additionally, patients should have the exact SMN2 copy number determined, and be checked for the SMN2 c.859G>C mutation, associated with a milder phenotype\textsuperscript{80}, for added prognostic information.\textsuperscript{44}
  - A variety of motor/neurologic assessments are available to help detect SMA symptom onset (eg, electromyography [EMG], compound muscle action potential [CMAP], myometry, physical examinations, and several motor function scales: Children’s Hospital of Philadelphia Infants Test of Neuromuscular Disorders [CHOP-INTEND], Hammersmith Infant Neurological Exam [HINE], Hammersmith Functional Motor Scale Expanded [HFMSE], six-minute walk test, and the Bayley Scales).\textsuperscript{44} Thus, the panel was in consensus with the recommendation that patients should be treated with any of the following: any active or chronic neurological change per EMG, below normative CMAP values for an age-matched child, physical exam changes with respect to loss of reflexes, weakness in trunk or proximities, regression or failure in age-appropriate motor milestones, or a drop in test score or failure to reach appropriate motor gains per motor function tests.\textsuperscript{44}
- The panel also noted that “…the attending physician’s clinical judgment, as well as the patient’s and/or the patient’s family’s wishes, should be the deciding factor on when to initiate treatment…”\textsuperscript{44}

Trials for nusinersen (NURTURE) and onasemnogene (SPR1NT) for presymptomatic treatment of SMA are in progress. Both studies include patients with 2 or 3 SMN2 copies, mostly reflecting SMA Type 1 or
Type 2, but may also include some Type 3 patients.\textsuperscript{3,20} Regarding risdiplam, a phase 2 is recruiting presymptomatic patients up to 6 weeks of age, identified via genetic screening.\textsuperscript{12,59,60} The primary endpoint, the percentage of patients able to sit without support at month 12, will be assessed in the patient subset having 2 SMN2 copies (excluding the known SMN2 gene modifier mutation c.859G> C) and with baseline CMAP of at least 1.5 millivolts (NCT03779334).\textsuperscript{12} Other real-world evidence in SMA cohorts identified via NBS and observed upon initiation of presymptomatic treatment with nusinersen (with up to 3 SMN2 copies) shows positive results.\textsuperscript{81}

Results from descriptive international studies of SMA cohorts (genetically confirmed) found about 15% of the SMA population has 4 copies.\textsuperscript{27,81} Of patients with 4 SMN2 copies, Type 3 SMA (84%) is most common, followed by Type 2 as 11%, Type 4 as 4%, and Type 1 as 0.2%.\textsuperscript{27} Within SMA Type, about 5% of patients with Type 2 SMA have 4 SMN2 copies. In Type 3 SMA, which accounts for as many as 27-30% of the total SMA cases, about 43% have 4 SMN2 copies.\textsuperscript{27} Less than 0.5% of patients with Type 1 SMA have 4 SMN2 copies.\textsuperscript{27} The decision of whether to presymptomatically treat patients with 4 SMN2 copies has been debated considering the lack of studies on presymptomatic treatment in this specific subpopulation with 4 copies (or more), and since the majority of patients with 4 copies are likely to have disease onset in childhood or adolescence (88% of patients with 4 copies manifest as Type 3 or 4 phenotype in the natural course of disease\textsuperscript{27}); yet, there is well-grounded evidence that loss of motor neurons could be prevented by presymptomatic treatment as shown in other subpopulations.\textsuperscript{82} In the face of high medication prices, drug-cost reimbursement in the event of an insufficient response to treatment could help facilitate access for patient subsets where treatment outcomes remain unclear (eg, effect magnitude, cost-effectiveness, or adverse event profile of long-term treatment).

Treating physicians have described the following barriers and suboptimal monitoring/treatment issues that arise with a wait-to-treat approach for patients with 4 SMN2 copies:

- While the first sign of SMA onset can be detected upon intensive monitoring, recurrent screening procedures can be burdensome to the patient/family considering the frequency of testing (eg, every 3 to 6 months\textsuperscript{44}) and discomfort associated with some procedures (eg, electromyography).\textsuperscript{82} Such burden (or even induced psychological stress) may cause the care-giver/patient to miss monitoring appointments and ultimately miss catching disease onset as early as possible.
- The age constraint of onasemnogene (for patients 2 years of age or younger) can influence preference away from a wait-to-treat approach, as parents may not want to miss the opportunity for their child to be treated with this 1-time dose.\textsuperscript{79,82}
- For those in whom symptom onset is identified, an insurance-coverage delay may negatively impact providers/caregivers\textsuperscript{82} and be viewed as a lost opportunity in treating irrecoverable muscle neuron damage. Treatment approval in the presymptomatic period could help avoid this scenario.
- Schorling et al and other SMA treating physicians have described discrepancies/inaccuracies in SMN2 copy number testing.\textsuperscript{83-85} The gold standard for determining SMN2 copy number is multiplex ligation-dependent probe amplification (MLPA), but has also been performed via quantitative real-time PCR, digital PCR, or next-generation sequencing methods.\textsuperscript{85} Experts urge that SMN2 copy number testing must be standardized and optimized if having this as a treatment-deciding factor. Schorling et al reported that 35% of a German SMA cohort were found to have an over-estimated copy number when patients were initially tested, mostly with MLPA.\textsuperscript{85} This has furthered the discussion regarding optimization and standardization of MLPA testing.\textsuperscript{83,84}
Safety

Adverse reactions

The most common adverse reactions (ARs) with risdiplam in clinical studies of later-onset SMA, with an incidence of at least 10% and occurring more frequently than in the control group, were fever, diarrhea, and rash. Additional ARs, reported in ≥5% of treated patients with later-onset SMA, which were ≥5% higher compared to the placebo group rate were mouth and aphthous ulcers, arthralgia, and urinary tract infection. In the single arm clinical trial of patients with infantile-onset SMA, common ARs were fever, diarrhea, rash, upper respiratory tract infection, pneumonia, constipation, and vomiting.

