

## Class Update: Spinal Muscular Atrophy

### New Drug Evaluation: onasemnogene abeparvovec, suspension for intravenous infusion

**Date of Review:** September 2019

**Generic Name:** onasemnogene abeparvovec-xioi

**End Date of Literature Search:** June 10, 2019

**Brand Name (Manufacturer):** Zolgensma® (AveXis, Inc.)

**Dossier Received:** yes

#### Research Questions:

1. Is there new published evidence regarding the safety and efficacy of nusinersen?
2. What is the comparative efficacy and effectiveness of onasemnogene abeparvovec in reducing symptoms and improving functional outcomes in patients with spinal muscular atrophy (SMA)?
3. What are the comparative harms of onasemnogene abeparvovec in SMA patients?
4. Are there certain sub-populations in which onasemnogene abeparvovec may be beneficial or cause more harm?
5. What is the evidence for the use of nusinersen after infusions of onasemnogene abeparvovec?

#### Conclusions:

##### *Nusinersen*

- The Canadian Agency for Drugs and Technologies in Health (CADTH) and United Kingdom (U.K.) National Institute for Health and Care Excellence (NICE) recently published evaluations of the available evidence for the use of nusinersen to treat SMA.<sup>1,2</sup>
- The CADTH clinical review evaluated 3 randomized clinical trials (RCTs), 4 phase 1 uncontrolled trials, and 2 phase 2 uncontrolled trials.<sup>1</sup> All of the trials are of poor quality with high risk of bias due to open label study design, inadequate assessment of all patients included in the study, imbalanced baseline characteristics of randomized patients, and use of different nusinersen dosing regimens.<sup>1</sup> According to the clinical experts consulted for the CADTH review, nusinersen would be beneficial to all infants with SMA type I, regardless of SMN2 gene copy number.<sup>1</sup> The shorter the duration since symptom onset, the younger the patient, and the more severe the prognosis (based on genetic testing), the higher the likelihood of observing a clinically meaningful response to treatment with nusinersen.<sup>1</sup>
- The NICE guidance concluded there is evidence to show nusinersen improves a range of outcomes that are important to people with early- (type 1) and later-onset (types 2 and 3) SMA.<sup>2</sup> Also, there is some evidence suggesting that nusinersen is effective for pre-symptomatic SMA.<sup>2</sup> However, there is insufficient long-term evidence, so the long-term benefits are highly uncertain.<sup>2</sup> Nusinersen is recommended as an option for treating SMA only if people have pre-symptomatic SMA, or SMA types 1, 2 or 3.<sup>2</sup> This recommendation is narrower than the full marketing authorization in the U.K. because current evidence does not address use of nusinersen in patients with Type 0 or Type 4 SMA.<sup>2</sup>

### *Onasemnogene abeparvovec*

- In August 2019 the Drug Effectiveness Review Project (DERP) completed a systematic review focused on clinical evidence for the use of onasemnogene abeparvovec in treating SMA.<sup>3</sup> One study that reported on effectiveness and harms of onasemnogene abeparvovec and 6 unpublished studies were identified. All studies were uncontrolled interventional studies or had indirect comparisons.<sup>3</sup> No studies involved a head-to-head comparison of nusinersen with onasemnogene abeparvovec.<sup>3</sup> The published and unpublished literature includes samples of participants with SMA type 1 and 2 and presymptomatic SMA.<sup>3</sup> Based on indirect comparisons and assumed natural history of SMA, onasemnogene abeparvovec appears to improve survival, increase motor function and achievement of motor milestones in patients with SMA type 1.<sup>3</sup>
- The Food and Drug Administration (FDA) approval of onasemnogene abeparvovec was based on safety and efficacy data from 1 ongoing phase 3 clinical trial (STR1VE) and a completed phase 1 clinical trial (START).<sup>4,5</sup> The FDA-approved indication for onasemnogene abeparvovec is for treatment of SMA patients under the age of 2 years.<sup>6</sup>
- The START trial enrolled 15 patients with SMA Type 1; 3 patients in a low-dose cohort and 12 patients in a high-dose cohort.<sup>5</sup> In this Phase 1 trial, onasemnogene abeparvovec was administered as a single-dose intravenous infusion in an open-label, single-arm study design at high risk of bias. Poor quality data showed that by 24 months, 0 patients in the low-dose group achieved any of the normal motor milestones, and 1 became dependent on ventilatory support.<sup>5</sup> The high-dose group had better results at 24 months: 9 of the 12 patients (75%) were able to sit without support for at least 30 seconds, and 2 (17%) were able to crawl, pull to stand, and walk independently.<sup>5</sup> All patients in both cohorts were alive and at least 20 months of age after 24 months of the trial.<sup>5</sup>
- The ongoing phase 3 STR1VE trial has enrolled 21 patients (10 male and 11 female) with a mean age of 3.9 months (range 0.5 to 5.9 months) at the start of treatment.<sup>4</sup> All patients recruited for the study had genetically confirmed bi-allelic survival motor neuron (SMN) 1 gene deletions, two copies of the SMN2 gene, and experienced onset of clinical symptoms consistent with SMA before 6 months of age, which is characteristic of SMA Type 1. By the time of the interim data analysis, 13 of the 19 patients continuing in the trial reached 14 months of age without permanent ventilation.<sup>4</sup> Ten of the 21 patients (47%) achieved the ability to sit without support for 30 seconds.<sup>4</sup> The data from this trial has not been published, and study quality could not be assessed.<sup>4</sup>
- Twelve patients (29%) experienced elevated transaminases during clinical trials with onasemnogene abeparvovec.<sup>6</sup> The onasemnogene abeparvovec manufacturer label contains a black box warning about the risk of acute serious liver injury and elevated aminotransferases which can occur after administration.<sup>6</sup> Patients with pre-existing liver impairment may be at higher risk for hepatic injury.<sup>6</sup> Prior to infusion, liver function of all patients should be assessed by clinical examination and laboratory testing (e.g., hepatic aminotransferases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], total bilirubin, and prothrombin time).<sup>6</sup> All patients should receive systemic corticosteroids starting 1 day before onasemnogene abeparvovec infusion and continuing for at least 30 days after infusion.<sup>6</sup> Liver function should be monitored for at least 3 months after infusion.<sup>6</sup>
- There is insufficient evidence regarding long term safety and efficacy for the use onasemnogene abeparvovec in managing SMA. Most of the evidence was evaluated in SMA Type 1 patients. The FDA label indicates onasemnogene abeparvovec is approved for use in pediatric patients less than 2 years of age with SMA with biallelic mutations in the SMN1 gene, which is a broader indication than the current published evidence in children with SMA Type 1.
- No ongoing or planned head-to-head studies and none evaluating the effectiveness and harms of nusinersen after infusion of onasemnogene abeparvovec were identified.<sup>3</sup> The DERP authors interviewed representatives from AveXis and Biogen, the manufacturers of Zolgensma® and Spinraza®, respectively to assess the use of nusinersen after infusions of onasemnogene abeparvovec. Currently, there is insufficient evidence to support the subsequent use of nusinersen in patients who received an infusion of onasemnogene abeparvovec.<sup>3</sup>

## Recommendations:

- Designate onasemnogene abeparvovec as a non-preferred agent on the Practitioner-Managed Prescription Drug Plan (PMPDP).
- Implement PA criteria to ensure one time administration of onasemnogene abeparvovec in appropriate SMA pediatric populations per the FDA labeling (**Appendix 4**).
- Revise nusinersen PA criteria to include an assessment of onasemnogene abeparvovec administration prior to nusinersen initiation (**Appendix 4**).
- Evaluate costs in executive session.