Hepatic or renal impairment

Avoid use of risdiplam in patients with hepatic impairment since the drug is hepatically metabolized and has not been studied in this population. Metabolism of risdiplam occurs mainly by flavin monooxygenase 1 and 3 (FMO1 and FMO3) and also with some contribution from cytochrome P450 (CYP) enzymes, 1A1, 2J2, 3A4, and 3A7. Excretion occurs through fecal (53%; with 14% unchanged drug), and 28% through renal (with 8% as unchanged drug) routes. Renal impairment is not expected to affect the exposure level so no renal dose adjustments are suggested.

Pregnancy

Based on animal data, risdiplam use during pregnancy may cause fetal harm. In animal models, exposed offspring during pregnancy and lactation experienced developmental defects “...embryofetal mortality, malformations, decreased fetal body weights, and reproductive impairment in offspring” at or above clinically relevant drug exposures.” A pregnancy test is advised prior to starting therapy, and use of contraception is recommended during risdiplam treatment and for a least 1 month following the last dose of risdiplam.

Fertility impact

It is possible that male fertility can be negatively affected by risdiplam treatment.

Drug interactions

Risdiplam can increase the plasma concentration of drugs that are substrates of multidrug and toxin extrusion (MATE) transporters, such as metformin. Such drug combinations should be avoided, or the dose of the substrate may be reduced.

Risdiplam is a weak inhibitor of CYP3A, but small increases of a sensitive CYP3A substrate (midazolam increase in AUC by 11% and maximum concentration by 16%) were not considered clinically relevant.
Other information regarding storage and administration

Risdiplam is available as a powder for oral solution (0.75ng/mL). Reconstituted risdiplam solution must be stored in the refrigerator (36°F to 46°F) and should be discarded 64 days after reconstitution. The medication should be administered within 5 minutes after it is drawn up into the oral syringe, otherwise it should be discarded from the syringe and a new dose used. The medication should be taken after a meal or after breastfeeding around the same time each day; however, the solution should not be mixed into formula or milk.\textsuperscript{13}
Discussion Topics for Developing Prescribing Criteria for Risdiplam Treatment

- Prior authorization (PA) criteria may require the provider’s attestation or documentation of a genotype (per genetic testing) consistent with SMN1-related SMA (eg, homozygous SMN1 deletion, or having a single SMN1 copy [heterozygous deletion] with compound point mutations predictive of loss of function).

- Prescribing may be limited to health care providers experienced in the treatment of neurological disorders or in consultation with a pediatric neuromuscular specialist or neurologist specializing in SMA.

- Only approved dosing of risdiplam may be permitted.

- The requirement to be at least 2 months of age at the first dose may be specified (to follow the FDA indication); however, consider allowing the PA to be submitted/pre-approved prior to 2 months of age to avoid any delay in treatment.

- When considering whether to further narrow the SMA population for use, consider the following:
  - The FDA indication for risdiplam is worded broadly for SMA, irrespective of SMA Type, disease onset, or SMN2 copy number.\textsuperscript{13}
  - Risdiplam has been studied in symptomatic patients with SMA. Risdiplam treatment improved motor function vs. placebo in symptomatic patients with Type 2 and 3 SMA (in SUNFISH). In symptomatic patients with Type 1 SMA, risdiplam improved motor function, survival, and reduced requirement for permanent ventilation compared to the natural history of disease (in FIREFISH).\textsuperscript{13} Planned phase 2 studies will assess safety/efficacy in presymptomatic patients (with (RAINBOWFISH: estimated primary completion date June 2021; final completion date March 2026)\textsuperscript{12}, and in patients who were previously treated with other disease modifying agents (JEWELFISH: estimated primary completion date Jan. 2022; final completion date Jan. 2025).\textsuperscript{64}
  - Criteria may be considered differentially based symptomatic or presymptomatic status:
    - For example you may wish to consider allowing treatment of all symptomatic patients with SMA, regardless of SMA Type or SMN2 copy number.
    - You may wish to restrict presymptomatic SMA treatment to those with 1 to 4 SMN2 copies (mostly representing Type 1, Type 2, and Type 3 SMA in the natural course of disease) considering the expert working group guidance by Glascock et al published in 2018 and 2020. Of note, these guidance statements do not distinguish preference of one medication over another and were published prior to the approval of risdiplam.
      - An alternative SMN2-copy threshold specific for risdiplam prescribing may be assigned for presymptomatic treatment while also considering the availability of other options for patient subsets and/or limited until there is evidence from studies with risdiplam in presymptomatic patients with 4 SMN2 copies. This decision is complex with the unknown durability of presymptomatic treatment into adolescents/adulthood in this subpopulation, and potentially un-divulged factors that might arise (eg, adverse effects) with a longer-course of treatment. It should also be considered that SMN2 copy number genetic assessment has
been identified as needing optimization to improve accuracy as a considerable amount of patients have had their SMN2 copy number over estimated.\textsuperscript{85}

- **For continuation of therapy**, the provider may be required to attest to at least 1 of the following:
  - (a) a lack of deterioration with maintained or improved motor function per motor milestone assessments;
  - (b) maintenance of motor milestones to ages at which loss would be expected with natural course of disease based on their predicted SMA type at baseline; or
  - (c) achievement of motor milestones that would not be expected considering their SMA type or SMN2 number.
- Flexibility may be considered especially if the patient has had a planned interruption in therapy.
- Re-assessment of risdiplam PA-criteria may be revisited in the future as more data emerges that may support broadening treatment subpopulations.