## Summary of Prior Reviews and Current Policy

The first medication FDA-approved for all types of SMA in both pediatric and adult populations was nusinersen.<sup>7</sup> This drug was presented to the Pharmacy and Therapeutics (P and T) Committee at the July 2017 meeting. One unpublished, low quality phase 3 trial (ENDEAR) with high risk of bias demonstrated the efficacy of nusinersen in improving motor skills in infants who presented with SMA type 1 before the age of 7 months.<sup>8</sup> Response was defined as a participant who was alive and participating in the study and demonstrated at least a two-point (level) increase in the ability to kick or a one-point increase using the a Hammersmith Infant Neurological Exam (HINE)-2 assessment in head control, rolling, sitting, crawling, standing, or walking.<sup>8</sup> A greater percentage of subjects achieved HINE motor milestone response in the nusinersen group (40%) compared to the control group (0%) which was statistically significant ( $p < 0.0001$ ).<sup>8</sup> Long term effects of nusinersen on survival and ventilator dependency are unknown at this time. Nusinersen can increase the risk of bleeding complications due to thrombocytopenia; platelet testing is required at baseline and before each dose.<sup>7</sup> Nusinersen also has a risk for renal toxicity. Quantitative spot urine testing is required at baseline and prior to each dose.<sup>7</sup> Additional trials in patients with SMA types 2 and 3 were ongoing and not published at the time of the 2017 P and T review. To ensure appropriate utilization of nusinersen in conditions with evidence of benefit, prior authorization (PA) criteria were implemented in 2017 (**Appendix 4**). In the past year, 8 patients within the Oregon Health Plan have had a diagnosis of SMA and a physician administered drug (PAD) claim for nusinersen administration. Seven of those patients were enrolled in a Coordinated Care Organization (CCO) and 1 patient was enrolled in Fee-For-Service (FFS).

## Background:

Spinal muscular atrophy is an autosomal recessive inherited neuromuscular disorder characterized by degeneration of motor neurons in the spinal cord, which results in progressive weakness, atrophy of skeletal muscles and hypotonia. Disease severity ranges from progressive infantile paralysis and premature death to limited motor neuron loss and normal life expectancy.<sup>9</sup> It is a rare disease and the incidence of SMA is estimated as 1 in 10,000 live births.<sup>10</sup> However, SMA is the most common genetic cause of death in infants due to respiratory insufficiency.<sup>11</sup> The phenotype is extremely variable, and patients are classified as SMA type 0 through 4 based on age at onset and motor milestone achievement. SMA Type 1 is the most common (45%) and severe type of SMA and occurs primarily in infants under 6 months of age.<sup>12</sup> These infants cannot sit unsupported and usually die within the first 2 years of life due to respiratory failure or infection. Infants with SMA Type 1 rarely achieve improvements in motor function or acquire motor developmental milestones.<sup>11</sup> The early signs of SMA Type 1 include generalized muscle weakness, hypotonia resulting in “floppiness,” abnormal flexibility of the joints, absent tendon reflexes, twitching of the tongue, a frog-like position with the hips moved apart and knees bent or flexed, and an alert appearance.<sup>13</sup> Muscles of the face are not affected initially and mental development is usually normal.<sup>13</sup> Children with SMA type 2 exhibit muscle weakness that is more prominent in the lower extremities. They are able to sit unassisted, but are never able to independently walk. Respiratory failure is less severe and develops later in life compared to children with SMA type 1.<sup>11</sup> Children with SMA type 3 develop variable muscle weakness after 18 months of age and are able to walk, although as the disease progresses they may become wheelchair bound. Respiratory muscles are rarely affected and life expectancy is normal in this group of SMA patients.<sup>11</sup> SMA type 4 generally occurs in the second or third decade of life and is the mildest form of the disease characterized by mild muscle weakness and normal life expectancy. The characteristics of each SMA type are described in **Table 1**.

**Table 1. SMA classification and characteristics<sup>10</sup>**

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

\*Natural history may vary depending on supportive interventions

SMA is caused by biallelic deletions or mutations of the survival motor neuron (SMN1) gene on chromosome 5q13.<sup>12</sup> The SMN gene product, SMN protein, is essential for motor neuron development and function. The SMN gene region consists of a two almost identical genes: SMN1 and SMN2.<sup>11</sup> The lack of SMN1 in patients with SMA results in a disruption of SMN function which is partially compensated by SMN2 protein synthesis. SMN2 produces transcripts of SMN protein lacking exon 7 which results in an alternatively spliced, truncated, and nonfunctional SMN protein.<sup>11</sup> Due to an incomplete exclusion of exon 7 from SMN2 messenger ribonucleic acid (mRNA), only a small part (10–15%) of the mRNA transcripts contain exon 7, resulting in a small proportion of normal SMN protein (5-10%).<sup>11</sup> The number of copies of SMN2 correlate with the functional status of patients with SMA.<sup>11</sup> Infants with SMN1 biallelic deletions and only two copies of SMN2 have a 97% risk of SMA type 1.<sup>5</sup> The presence of 3 or more copies of SMN2 is associated with milder SMA symptoms. As the number of SMN2 copies correlates inversely with disease severity, moderate increases in SMN protein levels may have significant beneficial effects.<sup>14</sup>

The standard diagnostic tool for SMA is genetic testing to assess for homozygous deletions or mutations in the SMN1 gene. In part because of SMA's rapid progression and the importance of early diagnosis to preserve motor functioning, the disease was recently added as a recommended condition for which to screen all newborns in the United States.<sup>15</sup> Different methods for a newborn screening have been developed to diagnose SMA from DNA extracted from newborn blood spots, including a liquid microbead array to detect the homozygous SMN1 exon 7 deletion, a high-resolution DNA melting analysis with the possibility to identify SMN1 and SMN2 deletion as well as to quantify copy numbers of both genes, and a real-time polymerase chain reaction.<sup>16</sup> Other laboratory tests can include muscle enzyme creatine kinase, electrophysiological testing such as electromyography (EMG), and nerve conduction study with repetitive stimulation. These tests help to identify other muscle diseases, motor neuropathies, and disorders of neuromuscular junctions.<sup>17</sup> Carrier testing is available and carrier frequency is estimated as 1:40 to 1:60 in the general population.<sup>18</sup> It is not possible to predict the severity of the SMA phenotype from carrier screening.