**Summary**

Prior to the approval of the first novel disease-modifying therapy in 2016, only supportive care interventions were available to help manage the pulmonary, orthopedic, and nutritional complications resulting from SMA disease progression. In August 2020, risdiplam became the third approved treatment for SMA, alongside nusinersen (an ongoing intrathecal injection) and onasemnogene (a 1-time IV injection). Similar to nusinersen, risdiplam is an SMN2 splicing modifier that increases SMN protein levels, a protein essential for maintaining motor-neuron viability. Unlike nusinersen, risdiplam is a small-molecule drug yet to be documented to elicit anti-drug antibodies. This oral option may be favorable especially for those with disease progression resulting in scoliosis and/or spinal fusion that makes intrathecal administration of nusinersen more challenging or sometimes too risky.\textsuperscript{10}

Like nusinersen, risdiplam is approved for patients with SMA regardless of prognostic markers of disease severity (eg, age of disease onset, or SMN2 copy number); however, the indication for risdiplam is specific to patients 2 months or older. These drugs were designed and tested in patients specifically with SMN1-related SMA. Results from clinical studies in symptomatic patients with Type 1, 2, or 3 SMA have shown motor function improvements with risdiplam treatment; additionally, improved survival without the need of permanent ventilation was demonstrated in Type 1 SMA (FIREFISH in Type 1 and SUNFISH in Type 2 and 3 SMA).

Topics encouraged for discussion include PA-criteria considerations based on the FDA indication, genetic diagnosis, and symptomatic vs. asymptomatic status, while also considering the limited completed research or indirect data for some clinical scenarios.
References


Appendix A: Orphan-Drug Background Info

An estimated 25 million Americans suffer from a rare or “orphan” disease, defined as a disease that affects fewer than 200-thousand people across the United States (US). There are approximately 7,000 known rare diseases, of which fewer than 5% have developed treatments. Today, biotechnology and pharmaceutical companies, small and large, are filling this treatment vacancy at an accelerated pace. The 1983 Orphan Drug Act (ODA) was enacted to spur meaningful advancements for persons with rare diseases by providing tax break and other marketing incentives to companies that brought “orphan drugs” (ie, drugs that have indications for orphan diseases) to the market. It was perceived that a drug company would not otherwise be motivated to develop products in the rare-disease arena because research expenditures would not be recouped, much less a profit realized.

The Orphan Drug Designation Program (ODDP), overseen by the FDA’s Office of Orphan Products Development, requires either that the orphan-designated product treat a rare disease affecting less than 200,000 Americans or that the manufacturer convincingly show it will not recoup developmental costs from sales within the US. Incentives for orphan-drug development include a tax discount (50% tax credit on certain research/development costs), an application fee waiver, grant availability, 7 year marketing exclusivity, and research design assistance. Additionally, there is flexibility in what the FDA considers to be substantial evidence for demonstrating the drug’s safety and efficacy profile. From 2013 through 2017, an average of 49 orphan-designated drug approvals per year were granted by the FDA. This is a dramatic increase compared to pre-1983 when there were fewer than 10 orphan-related products that entered the market between 1973 and 1983.

Prior to performing a pivotal clinical trial, manufacturers must detail the natural history of the rare condition (e.g. disease manifestations, variability in the course and possible subtypes of the disease) and propose trial design and endpoints to the FDA. The challenge of small patient populations has stemmed a case-by-case evidence consideration approach by the FDA. Evidence from small trial populations and retrospective data from case reports may be considered.

Uncertainty may arise concerning the value of the drug for subgroups not in included in robust studies. When data on efficacy isn’t fully elucidated by thorough investigation in clinical studies, Dr. Prasad, M.D. MPH. highlights the paradox of lofty medication prices for agents that are often non-curative, with significant yet small or even unclear benefits for certain populations: “Irrespective of cost, a fundamental principle of evidence-based medicine—caution in extrapolating benefits shown in severe disease settings to more indolent settings— may form the basis for denial of coverage…”

Websites with Additional Background Info on Orphan disease states

CureSMA.org Educational Resources
Conference Medical Presentations
• http://www.curesma.org/support-care/for-healthcare-providers/educational-resources/
Appendix B: Literature Search

**EMBASE**

- ‘risdiplam’/exp OR (risdiplam OR rg7916 OR rg-7916 OR ro7034067 OR ro-7034067):ti,ab,kw
  [87 results on July 6th, 2020; 91 on August 11th, 2020, then limited to 2020 => 16]

**Ovid-Medline**

(risdiplam OR rg7916 OR rg-7916 OR ro7034067 OR ro-7034067).ti,ab,kw,kf,rn. {12 results on July 6th, 2020}.

**ClinicalTrials.gov**

(risdiplam OR rg7916 OR ro7034067) AND limit study phase (2, 3, and 4) => 4 studies

(Onasemnogene OR AVXS-101) AND limit study phase (2, 3, and 4) => 6 studies

(Nusinersen OR ISIS 396443) AND AND limit study phase (2, 3, and 4) => 9 studies
### Appendix C: Clinical Study Information

#### Table 1. Phase 2 and 3 Studies for Risdiplam\(^{62,63}\)

<table>
<thead>
<tr>
<th>Brief Trial Overview</th>
<th>FIREFISH: Open-label, multi-center clinical study is to assess the safety, tolerability, pharmacokinetic (PK), pharmacodynamics (PD), and efficacy of risdiplam in infants with Type 1 spinal muscular atrophy (SMA) with 2 parts: exploratory dose finding part 1 and a confirmatory part 2 with treatment for 24-months at the dose selected in part 1.</th>
</tr>
</thead>
</table>
| SUNFISH: Multi-center, BD-RCT, placebo-controlled, Phase 2 study, followed by Phase 3 study with integrated placebo crossover to active treatment. Together, these studies will assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of risdiplam in adult and pediatric participants with Type 2 and Type 3 SMA (dose finding part 1 for 12 weeks and confirmatory part 2 for 24 months) | ClinicalTrials.gov  
  - Study start date: Dec. 2016; enrolled 62 patients  
  - Primary completion date: Nov. 2019  
  - Estimated completion date: Nov. 2023  
  - Last Update Posted Apr. 2020 |
| ClinicalTrials.gov  
  - Study start date: Oct. 2016; enrolled 231 patients  
  - Primary completion date: Sep. 2019  
  - Estimated completion date: Sep 2023  
  - Last Update Posted Mar. 2020 | Signs or symptoms attributable to Type 1 SMA with onset after 28 days but prior to the age of 3 months, with genetic diagnosis of 5q-autosomal recessive SMA, and with 2 copies of SMN2 confirmed by central testing  
  - Gestational age of 37 to 42 weeks with body weight at least in the 3\(^{rd}\) percentile or higher  
  - Receiving adequate nutrition and hydration (with or without gastrostomy) at the time of screening, in the opinion of the investigator  
  - Adequately recovered from any acute illness at the time of screening and considered well-enough to participate in the opinion of the investigator |
| Patients ages 2 to 25 years with Type 2 or 3 SMA, with genetic diagnosis of 5q-autosomal recessive SMA  
 Ambulation: For Part 1 patient could be ambulant or non-ambulant. For Part 2, only non-ambulant patients included  
 For Part 2: 1) RULM entry item A of at least 2, and ability to sit independently as assessed by item 9 of the MFM  
 Negative blood pregnancy test at screening and agreement to comply with measures to prevent pregnancy and restrictions on sperm donation | Use of investigational drug or device study within 90 days prior to screening, or 5 half-lives of the drug, whichever is longer |
<p>| Key Eligibility Criteria | Use of a SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier, gene therapy, or cell therapy |
| Exclusion Criteria | Hospitalization for a pulmonary event within the last 2 months or planned at time of screening | Use of a SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier, gene therapy, or cell therapy |
| Hospitalization for a pulmonary event within the last 2 months or planned at the time of screening | Hospitalization for pulmonary event within the last 2 months, or planned at the time of screening |</p>
<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery for scoliosis or hip fixation in the one year preceding screening or planned within the next 18 months</td>
<td>Clinically relevant electrocardiogram (ECG) abnormalities before study drug administration</td>
</tr>
<tr>
<td>Unstable gastrointestinal, renal, hepatic, endocrine, or cardiovascular system diseases as considered to be clinically significant by the investigator</td>
<td>Unstable gastrointestinal, renal, hepatic, endocrine or cardiovascular system diseases</td>
</tr>
<tr>
<td>Clinically significant electrocardiogram abnormalities before study drug administration</td>
<td>Participants requiring invasive ventilation or tracheostomy</td>
</tr>
<tr>
<td>Any major illness within 1 month before the screening examination or any febrile illness within 1 week prior to screening and up to first dose administration</td>
<td>Participants requiring awake non-invasive ventilation or with awake hypoxemia</td>
</tr>
<tr>
<td>Recently initiated treatment (within 6 months) with oral salbutamol or another beta 2-adrenergic agonist</td>
<td>Participants with a history of respiratory failure or severe pneumonia, and have not fully recovered their pulmonary function at the time of screening</td>
</tr>
<tr>
<td>Any prior use of chloroquine, hydroxychloroquine, retigabin, vigabatrin or thioridazine</td>
<td>Multiple or fixed contractures and/or hip subluxation or dislocation at birth</td>
</tr>
<tr>
<td>Participants requiring invasive ventilation or tracheostomy</td>
<td>Presence of non-SMA related concurrent syndromes or diseases</td>
</tr>
<tr>
<td>Any major illness within one month before the screening examination or any febrile illness within one week prior to screening and up to first dose administration</td>
<td>Any major illness within one month before the screening examination or any febrile illness within one week prior to screening and up to first dose administration</td>
</tr>
<tr>
<td>Any inhibitor of CYP3A4 and/or any Organic Cation Transporter 2 (OCT-2) and multidrug and toxin extrusion (MATE) substrates taken within 2 weeks and/or any inducer of CYP3A4 taken within 4 weeks (or within 5-times the elimination half-life, whichever is longer) prior to dosing or participants (and the mother, if breastfeeding the infant) taking any nutrients known to modulate CYP3A activity and any known flavin containing monoxygenase (FMO) 1 or FMO3 inhibitors or substrates</td>
<td>Any inhibitor of CYP3A4 and/or any Organic Cation Transporter 2 (OCT-2) and multidrug and toxin extrusion (MATE) substrates taken within 2 weeks and/or any inducer of CYP3A4 taken within 4 weeks (or within 5-times the elimination half-life, whichever is longer) prior to dosing or participants (and the mother, if breastfeeding the infant) taking any nutrients known to modulate CYP3A activity and any known flavin containing monoxygenase (FMO) 1 or FMO3 inhibitors or substrates</td>
</tr>
<tr>
<td>Prior use and/or anticipated need for quinolones (chloroquine and hydroxychloroquine), thioridazine, vigabatrin, retigabine, or any other drug known to cause retinal toxicity during the study; or infants exposed to chloroquine, hydroxychloroquine, thioridazine, vigabatrin, retigabine</td>
<td>Prior use and/or anticipated need for quinolones (chloroquine and hydroxychloroquine), thioridazine, vigabatrin, retigabine, or any other drug known to cause retinal toxicity during the study; or infants exposed to chloroquine, hydroxychloroquine, thioridazine, vigabatrin, retigabine</td>
</tr>
<tr>
<td>Recent history (within 6 months) of ophthalmic disease that would interfere with the conduct of the study as assessed by an ophthalmologist</td>
<td>Recent history (within 6 months) of ophthalmic disease that would interfere with the conduct of the study as assessed by an ophthalmologist</td>
</tr>
</tbody>
</table>
| Use for 8 weeks or longer, of the following medications within 90 days prior to enrollment: riluzole, valproic acid, hydroxyurea, sodium phenylbutyrate, butyrate derivatives, creatine, carnitine, growth hormone, anabolic steroids, probenecid, agents anticipated to increase or decrease muscle strength, agents with known or presumed histone deacetylase inhibitory effect, medications known to or suspected of causing retinal toxicity (deferoxamine,
**Interventions**

| Part 1 | Patients randomized to oral risdiplam (dose finding range not specified) or placebo for 12 weeks; after 12 weeks patients then could enter the open label study on part 2 dose |
| Part 2 | (with different set of patients than those in part 1) Patients randomized to risdiplam for 24 months (dose selected based on performance in part 1), or placebo for 12 months followed by cross over to risdiplam for 12 months |