Due to the difficulties in quantifying motor abilities in these patients, several functional motor scales were developed to assess functional status in children with SMA. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) was developed by physical therapists to provide a standardized method for motor skill evaluation of neck, trunk, and limb strength of SMA patients aged 4 months to 4 years.<sup>19</sup> The assessment incorporates the limited abilities of SMA patients to sit and roll over and focuses on motor assessment in the prone position. It is a 16 item assessment of functional muscle strength and is scored on a 0 to 4 scale: no response (0), minimal (1), partial (2), nearly full (3) and complete (4) level of response; with a total score ranging from 0 to 64 points. Higher scores on the CHOP-INTEND scale equate to better motor function. The maintenance of scores of more than 40 points has been

considered to be clinically meaningful in SMA patients.<sup>20</sup> CHOP INTEND was validated in a small population of children (n = 27) with SMA aged 3 to 260 months (mean age = 49 months).<sup>21</sup>

The Hammersmith Infant Neurological Exam (HINE) was developed by pediatric neurologists to assist in assessment of neurologic function of infants between 2 and 24 months of age.<sup>22</sup> It includes 3 sections with a total of 26 items assessing neurologic function, developmental milestone achievement, and behavioral assessment. Each item is scored individually (0, 1, 2, or 3), with a sum score of all individual items (range 0 to 78). At 9 or 12 months, a score  $\geq 73$  is considered optimal.<sup>22</sup> Sequential use of the HINE allows the identification of early signs of neuromotor disorders, whereas individual items are predictive of motor outcomes.<sup>23</sup> For example, in preterm infants assessed between six and 15 months corrected age, scores greater than 64 predict independent walking with a sensitivity of 98% and specificity of 85%.<sup>23</sup> Conversely, scores less than 52 are highly predictive of cerebral palsy and other severe motor impairments.<sup>23</sup> The HINE screening can be used as a tool to capture motor milestones in patients with SMA, including head control, sitting, voluntary grasp, ability to kick in supine, rolling, crawling or bottom shuffling, standing, and walking.<sup>16</sup> Increase in score indicates improved function with a maximum score between 2 to 4 points for each category and a total maximum score of 26.<sup>8</sup>

The Hammersmith Functional Motor Scale (HFMS) was developed by physical therapists to assess SMA type 2 and 3 patients.<sup>24</sup> The 20 item assessment provides information on motor ability and clinical progression in children with limited ambulation.<sup>24</sup> The HFMS motor assessment includes upper and lower limb activities as well as head and trunk control. Specific motor functions include rolling, sitting, lifting the head from prone to supine, propping on arms, 4 point kneeling, crawling and standing. Each item is scored on a 3 point scoring system: inability (0), assistance (1), and unaided (2). The total score ranges from 0 (all activities are failed) to 40 (all activities are achieved). Inter-rater reliability was tested on 35 children with an inter observer agreement  $> 99\%$ .<sup>24</sup> Untreated patients with SMA Type II or Type III are unlikely to improve by more than 2 points; patients and caregivers consider a 1-point increase to be meaningful.<sup>24</sup> For ambulatory patients with SMA type 3, the HFMS was extended with 13 items to assess walking, running and jumping which resulted in the HFMS-Expanded (HFSME) score.<sup>25</sup>

There is no known cure for SMA. Management focuses on providing respiratory support, assisting with motor function as needed, and optimizing nutritional status. Respiratory care includes the use of devices that improve ventilation, especially during sleep and viral illnesses when hypoventilation is most likely to occur, as well as methods to mechanically augment cough and clearance of respiratory secretions.<sup>26</sup> Pulmonary related complications are a major source of morbidity and mortality in severe cases of SMA. Full-time, noninvasive ventilation greater than 16 hours per day may be required to provide respiratory support in patients with SMA type 1. Difficulties in feeding and swallowing can lead to gastrointestinal complications and malnutrition. Nutritional support includes the use of non-oral methods to deliver enteral nutrition, typically through a surgically placed feeding tube or temporary nasal tube, plus medical or surgical interventions to control gastroesophageal reflux.<sup>26</sup> Management of joint contractures and scoliosis involves aggressive physical therapy assessments, daily passive range of motion exercises, and use of bracing to facilitate and maintain optimal positioning of extremities and maintain the spine upright against gravity.<sup>27</sup>

Emerging therapies for SMA include modulation of SMN2 encoded full-length protein levels, SMN1 gene replacement, neuroprotection, and improvements of muscle strength and function.<sup>9</sup> In 2016, nusinersen was the first FDA-approved therapy for treatment of SMA. It is an antisense oligonucleotide (ASO) which increases exon 7 inclusion in SMN2 mRNA leading to production of full-length SMN protein, which can partially compensate for mutations of the SMN1 gene.<sup>7</sup> Nusinersen is delivered by repeated intrathecal injections because ASOs do not efficiently cross the blood-brain barrier. The newest therapy, onasemnogene abeparvovec, formerly known as AVXS-101, is a SMN1 gene therapy that replaces the defective or missing SMN1 gene. Onasemnogene abeparvovec is a one-time intravenous treatment that is designed to deliver a functional SMN1 gene, potentially enabling the production of SMN protein, resulting in the normal

development of motor neurons.<sup>6</sup> This therapy will be discussed in more depth later in this report. Novel oral therapies (risdiplam, branaplam) targeted towards improving survival in SMA patients are currently being evaluated in clinical trials.<sup>28</sup>

## **Systematic Reviews**

### Canadian Agency for Drugs and Technologies in Health: Nusinersen in Spinal Muscular Atrophy

In April 2019 CADTH published a clinical review of nusinersen treatment in SMA patients.<sup>1</sup> A total of 15 studies were included in the report.<sup>1</sup> Of the 10 studies, 3 were randomized controlled trials (ENDEAR, CHERISH, and EMBRACE), four were phase 1 uncontrolled trials along with their extension studies (CS1, CS2, CS10, and CS12), two were phase 2 uncontrolled trials (CS3A, and NURTURE), and 1 trial was an extension study that included participants from all trials except EMBRACE and NURTURE (SHINE).<sup>1</sup>

The single arm studies share a common limitation pertaining to the study design: the lack of a control group to draw a statistical causal inference.<sup>1</sup> Without a control group, it is difficult to attribute any benefit observed to nusinersen alone, where other confounding factors are potentially present.<sup>1</sup> In addition, while objective clinical outcomes such as death or need for ventilation may have less potential to be biased by the open-label design of the study, other more subjective outcomes may be biased.<sup>1</sup> The NURTURE trial is an ongoing phase 2 study evaluating patients with pre-symptomatic SMA. The interim results from NURTURE may not reflect the final planned analysis of the predefined end point, also considering that for some outcomes, not all patients were assessed and this missing data might affect the outcome.<sup>1</sup> SHINE is also an ongoing extension study and the interim results may be confounded by the drop-outs and missing data from the original trials.<sup>1</sup> The inclusion of patients who participated in dose-finding studies resulted in a heterogeneous population in terms of drug exposure, which also limits applicability to patients with SMA.<sup>1</sup> EMBRACE was a small exploratory phase II trial that showed significant imbalances in the baseline characteristics of randomized patients and was terminated prematurely.<sup>1</sup> CHERISH had a main limitation of using a nusinersen dosage schedule that is different from the Health Canada's recommended dosage schedule.<sup>1</sup> The five observational, non-comparative, case-series studies share a common limitation pertaining to the study design: the study design is descriptive in nature and cannot draw any association between an observed potential benefit and nusinersen treatment.<sup>1</sup> Two of these studies were addressing SMA in adult patients; these studies further suffer from important limitations in reporting pertinent information and data regarding the patient population and outcome, and thus are unable to provide evidence of nusinersen efficacy in adult patients with SMA.<sup>1</sup>