**Endpoints**

| Primary endpoint: |
| Part 2: Percentage of Infants who are sitting without support at 12-months, assessed by the Gross Motor Scale of the Bayley Scales of Infant and Toddler development Third Edition (BSID-III) |
| Part 1: Recommended Part 2 Dose of risdiplam, based on 2 weeks of treatment |

| Secondary endpoints: |
| Quantification of SMN2 mRNA |
| Quantification of SMNp in blood |
| Change from baseline in HFMSE at month 12 |
| Change from baseline in RULM |
| Percentage of patients achieving stabilized or improved MFM score; assessment of individual domains of the MFM |
| Percentage of patients by global impression per CGI-C and change from baseline in independence per SMAIS or suicidal ideation per C-SSRS |
| Respiratory measures (change from baseline) in SNIP, FEV1, FVC, PCF, MIP, MEP |
| Safety: adverse events and serious adverse events |

| Primary end point: |
| Part 2: Change from baseline in the Total Motor Function Measure 32 (MFM-32) score at month 12 |
| Part 1: Recommended Part 2 Dose of risdiplam, based on 120 days of treatment |

| Secondary endpoints: |
| Quantification of SMN2 mRNA |
| Quantification of SMNp in blood |
| Change from baseline in the raw BSID-III score at month 12 and 24 |
| Percentage of infants achieving highest motor milestone as assessed per HINE-2 and BSID-III |
| Percentage of infants achieving a CHOP-INTEND score of 40 or higher; head control, or an increase of at least 4 points |
| Proportion requiring respiratory support, able to orally feed, crawling, sitting, standing alone, or walking alone. |
| Safety: adverse events and serious adverse events |

Abbreviations: AUC, Area Under the Curve; Cmax, Maximum Plasma Concentration; C-SSRS, Columbia-Suicide Severity Rating Scale; CGI-C, Clinical Global Impression of Change; CYP, cytochrome P450; DB-RCT, double blinded randomized control trial; FEV1, Forced Expiratory Volume in 1 Second; FVC, Forced Vital Capacity; HFMSE, Hammersmith Functional Motor Scale Expanded; HR, hazard ratio; MFM, Total Motor Function Measure; MEP, Maximal Expiratory Pressure; MIP, Maximal Inspiratory Pressure; NUS, nusinersen; PCF, Peak Cough Flow; RULM, Revised Upper Limb Module; SNIP, Sniff Nasal Inspiratory Pressure; SMA, spinal muscular atrophy; SMAIS, SMA Independence Scale; SMN2 mRNA, Survival of Motor Neuron 2 Messenger Ribonucleic Acid; SMNp, Survival of Motor Neuron Protein
Nusinersen Clinical Trial Information

In the published final analysis for ENDEAR, at 9 months, significantly more infants in the nusinersen group had a motor-milestone response compared to the control group (37 of 73 infants [51%] vs. 0 of 37 [0%]). Comparing the nusinersen group to the control group, 22% of infants achieved full head control vs. 0%; 10% were able to roll over vs. 0%; 8% were able to sit independently vs. 0%; and 1% were able to stand vs 0%. Overall risk of death or the use of permanent assisted ventilation was 47% lower in the treatment group compared to control (hazard ratio 0.53; P = 0.005).67

The primary endpoint definition from the ENDEAR trial was the proportion of patients with a motor-milestone response. Motor-milestone response was defined as meeting the following two criteria: (1) improvement in at least one of the following 7 HINE-2 categories (ie, an increase in the score for head control, rolling, sitting, crawling, standing, or walking of ≥1 point, an increase in the score for kicking of ≥2 points, or achievement of the maximal score for kicking) and (2) more categories with improvement than categories with worsening. The total HINE-2 score range is 0 to 23.

The CHERISH phase 3 study enrolled patients between 2 to 12 years old, with symptom onset occurring after 6 months old and be able to sit but walk independently (most patients having a diagnosis of Type 2 SMA and some with Type 3).68 The primary endpoint was the least-squares mean change from baseline (LMCb) in the total HFMSE score at month 15; there was a significantly greater improvement from baseline in the HFMSE score with nusinersen versus a decline seen in the control group (difference in HFMSE LMCb of 4.9 points; 95% CI, 3.1 to 6.7).102 Regarding secondary endpoints, although there were significantly more patients in the treatment group with an increase in the HFMSE score of at least 3 points (57% vs. 26%, P<0.001), there was no significant difference in the number of patients who achieved at least one World Health Organization motor milestone compared to the controlled group.102
Table 2. Published Phase 3 Trial Information for Nusinersen

**ENDEAR:** 13 month, international, DB-RCT assessing NUS versus a sham procedure in infants with SMA. Patients had documentation of a homozygous deletion or mutation in SMN1, two copies of SMN2, and with onset of SMA before 6 months of age. A total of 122 patients were randomized into the treatment groups.

The two primary endpoints included (1) the proportion of patients with a motor-milestone response, according to the Hammersmith Infant Neurological Examination Section 2 (HINE-2) assessment and (2) the event-free survival defined as the time to death or the use of permanent assisted ventilation and stratified based on disease duration of more or less than 12 weeks (age at screening minus the age of symptom onset).

**CHERISH:** a 15 month, international, DB-RCT assessing NUS versus a sham procedure in pediatric patients (2-12 years old at screening) with SMA. Patients had genetic documentation of 5qSMA, 2-4 copies of SMN2, onset of SMA after 6 months of age, and the ability to sit independently. A total of 126 patients were randomized into the treatment groups and stratified by age (greater or less than 6 years old).

**Brief Trial Overview**

Children with infantile-onset SMA:
- genetic diagnosis of 5q-linked spinal muscular atrophy (SMA) due to homozygous gene deletion or compound heterozygote deletion/mutation of SMN1
- 2 copies of SMN2
- younger than 6 months of age at SMA symptom onset and younger than 7 months of age (210 days) at screening
- receiving adequate nutrition and hydration (with or without gastrostomy) in the opinion of the site investigator; measuring to at least the third percentile in body weight using country-specific guidelines
- adherence to the consensus statement for standard of care in SMA
- gestational age of 37 to 42 weeks
- ability to complete all study procedures and parent/guardian has adequate psychosocial support

Children with later-onset SMA:
- genetic diagnosis of 5q-linked spinal muscular atrophy (SMA) due to homozygous gene deletion or compound heterozygote deletion/mutation of SMN1
- onset at greater than 6 months of age
- males/females between 2 and 12 years old at screening
- able to sit independently, but never had ability to walk independently (ability to walk defined as ≥15 ft)
- have a HFME score ≥ 10 and ≤ 54 at screening
- have an estimated life expectancy of > 2 years from screening
- meet age-appropriate institutional criteria anesthesia and sedation, if use is planned for study procedures

**Key Eligibility Criteria**

Children with infantile-onset SMA:
- genetic diagnosis of 5q-linked spinal muscular atrophy (SMA) due to homozygous gene deletion or compound heterozygote deletion/mutation of SMN1
- 2 copies of SMN2
- younger than 6 months of age at SMA symptom onset and younger than 7 months of age (210 days) at screening
- receiving adequate nutrition and hydration (with or without gastrostomy) in the opinion of the site investigator; measuring to at least the third percentile in body weight using country-specific guidelines
- adherence to the consensus statement for standard of care in SMA
- gestational age of 37 to 42 weeks
- ability to complete all study procedures and parent/guardian has adequate psychosocial support

Children with later-onset SMA:
- genetic diagnosis of 5q-linked spinal muscular atrophy (SMA) due to homozygous gene deletion or compound heterozygote deletion/mutation of SMN1
- onset at greater than 6 months of age
- males/females between 2 and 12 years old at screening
- able to sit independently, but never had ability to walk independently (ability to walk defined as ≥15 ft)
- have a HFME score ≥ 10 and ≤ 54 at screening
- have an estimated life expectancy of > 2 years from screening
- meet age-appropriate institutional criteria anesthesia and sedation, if use is planned for study procedures
**Exclusion Criteria**

- Peripheral oxygen desaturation (O2 saturation below 96% without ventilation support) during screening
- SMA symptoms within the first week of birth
- Presence of an active infection requiring systemic antiviral or antibacterial treatment during screening
- History of brain or spinal cord disease that would interfere with lumbar punctures, cerebrospinal fluid circulation, or safety assessments; presence of an implanted cerebrospinal fluid drainage shunt or central nervous system catheter;
- Abnormalities in hematology or clinical chemistry parameters at screening that would prevent inclusion as assessed by the site investigator;
- Treatment of SMA with an investigational drug, biological agent, or device within 30 days of screening; history of gene therapy, prior antisense oligonucleotide therapy, or cell transplantation; the parent/guardian is unable to understand a basic description of the study or does not agree to comply with the schedule of assessments as defined by the protocol; the infant’s caregiver does not adhere to the standard-of-care guidelines; presence of a medical condition that would interfere with the infant’s ability to participate in the study as assessed by the site investigator;
- Respiratory insufficiency, defined by the medical necessity for invasive or non-invasive ventilation for greater than 6 hours during a 24 hour period, at screening
- Gastric feeding tube use, where the majority of feeds are given by this route
- Severe contractures or severe scoliosis evident on X-ray
- Hospitalization for surgery within 2 months of screening or planned during the duration of the study
- Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy at any time during the screening period. History of bacterial meningitis
- History of brain or spinal cord disease or abnormalities by MRI or CT that would interfere with the LP procedures or CSF circulation
- Presence of an implanted shunt for the drainage of CSF or an implanted CNS catheter
- Prior injury or surgical procedure which impacts the subject’s ability to perform any of the outcome measure testing required in the protocol and from which the subject has not fully recovered or achieved a stable baseline
- Clinically significant abnormalities in hematology or clinical chemistry parameters or ECG
- Treatment with another investigational drug, valproate, or hydroxyurea within 3-months of screening. Any history of gene therapy, antisense oligonucleotide therapy, or cell transplantation.
- Ongoing condition that would interfere with the conduct and assessments of the study (e.g., wasting or cachexia, severe anemia, etc.) that would interfere with the assessment of safety or would compromise the ability of the subject to undergo study procedures