The phase 3 randomized, double-blind, sham controlled trial CHERISH evaluated patients with early childhood SMA onset. The children were randomly assigned, in a 2:1 ratio, to undergo intrathecal administration of nusinersen at a dose of 12 mg (nusinersen group) or a sham procedure (control group) on days 1, 29, 85, and 274. The primary outcome, the change in HFMSE score from baseline to month 15, showed a statistically significant and potentially clinically meaningful difference between groups (least squares mean difference = 5.9 [95% confidence interval [CI], 3.7 to 8.1]).<sup>1</sup> This was further supported by a statistically significant difference in the first secondary outcome of HFMSE responders ( $\geq 3$  points increase) at 15 months, showing a difference in proportion of 30.5% (95% CI, 12.74 to 48.31).<sup>1</sup> The second outcome to be tested in the statistical hierarchy (proportion of patients achieving new motor milestones at 15 months) failed to show statistical significance.<sup>1</sup> Overall, patients in the nusinersen group had a mean of 0.2 new motor milestones achieved (95% CI, 0.1 to 0.3) compared with a mean of -0.2 in the sham control group (95% CI, -0.4 to 0).<sup>1</sup>

According to the clinical experts consulted for the CADTH review, nusinersen would be beneficial to all infants with SMA type I, regardless of SMN2 gene copy number.<sup>1</sup> Based on the available clinical data, the mechanism of action of nusinersen, and clinical experience, the two most important factors in determining an optimal response to treatment with nusinersen are time since symptom onset and the age of the patient; this is due to the fact that motor neuron deterioration is irreversible and early intervention is essential to prevent deterioration of motor function.<sup>1</sup> The shorter the duration since symptom onset, the younger the patient, and the more severe the prognosis (based on genetic testing), the higher the likelihood of observing a clinically meaningful response to treatment with a

drug such as nusinersen.<sup>1</sup> Clinical experts believe that an assessment of whether patients have responded to treatment should be carried out approximately 18 months after the initiation of the first dose of nusinersen, when patients are expected to have gained and maintained new motor milestones.<sup>1</sup> In adults with SMA (including those with type IV and type III who reach adulthood), it is unclear what the potential benefits of treatment with nusinersen would be, as clinical experience and natural history data indicate a plateau of the disease progression in the adult population.<sup>1</sup>

The December 2017 CADTH guidance recommends nusinersen use for the treatment of SMA if the following criteria are met:

- Under the care of a specialist with experience in the diagnosis and management of SMA.<sup>29</sup>
- Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote.<sup>29</sup>
- Genetic documentation of two copies of the survival motor neuron 2 (SMN2) gene.<sup>29</sup>
- Disease duration less than 26 weeks with onset of clinical signs and symptoms consistent with SMA after the first week after birth and on or before 7 months of age.<sup>29</sup>
- Patient is not currently requiring permanent invasive ventilation.<sup>29</sup>
- Treatment should be discontinued if, prior to the fifth dose or every subsequent dose of nusinersen:
  - there is no demonstrated maintenance of motor milestone function (as assessed using the Hammersmith Infant Neurological Examination [HINE] Section 2
  - or there is no demonstrated improvement in motor milestone function (as assessed using the HINE Section 2);
  - or if permanent invasive ventilation is required.<sup>29</sup>

#### National Institute for Health and Care Excellence: Nusinersen in Spinal Muscular Atrophy

In July 2019, NICE published guidance for using nusinersen to treat SMA.<sup>2</sup> Clinical trial evidence shows that nusinersen improves a range of outcomes that are important to people with early- (type 1) and later-onset (types 2 and 3) SMA.<sup>2</sup> Also, there is some evidence suggesting that nusinersen is effective for pre-symptomatic SMA.<sup>2</sup> However, there is no long-term evidence, so the long-term benefits are highly uncertain.<sup>2</sup> The committee considered that further data collection would help address these uncertainties. Evidence from the clinical trials, including ENDEAR and CHERISH, is uncertain but relevant for decision making.<sup>2</sup>

Results from ENDEAR showed that, compared with sham, nusinersen statistically significantly improved event-free survival, overall survival and motor function in patients with type1 SMA.<sup>2</sup> The hazard ratio for event-free survival (defined as time to death or permanent ventilation) was 0.53 (95% confidence interval [CI] 0.32 to 0.89; p=0.005).<sup>2</sup> The hazard ratio for overall survival was 0.37 (95% CI 0.18 to 0.77; p=0.004).<sup>2</sup> In terms of motor function, 51% of patients in the nusinersen group reached motor milestone responses compared with none in the control group (as measured by a modified version of the HINE-2).<sup>2</sup>

Results from CHERISH showed that, compared with sham, nusinersen statistically significantly improved motor function of children with later-onset SMA.<sup>2</sup> Motor function as measured by HFMSE had a least-squares mean difference of 4.9 (95% CI 3.1 to 6.7; p<0.001).<sup>2</sup> The NICE committee agreed that nusinersen provides important health benefits for people with later-onset SMA, but it was unclear how this affects survival because there were no deaths during the CHERISH trial.<sup>2</sup> The committee noted that both ENDEAR and CHERISH had short follow-up periods: ENDEAR had a follow-up of only 13 months, 16% of people having nusinersen and 39% of those having sham died; CHERISH had a follow-up of only 15 months, and there were no deaths.<sup>2</sup> However, it is possible that some people with SMA may not reach motor function milestones despite having nusinersen, and it is unclear what the relationship is between improvements in motor function and a long term survival benefit.<sup>2</sup> Nusinersen is recommended as an option for treating SMA only if people have pre-symptomatic SMA, or SMA types 1, 2 or 3.<sup>2</sup> This

recommendation is narrower than the full marketing authorization in the U.K. because current evidence does not address use of nusinersen in Type 0 or Type 4 SMA.<sup>2</sup>

The NICE Managed Care Access agreement entry criteria include:<sup>30</sup>

- No permanent ventilation ( $\geq 16$  hours/day for 21 consecutive days in the absence of acute reversible infection)/ tracheostomy requirement at baseline
- Intrathecal injection must be technically feasible in the opinion of the treating clinician and not contraindicated
- Must not be type IV SMA patient i.e. must not have symptom onset at or after 19 years of age
- Must not be type 0 SMA patient

#### Drug Effectiveness Review Project 2019: Clinical Evidence Use of Onasemnogene Apeparovvec in Treating Spinal Muscular Atrophy

In August 2019 the Drug Effectiveness Review Project (DERP) completed a systematic review focused clinical evidence for the use of onasemnogene abeparovvec in treating SMA.<sup>3</sup> The literature search was conducted through June 2019. In addition, DERP authors interviewed representatives from AveXis and Biogen, the manufacturers of Zolgensma<sup>®</sup> and Spinraza<sup>®</sup>, respectively. One published study that reported on effectiveness and harms of onasemnogene abeparovvec and 6 unpublished studies were identified. All studies were uncontrolled interventional studies or had indirect comparisons.<sup>3</sup> No studies involved a head-to-head comparison of nusinersen with onasemnogene abeparovvec. The published and unpublished literature includes samples of participants with SMA type 1 and 2 and presymptomatic SMA.<sup>3</sup> Six ongoing studies with expected completion dates ranging from November 2019 to December 2033 were also identified.<sup>3</sup> Five of the 6 ongoing studies have preliminary data.<sup>3</sup> The largest estimated sample consists of 33 participants.<sup>3</sup> SMA type 1 is being studied in 4 ongoing studies and SMA type 2 and presymptomatic SMA are being evaluated in 1 study each.<sup>3</sup> One ongoing study (STRONG) is evaluating the intrathecal administration of onasemnogene abeparovvec; all others (including the published evidence) are evaluating IV administration of onasemnogene abeparovvec.<sup>3</sup> No ongoing or planned head-to-head studies and none evaluating the effectiveness and harms of nusinersen after infusion of onasemnogene abeparovvec were identified.<sup>3</sup>

The START trial (NCT 02122952) enrolled patients with genetically confirmed diagnosis of SMA1 with homozygous SMN1 exon 7 deletions and two copies of SMN2.<sup>5</sup> This study was rated as poor quality because it lacked a control group or a direct control group (i.e., concurrently selected in the same source population), precluding determining with confidence that the intervention was causing the outcome.<sup>3</sup> Furthermore the investigators and outcome assessors were unblinded to who received treatment.<sup>3</sup> Unblinding increases risk of bias because the outcome assessors will be completing instruments, such as the CHOP-INTEND, knowing the participants is being treated.<sup>3</sup> The sample size of the study was also very small (15 participants) and industry was involved in funding and conducting the study, which has been shown to introduce bias.<sup>3</sup> However, an independent data and safety monitoring board (DSMB) was used.<sup>3</sup> An independent DSMB generally provides oversight of study data and an objective determination of adverse events and serious harms.<sup>3</sup>

Two years after infusion of onasemnogene abeparovvec, all participants in the high-dose group (n = 12) were alive and none required permanent ventilation.<sup>5</sup> However, about half of the sample required noninvasive ventilation.<sup>5</sup> Nearly all participants (11 of 12; 92%) achieved motor milestones; the following were potentially the most clinically important: 2 of 12 participants (17%) achieved the ability to stand with assistance and 2 of 12 (17%) achieved the ability to walk independently.<sup>5</sup> At baseline, average CHOP-INTEND scores were 16.3 (low-dose group) and 28.2 (high-dose group).<sup>5</sup> The maximum score of CHOP-INTEND is 64. In the high-dose group, CHOP-INTEND scores, on average, improved by 9.8 and 15.4 points from baseline to 1 and 3 months, respectively.<sup>3</sup> By the study cutoff, average increases in CHOP-INTEND scores were 7.7 in the low-dose group and 24.6 points in the high-dose group.<sup>3</sup>

The only adverse event that the authors believed to be treatment-related was elevated serum aminotransferase levels (4 of 12; 33%), which was managed with prednisolone.<sup>3</sup> One patient had up to 35 times the upper limit of the normal range for alanine aminotransferase (ALT) and 37 times the upper limit of the normal range for aspartate aminotransferase (AST).<sup>3</sup> Similar to other instances of elevated serum aminotransferase levels, this issue was resolved with prednisolone.<sup>3</sup>

Key DERP conclusions include:

- Based on indirect comparisons and assumed natural history of SMA, onasemnogene abeparvovec appears to improve survival, increase motor function and achievement of motor milestones in patients with SMA type 1.<sup>3</sup>
- Unpublished studies of presymptomatic SMA showed improvements in motor function and achievement of motor milestones; however, the validity of these findings is uncertain because no control group was used. The 1 unpublished study of SMA type 2, which tested intrathecally administered onasemnogene abeparvovec, also showed improvements in achievement of motor milestones and a slight reduction in liver-related adverse events relative to studies of intravenous (IV) administration of onasemnogene abeparvovec.<sup>3</sup>
- The main harm related to treatment with onasemnogene abeparvovec was elevated serum aminotransferase levels, potentially indicating liver or muscle injury.<sup>3</sup> This issue was resolved with use of corticosteroids. Two patients who received onasemnogene abeparvovec died during the follow-up period. The study authors believed that one death was unrelated to treatment, and reported uncertainty about the cause of the other death.<sup>3</sup>
- Concerns about this limited body of evidence include the small number of individuals studied, uncontrolled study designs, uncertain long-term benefits and harms, and the long-term durability of onasemnogene abeparvovec because it does not self-replicate.<sup>3</sup>
- AveXis representatives stated that there is not a biologically plausible reason to use nusinersen after infusion of onasemnogene abeparvovec.<sup>3</sup> Biogen representatives noted that use of nusinersen after infusion of onasemnogene abeparvovec has not been studied and have stated that using nusinersen after onasemnogene abeparvovec should be a decision between a patient and provider.<sup>3</sup> AveXis and Biogen have no current plans to study the effectiveness and harms of using nusinersen after infusion of onasemnogene abeparvovec.<sup>3</sup>

### Randomized Controlled Trials

A total of 74 citations were manually reviewed from the initial literature search. After further review, 73 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in **Table 2** below. The full abstract is included in **Appendix 3**.

**Table 2. Summary of Pivotal Study for Nusinersen**

Study	Comparison	Population	Primary Outcome	Results
Mercuri et al. <sup>31</sup>  CHERISH  Phase 3 DB, PC, MC, RCT  N=126	1. 12 mg nusinersen administered intrathecal by lumbar puncture days 1, 29, 85, and 274  2. Sham procedure on days 1, 29, 85, and 274	-Genetic documentation of 5q SMA homozygous gene deletion, homozygous mutation, or compound heterozygote -Onset of clinical signs and symptoms consistent with SMA at < 6 months of age -Males and females 2 to 12 years of age	Change from baseline in HFMSE score at 15 months	Change in HFSME score from baseline to month 15 1. +4 2. -1.9 LSMD = 5.9 95% CI 3.7 to 8.1 P<0.001  <i>Favors nusinersen over sham procedure</i>

	Over 9 months with 6 month follow up	-Could sit independently, but has never had the ability to walk independently ---Motor Function Score (HFMSE) $\geq 10$ and $\leq 54$ at screening		
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Abbreviations: HFSME = Hammersmith Functional Motor Scale; LSMD = least squares mean difference

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## **New Drug Evaluation: Onasemnogene abeparvovec (Zolgensma®)**