**Interventions**

<table>
<thead>
<tr>
<th>A. Intrathecal nusinersen procedure: the dose was adjusted according to the estimated volume of cerebrospinal fluid for the infant’s age to be equivalent to administering a 12-mg dose in a person 2 years of age or older</th>
<th>A. Intrathecal nusinersen procedure: 12mg per dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. Sham procedure: “The sham procedure consisted of a small needle prick to the skin over the lumbar spine, which was covered with a bandage to simulate the appearance of a lumbar-puncture injection.”</td>
<td>B. Sham procedure: “…consisted of a small needle prick to the skin over the lumbar spine, which was covered with a bandage to simulate the appearance of a lumbar-puncture injection.”</td>
</tr>
<tr>
<td>Dosing on day 1, 15, 29 and 64, 183, and 302</td>
<td>Dosing on day 1, 29, 85 and 274</td>
</tr>
<tr>
<td><strong>Endpoints</strong></td>
<td><strong>Primary endpoints:</strong></td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------</td>
</tr>
<tr>
<td></td>
<td>(1) proportion of patients with a motor-milestone response, according to the Hammersmith Infant Neurological Examination Section 2 (HINE-2) assessment</td>
</tr>
<tr>
<td></td>
<td>(2) the event-free survival defined as the time to death or the use of permanent assisted ventilation.</td>
</tr>
<tr>
<td></td>
<td><strong>Secondary endpoints:</strong></td>
</tr>
<tr>
<td></td>
<td>(1) proportion of Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) responders (≥4-point score increase from baseline at the later of day 183, 302, or 394 assessments)</td>
</tr>
<tr>
<td></td>
<td>(2) overall survival rate</td>
</tr>
<tr>
<td></td>
<td>(3) percentage of infants not requiring permanent ventilation</td>
</tr>
<tr>
<td></td>
<td>(4) proportion of compound muscle action potential (CMAP) responders (peroneal CMAP amplitude increasing to or maintained at ≥1 mV versus baseline at the later of day 183, 302, or 394 assessments)</td>
</tr>
<tr>
<td></td>
<td>(5) two subgroup analyses of time to death or permanent ventilation in patients below the study median disease duration</td>
</tr>
<tr>
<td></td>
<td>(6) two subgroup analyses for time to death or permanent ventilation in patients above the study median disease duration</td>
</tr>
</tbody>
</table>

### Duration

A prespecified interim analysis occurred when enrollment achieved approximately 80 infants for at least 6 months. Upon finding a positive benefit–risk assessment in favor of nusinersen, the trial was terminated early. Assessments scheduled for day 394 were instead performed at the end-of-trial visit, 2 weeks after the patient received their last dose. Patients were invited to enroll in the open-label extension study SHINE (ClinicalTrials.gov number, NCT02594124).

A prespecified interim analysis was conducted when all patients had been enrolled for at least 6 months and at least 39 children had completed the 15-month assessment. A multiple-imputation method to account for missing data was used for those patients that did not have 15 month results at the interim analysis. Patients lacking a 15-month assessment were invited to attend a last visit (end of the double-blind visit) where all assessments scheduled for the 15-month assessment were captured. Patients were invited to enroll in the open-label extension study SHINE (ClinicalTrials.gov number, NCT02594124).

### Primary endpoints:

1. proportion of patients with a motor-milestone response, according to the Hammersmith Infant Neurological Examination Section 2 (HINE-2) assessment
2. the event-free survival defined as the time to death or the use of permanent assisted ventilation.

### Secondary endpoints:

1. proportion of Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) responders (≥4-point score increase from baseline at the later of day 183, 302, or 394 assessments)
2. overall survival rate
3. percentage of infants not requiring permanent ventilation
4. proportion of compound muscle action potential (CMAP) responders (peroneal CMAP amplitude increasing to or maintained at ≥1 mV versus baseline at the later of day 183, 302, or 394 assessments)
5. two subgroup analyses of time to death or permanent ventilation in patients below the study median disease duration
6. two subgroup analyses for time to death or permanent ventilation in patients above the study median disease duration

### Primary end point:

1. least-squares mean change from baseline in the total HFMSE score at month 15. (HFMSE assessments performed at 3, 6, 9, 12, and 15 months; authors cite that a change in the HFMSE score of at least 3 points is considered to be clinically significant.

### Secondary end points

1. percentage of patients who had an increase from baseline to month 15 in the HFMSE score of at least 3 points
2. percentage of patients who achieved at least one new World Health Organization motor milestone (out of a total of six milestones), (3) the change from baseline in the Revised Upper Limb Module (RULM) score (which ranges from 0 to 37, with higher scores indicating better function)
3. proportion of children who had achieved the ability to stand alone or walk with assistance
4. change from baseline to month 15 in the HFMSE score according to age and disease duration
Final Analysis Results

- A significantly higher proportion of infants in the nusinersen group versus control group had a motor-milestone response (37 of 73 infants [51%] vs. 0 of 37 [0%]).
- The likelihood of event-free survival was higher in the nusinersen group versus the control group (HR for death or the use of permanent assisted ventilation, 0.53; P = 0.005).
- The likelihood of overall survival was higher in the nusinersen group than in the control group (hazard ratio for death, 0.37; P = 0.004).
- Infants with a shorter disease duration at screening were more likely than those with a longer disease duration to benefit from nusinersen. The incidence and severity of adverse events were comparable between the treatment and control arm.

Abbreviations: DB-RCT, double blinded randomized control trial; HFMSE, Hammersmith Functional Motor Scale Expanded; HR, hazard ratio; NUS, nusinersen; SMA, spinal muscular atrophy

- A significantly larger proportion of children in the nusinersen arm compared to the control arm had an increase from baseline to month 15 in the HFMSE score of at least 3 points (57% versus 26%, P < 0.001).
- The overall incidence of adverse events was similar in the nusinersen group and the control group.
Appendix D: Assessment Tools for Motor Development

- **Total Motor Function Measure 32 (MFM-32)** is used as part of the primary endpoint for the SUNFISH study of risdiplam treatment in patients with Type 2 and 3 SMA (ages 2 to 25 years)
  - The MFM-32 is a 32-item assessment tool designed to evaluate all degrees of neuromuscular disease severity, for ambulatory and non-ambulatory patients, and is validated for patients 6 to 60 years of age. A 4-point Likert scale is used to rate performance in items grouped into 3 main subscore areas: standing position and transfers (D1 subscore with 13 items), axial and proximal motor function (D2 subscore with 12 items), and distal motor function (D3 subscore with 7 items). The patient’s score is usually expressed as a percentage of the maximal score possible; thus, higher scores are indicative of greater motor function.
  - In 2013 authors noted that for young children under 6 years of age, the standard MFM-32 was not validated for patients below 6 years old, with some items being too difficult to instruct and understand for the cognitive level of this younger age group. Thus, authors developed a short form of this tool and validated the MFM-20 for use in children less than 7 years.

- **The Hammersmith Infant Neurological Exam Section 2 (HINE-2)** includes: 8 main motor-milestone categories (voluntary grasp, kicking, head control, rolling, sitting, crawling, standing, and walking) with each having subcategories to track incremental changes in functional gain that leads up to achieving the milestone. The maximum total score possible is 26. By 18 months, more than 90% of healthy toddlers are able to achieve each milestone. This scale been used for SMA type 1 patients.

- **The Hammersmith Functional Motor Scale Expanded (HFMSE)** is designed for ambulatory SMA patients. The assessment includes 33 items total, with 66 maximal points. Per-item scores range from 0 to 2, with higher scores representing a higher degree of motor ability. The scale was designed for patients “...for use in children with SMA Type 2 and Type 3 with limited ambulation to give objective information on motor ability and clinical progression.” This assessment was employed in the phase 3 CHERISH study of nusinersen for late-onset SMA and is also part of a secondary endpoint in the Risdiplam SUNFISH study. Furthermore, authors of the CHERISH study note, “A change in the HFMSE score of at least 3 points is considered to be clinically meaningful.”

- **The Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND)** includes 16 items, each of which is scored based on a 0 to 4 point scale (0 for no response, 1 for minimal, 2 for partial, 3 for nearly full, 4 for complete). The maximum total score possible is 64. It has been validated for use in SMA type 1 infants.

- Gross Motor Scale of the Bayley Scales of Infant and Toddler development Third Edition (BSID-III) used in FIREFISH risdiplam study
Appendix E: Select Prescribing Information of Other Disease-Modifying Drugs

Table 1. Dosing Information

**Spinraza - nusinersen**: 12 mg/5 mL solution (single dose vials) for intrathecal administration

**Loading dose**: initiate with 4 loading doses (12mg each – administered intrathecally)—the first three doses should be administered at 14-day intervals, followed by the 4th loading dose 30 days later

**Maintenance dose**: a maintenance dose (12mg intrathecally), should be administered once every 4 months following the last loading dose.

- Should be administered by or under the direction of healthcare professionals experienced in performing lumbar punctures using aseptic technique; consider sedation and ultrasound or other imaging techniques to guide intrathecal administration

**Zolgensma - onasemnogene abeparvovec-xioi**: intravenous-vial kit per weight based

**Single-dose**: 1.1 × 10¹⁴ vector genomes per kilogram (vg/kg) of body weight by intravenous administration

- Requires pre-treatment with corticosteroid 1 day prior to infusion and continuing for 30-days total

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Table 2. Warnings and Precaution Information for Spinraza

**Thrombocytopenia and coagulation abnormalities**: In infant-onset and later-onset SMA, 16% of treated patients developed below normal platelet counts (vs. 14% in sham-control group). Coagulation abnormalities and thrombocytopenia have been observed post-administration of some antisense oligonucleotides.

**Renal toxicity**: higher rates of urine protein elevation occurred in treated patients (58%) vs. controls (34%). Renal toxicity has been observed after administration of some antisense oligonucleotides.

**Adverse reactions**:

- In the infant population (at least in 10%, and 5% more frequent than in control patients): lower respiratory infection, teething, and constipation
- In the later-onset population (at least in 10%, and 5% more frequent than in control patients): headache, vomiting, and back pain, and pyrexia

**Immunogenicity**: Nusinersen is a large molecule oligonucleotide with potential for the development of anti-drug antibodies. Out of 294 patients, 17 had measurable anti-drug antibodies (ADA). Of these, 5 patients had only transient ADAs and the remainder had persistent ADAs (4% of the 294 measured patients). Nonetheless, the effect of ADAs on clinical efficacy significantly is not yet known.

**Other rare serious reactions**: the package insert discusses case reports of

- Severe hyponatremia (1 patient report)
- Rash, skin ulcers, and spontaneous resolution (2 patient reports)
- Possible reduction in growth (as measured by height)
- Post lumbar puncture syndrome
- Post marketing experience: case reports of serious infections, including meningitis
- Other serious case reports include hydrocephalus, aseptic meningitis and hypersensitivity reactions

**Monitoring**: Assess at baseline, prior to each dose, and as clinically needed: platelet count, prothrombin time; activated partial thromboplastin time, quantitative spot urine protein testing
Table 3. Warnings and Precaution Information for Zolgensma®

**Thrombocytopenia** was observed at various time points after treatment; should monitor platelets prior to and following treatment

**Transient elevated troponin-I** was observed at various time points after treatment; should monitor prior to and following treatment

**Serious Liver Reactions:** the package insert discusses case reports of
- 1 case of acute serious liver injury with onset occurring 7 weeks after treatment
- 2 cases with liver enzymes above 48 X the upper limit of normal

**Prematurity:** Avoid in premature neonates since concomitant treatment with corticosteroids may adversely affect neurological development

**Most common adverse reactions** (incidence ≥ 5%) were elevated aminotransferases and vomiting

**Monitoring:** Assess at baseline and following treatment liver function, platelet count, and troponin-I at intervals specified in prescribing information

Pre-screen for presence of anti-AAV9 antibodies; not established in patients with anti-AAV9 antibody titers of above 1:50, though this is uncommon