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

Onasemnogene abeparvovec (Zolgensma®) is an adeno-associated viral serotype 9 (AAV9) vector-based gene therapy indicated for the treatment of pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the SMN1 gene.<sup>6</sup> The AAV9 vector is an ideal method of administering gene therapy because it has rapid onset of transgene expression, can cross the blood-brain barrier, is small in size with a simple structure, and has low immunogenicity.<sup>4</sup> Onasemnogene abeparvovec therapy is designed to deliver a copy of the SMN gene to motor neurons, which restores the ability of these cells to produce SMN protein. The safety and effectiveness of repeated administration of onasemnogene abeparvovec have not been evaluated. In addition, its use in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been studied.<sup>6</sup> Onasemnogene abeparvovec was granted breakthrough therapy designation after the FDA fast-tracked a priority review of this treatment.<sup>4</sup> Onasemnogene abeparvovec also received orphan drug designation, which provides incentives to encourage the development of drugs for rare diseases.<sup>4</sup> The FDA also awarded the manufacturer a rare pediatric disease priority review voucher, under a program intended to encourage the development of new drugs and biological products for the prevention and treatment of certain rare pediatric diseases.<sup>4</sup> The product is shipped frozen and supplied as a customized kit to meet individualized weight based dosing requirements for each patient.

### **Clinical Efficacy:**

The FDA approval of onasemnogene abeparvovec was based on data from an ongoing Phase 3 clinical trial (STR1VE) and a completed Phase 1 clinical trial (START).<sup>4,5</sup> Efficacy was established based on survival, and achievement of developmental motor milestones such as sitting without support. Survival was defined as time from birth to either death or permanent ventilation. Permanent ventilation was defined as requiring invasive ventilation (tracheostomy), or respiratory assistance for 16 or more hours per day (including noninvasive ventilatory support) continuously for 14 or more days in the absence of an acute reversible illness, excluding perioperative ventilation. Efficacy was also supported by assessments of ventilator use, nutritional support and scores on the CHOP-INTEND scale.

The START trial (NCT 02122952) enrolled patients with genetically confirmed diagnosis of SMA1 with homozygous SMN1 exon 7 deletions and two copies of SMN2. Patients with a c.859G→C exon 7 mutation of SMN2 were excluded from the trial as this mutation is believed to be associated with a milder clinical phenotype.<sup>5</sup> Three patients were enrolled in a low-dose cohort and 12 patients in a high-dose cohort.<sup>5</sup> Onasemnogene abeparvovec was administered as a single-dose intravenous infusion in an open-label, single-arm study design. At the time of treatment, the mean age of patients in the low-dose cohort was 6.3 months and 3.4 months in the high-dose cohort.<sup>5</sup> At baseline, average CHOP-INTEND scores were 16.3 (low-dose group) and 28.2 (high-dose group).<sup>5</sup> The dosage received by patients in the low-dose cohort was approximately one-third of the dosage received by patients in the high-dose cohort. Follow-up was conducted on days 7, 14, 21, and 30 followed by monthly visits through 12 months post-dosing, and then every three months through two years post-dosing. The primary endpoint was safety and the secondary endpoints were efficacy based on duration of survival and achievement of normal motor milestones. Due to serum aminotransferase elevations in 1 patient in the low dose cohort, the protocol was amended so that all subsequent patients started oral prednisolone 1 mg/kg/day, 24 hours before the administration of onasemnogene abeparvovec, and continued oral corticosteroids for 30 days.<sup>5</sup> No patients in the low-dose group achieved any of the normal motor milestones, and 1 became dependent on ventilatory support at after 24 months of follow-up.<sup>5</sup> The high-dose group had better results at 24 months: 9 of the 12 patients (75%) were able to sit without support for at least 30 seconds, and 2 (17%) were able to crawl, pull to stand, and walk independently.<sup>5</sup> By the study cutoff, average increases in CHOP-INTEND scores were 7.7 in the low-dose group and 24.6 points in the high-dose group.<sup>5</sup> All patients in both cohorts were alive and at least 20 months of age after 24 months of the trial.<sup>5</sup> The precise dosages of onasemnogene abeparvovec received by

patients in the START trial are unclear due to a change in the method of measuring onasemnogene abeparvovec concentration and decreases in the concentration of stored onasemnogene abeparvovec over time.<sup>4</sup> In subsequent trials, the onasemnogene abeparvovec dose was directly measured by a validated and more precise droplet digital polymerase chain reaction method.<sup>4</sup>

The START trial was a poor quality trial due to its small sample size, single arm, open-label study design and significant differences in baseline characteristics between the low dose and high dose cohorts. Investigators were not blinded to treatment, which increased the risk of bias when completing motor function assessments such as the CHOP-INTEND instrument. More details about the Phase 1 START trial are presented in **Table 5**.

STRIVE, an ongoing, open-label, single-arm phase 3 study (NCT 03505099), is currently evaluating patients with infantile-onset SMA using available natural history data as a control.<sup>4</sup> The data from this trial has not been published, so details about this trial were obtained from the FDA approval summary report.<sup>4</sup> All patients recruited for the study had genetically confirmed bi-allelic SMN1 gene deletions, two copies of the SMN2 gene, and experienced onset of clinical symptoms consistent with SMA before 6 months of age.<sup>4</sup> Based on historical categorization of SMA, many of the patients enrolled would have SMA type 1. As in the START trial, onasemnogene abeparvovec was delivered as a single-dose intravenous infusion; however the dose was increased to  $1.1 \times 10^{14}$  vg per kg for all subjects based on poor results from the low dose cohort in the START trial.<sup>4</sup> Sixteen sites in the United States are participating in this trial. STRIVE has enrolled 21 patients (10 male and 11 female) with a mean age of 3.9 months (range 0.5 to 5.9 months) at the start of treatment.<sup>4</sup> The mean CHOP-INTEND score at baseline was 31.0 (range 18 to 47).<sup>4</sup> The 2 primary efficacy endpoints are survival at 14 months of age and the proportion of patients achieving the milestone of sitting without support for least 30 seconds at 18 months of age.<sup>4</sup> Survival was defined as previously described. By the time of data cutoff, 13 of the 19 patients continuing in the trial reached 14 months of age without permanent ventilation.<sup>4</sup> Ten of the 21 patients (47%) achieved the ability to sit without support for 30 seconds.<sup>4</sup> Based on the natural history of the disease, patients who met the study entry criteria would not be expected to attain the ability to sit without support, and only approximately 25% of these patients would be expected to survive beyond 14 months of age.<sup>4</sup>

SPR1NT is another ongoing Phase 3 trial currently being conducted in the U.S., Canada, Europe, Australia and Asia in the treatment of patients with presymptomatic SMA possessing 2 or 3 copies of SMN2. As of March 2019, 18 patients had been enrolled and treated in this study. An additional phase 1 trial (STRONG) is evaluating 3 different doses of intrathecal injection of onasemnogene abeparvovec as preliminary results indicate less liver toxicity with this route of administration.<sup>3</sup>

#### **Clinical Safety:**

Adverse effects associated with the use of onasemnogene abeparvovec during clinical trials included elevated aminotransferases and vomiting.<sup>6</sup> The incidence of adverse effects that occurred more frequently than 5% are outlined in **Table 3**. Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, and increases in cardiac troponin-I levels were observed at different time points after onasemnogene abeparvovec infusion.<sup>4</sup> The clinical importance of these findings is not known as there were no clinical cardiac sequelae.<sup>4</sup>

**Table 3.** Adverse Reactions Following Treatment with Onasemnogene Abeparvovec (n=44)<sup>6</sup>

<b>Adverse Reactions</b>	<b>Number of Patients (%)</b>
Elevated aminotransferase	12 (27.3%)
Vomiting	3 (6.8%)

The onasemnogene abeparvovec manufacturer label contains a boxed warning about the risk of acute serious liver injury and elevated aminotransferases which can occur after infusion.<sup>6</sup> Patients with pre-existing liver impairment may be at higher risk for hepatic injury. Prior to infusion, liver function of all patients should be assessed by clinical examination and laboratory testing (e.g., hepatic aminotransferases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], total bilirubin, and prothrombin time).<sup>6</sup> All patients should receive systemic corticosteroids starting 1 day before onasemnogene abeparvovec infusion and continuing up to 60 days after infusion.<sup>6</sup> Liver function should be monitored for at least 3 months after infusion.<sup>6</sup>

In the onasemnogene abeparvovec clinical trials, patients were required to have baseline anti-AAV9 antibody titers of  $\leq 1:50$ , measured using an enzyme-linked immunosorbent assay (ELISA).<sup>4</sup> The safety and efficacy of ZOLGENSMA in patients with anti-AAV9 antibody titers above 1:50 have not been evaluated.<sup>4</sup> Following onasemnogene abeparvovec infusion, increases from baseline in anti-AAV9 antibody titers occurred in all patients. In the completed Phase 1 clinical trial, anti-AAV9 antibody titers reached at least 1:102,400 in every patient, and titers exceeded 1:819,200 in most patients.<sup>4</sup> High anti-AAV9 antibody titers resulting from the initial onasemnogene abeparvovec infusion are expected to preclude the possibility of re-administration of AAV9 vector-based gene therapy.<sup>4</sup>

Currently, there is insufficient data to establish safety and insufficient evidence for efficacy, although observational data is encouraging. The manufacturer of onasemnogene abeparvovec plans to conduct long-term follow up studies to collect safety and efficacy information on patients who participate in clinical trials for this gene therapy. Safety monitoring will be conducted for 15 years with in-person yearly visits for the first 5 years followed by yearly telephonic contact for 10 years.<sup>4</sup>

**Look-alike / Sound-alike Error Risk Potential:** No issues identified

**Comparative Endpoints:**

Clinically Meaningful Endpoints:

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

Primary Study Endpoint:

- 1) Survival at 14 months of age
- 2) Ability to sit unsupported  $\geq 30$  seconds by 18 months of age

**Table 4. Pharmacology and Pharmacokinetic Properties.**

Parameter	
Mechanism of Action	Gene replacement therapy
Oral Bioavailability	N/A: administered via intravenous infusion
Distribution and Protein Binding	Highest vector DNA levels detected in the liver
Elimination	Vector DNA detected in saliva, urine and stool after infusion
Half-Life	N/A
Metabolism	N/A

Abbreviations: DNA = deoxyribonucleic acid; N/A = not applicable

**Table 5. Comparative Evidence Table.**

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Mendell <sup>5</sup> START trial NCT02122952  Phase 1, OL  N=15	1. Low dose: onasemnogene abeparvec 6.7 x 10 <sup>13</sup> vg per kg x 1 IV infusion  2. High dose: onasemnogene abeparvec 2.0 x 10 <sup>14</sup> vg per kg x 1 IV infusion  2 year study with long-term safety follow-up	<u>Demographics:</u> 1. Mean age Low dose: 6.3 months High dose: 3.4 months 2. Mean weight: 5.7 to 6.6 kg 3. Gender: female 58% 3. Race: White: 92% 4. Baseline CHOP- INTEND scores- Low dose: 16.3 High dose:28.2  <u>Key Inclusion Criteria:</u> 1. Genetically confirmed diagnosis of SMA1 with homozygous SMN1 exon 7 deletions and 2 copies of SMN2 2. Onset of disease from birth to 6 months 3. Hypotonia assessed by TIMP and 2 SD below the mean  <u>Key Exclusion Criteria:</u> 1. Active viral infection 2. Use of ventilator support 3. Anti-AAV9 antibody titer >1:50	<u>ITT:</u> 1. 3 2. 12  <u>PP:</u> 1. 3 2. 12  <u>Attrition:</u> 1. 0 2. 0	<u>Primary Endpoint:</u> 1.Safety: Number of patients who developed unacceptable toxicity (i.e.; 1 Grade 3 or 2 Grade 2 treatment-related toxicities) 1. 1 (33%) 2. 3 (25%)  <u>Secondary Endpoints:</u> 1.Survival at 24 months 1. 3 (100%) 2. 12 (100%)  2. Sitting without support for ≥ 30 seconds 1. 0 (0%) 2. 9 (75%)  3.Need for permanent ventilator assistance (16 hours per day) at 20 months of age 1. 1 (33%) 2. 0 (0%)  3.Mean increase in CHOP INTEND score from baseline at 25 months 1. 7.7 points 2. 24.6 points p-value and CI NR	NA	<u>Any AE</u> 1. 3 (100%) 2. 12 (100%)  <u>Serious AE</u> 1. 3 (100%) 2. 10 (83%)  <u>Treatment associated-AE</u> 1. 1 (33%) 2. 3 (25%)  p-value and CI NR for all	NA	<b>Risk of Bias (low/high/unclear):</b> <u>Selection Bias:</u> High. Trial was not randomized. <u>Performance Bias:</u> High. Investigators not blinded to treatment. <u>Detection Bias:</u> High. Open label, single arm trial design. <u>Attrition Bias:</u> Low. No patients withdrew from trial and at 24 month follow-up all patients were alive. <u>Reporting Bias:</u> Low. Trial protocol available in supplementary materials. <u>Other Bias:</u> Unclear. Sponsored by the manufacturer AveXis, who provided data management and statistical analysis. Several authors received financial support from AveXis either through grants or personal fees.  <b>Applicability:</b> <u>Patient:</u> Patients with genetically confirmed diagnosis of SMA1 with homozygous SMN1 exon 7 deletions and 2 copies of SMN2. Not clear if this was limited to SMA type 1 patients. <u>Intervention:</u> Dose finding and safety assessment in a phase 1 trial. <u>Comparator:</u> Historical controls <u>Outcomes:</u> Safety is the primary endpoint. Secondary endpoints included survival and motor achievements. <u>Setting:</u> Single site: Nationwide Children’s Hospital in Columbus, Ohio

		4. Patients with c.859G→C disease modifier in exon 7 of SMN2						
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Abbreviations : AE = adverse event; ARR = absolute risk reduction; CHOP-INTEND = Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI = confidence interval; ITT = intention to treat; IV = intravenous; kg = kilogram; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; OL = open-label; PP = per protocol; SD = standard deviations; SMA = spinal muscular atrophy; SMN = survival motor neuron; TIMP = Test for Infant Motor Performance; vg = vector genomes

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## Appendix 1: Prescribing Information Highlights

### HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**ZOLGENSMA® (onasemnogene abeparvovec-xioi)**

**Suspension for intravenous infusion**

**Initial U.S. Approval: 2019**

#### **WARNING: ACUTE SERIOUS LIVER INJURY**

See full prescribing information for complete boxed warning.

- Acute serious liver injury and elevated aminotransferases can occur with ZOLGENSMA. (5.1)
- Patients with pre-existing liver impairment may be at higher risk. (8.6)
- Prior to infusion, assess liver function of all patients by clinical examination and laboratory testing (e.g., hepatic aminotransferases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], total bilirubin, and prothrombin time). Administer systemic corticosteroid to all patients before and after ZOLGENSMA infusion. Continue to monitor liver function for at least 3 months after infusion (2.1) (2.3).

### INDICATIONS AND USAGE

ZOLGENSMA (onasemnogene abeparvovec-xioi) is an adeno-associated virus vector-based gene therapy indicated for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the *survival motor neuron 1 (SMN1)* gene. (1)

Limitation of Use:

- The safety and effectiveness of repeat administration of ZOLGENSMA have not been evaluated. (1, 6.2)
- The use of ZOLGENSMA in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been evaluated. (1, 14)

### DOSAGE AND ADMINISTRATION

ZOLGENSMA is for single-dose intravenous infusion only (2).

- The recommended dosage of ZOLGENSMA is  $1.1 \times 10^{14}$  vector genomes (vg) per kg of body weight.
- Administer ZOLGENSMA as an intravenous infusion over 60 minutes. (2.1, 2.3)
- Starting one day prior to ZOLGENSMA infusion, administer systemic corticosteroids equivalent to oral prednisolone at 1 mg/kg

of body weight per day for a total of 30 days. At the end of the 30-day period of systemic corticosteroid treatment, check liver function by clinical examination and by laboratory testing. For patients with unremarkable findings, taper the corticosteroid dose over the next 28 days. If liver function abnormalities persist, continue systemic corticosteroids (equivalent to oral prednisolone at 1 mg/kg/day) until findings become unremarkable, and then taper the corticosteroid dose over the next 28 days. Consult expert(s) if patients do not respond adequately to the equivalent of 1 mg/kg/day oral prednisolone. (2.1)

### DOSAGE FORMS AND STRENGTHS

ZOLGENSMA is a suspension for intravenous infusion, supplied as single-use vials.

ZOLGENSMA is provided in a kit containing 2 to 9 vials, as a combination of 2 vial fill volumes (either 5.5 mL or 8.3 mL). All vials have a nominal concentration of  $2.0 \times 10^{13}$  vector genomes (vg) per mL. Each vial of ZOLGENSMA contains an extractable volume of not less than either 5.5 mL or 8.3 mL.

### CONTRAINDICATIONS

None

### WARNINGS AND PRECAUTIONS

- Thrombocytopenia: Monitor platelet counts before ZOLGENSMA infusion, and weekly for the first month and then every other week for the second and third month until platelet counts return to baseline. (2.3, 5.2)
- Elevated Troponin-I: Monitor troponin-I before ZOLGENSMA infusion, and weekly for the first month and then monthly for the second and third month until troponin-I level returns to baseline. (2.3, 5.3)

### ADVERSE REACTIONS

The most common adverse reactions (incidence  $\geq 5\%$ ) were elevated aminotransferases and vomiting. (6)

To report SUSPECTED ADVERSE REACTIONS, contact AveXis at 1-833-828-3947 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### USE IN SPECIFIC POPULATIONS

Pediatric use: Use of ZOLGENSMA in premature neonates before reaching full term gestational age is not recommended because concomitant treatment with corticosteroids may adversely affect neurological development. Delay ZOLGENSMA infusion until full-term gestational age is reached. (8.4)

See 17 for PATIENT COUNSELING INFORMATION

## Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to July Week 4 2019 and Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to July 31, 2019

1. Muscular Atrophy, Spinal	2436
2. Oligonucleotides, Antisense/	9299
3. nusinersen.mp	114
4. AVXS-101.mp	7
5. 2 or 3 or 4	9405
5. 1 and 5	94
6. limit 5 to (english language and humans	79

## Appendix 3: Abstract from Randomized Clinical Trial

**Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. *N Engl J Med.* 2018;378(7):625-635.**

**Background:** Nusinersen is an antisense oligonucleotide drug that modulates pre-messenger RNA splicing of the survival motor neuron 2 (*SMN2*) gene. It has been developed for the treatment of spinal muscular atrophy (SMA).

**Methods:** We conducted a multicenter, double-blind, sham-controlled, phase 3 trial of nusinersen in 126 children with SMA who had symptom onset after 6 months of age. The children were randomly assigned, in a 2:1 ratio, to undergo intrathecal administration of nusinersen at a dose of 12 mg (nusinersen group) or a sham procedure (control group) on days 1, 29, 85, and 274. The primary end point was the least-squares mean change from baseline in the Hammersmith Functional Motor Scale–Expanded (HFMSE) score at 15 months of treatment; HFMSE scores range from 0 to 66, with higher scores indicating better motor function. Secondary end points included the percentage of children with a clinically meaningful increase from baseline in the HFMSE score ( $\geq 3$  points), an outcome that indicates improvement in at least two motor skills.

**Results:** In the prespecified interim analysis, there was a least-squares mean increase from baseline to month 15 in the HFMSE score in the nusinersen group (by 4.0 points) and a least-squares mean decrease in the control group (by  $-1.9$  points), with a significant between-group difference favoring nusinersen (least-squares mean difference in change, 5.9 points; 95% confidence interval, 3.7 to 8.1;  $P < 0.001$ ). This result prompted early termination of the trial. Results of the final analysis were consistent with results of the interim analysis. In the final analysis, 57% of the children in the nusinersen group as compared with 26% in the control group had an increase from baseline to month 15 in the HFMSE score of at least 3 points ( $P < 0.001$ ), and the overall incidence of adverse events was similar in the nusinersen group and the control group (93% and 100%, respectively).

**Conclusions:** Among children with later-onset SMA, those who received nusinersen had significant and clinically meaningful improvement in motor function as compared with those in the control group. (Funded by Biogen and Ionis Pharmaceuticals; CHERISH ClinicalTrials.gov number, [NCT02292537](https://clinicaltrials.gov/ct2/show/study/NCT02292537) opens in new tab.)

Appendix 4: Proposed Prior Authorization Criteria

**Onasemnogene abeparvovec (Zolgensma®)**

**Goal(s):**

- Ensure utilization of onasemnogene abeparvovec in appropriate SMA (spinal muscular atrophy) populations with demonstrated efficacy.

**Length of Authorization:**

- Once in a lifetime dose

**Requires PA:**

- Onasemnogene abeparvovec

**Covered Alternatives:**

- Current PMPDP preferred drug list per OAR 410-121-0030 at [www.orpdl.org](http://www.orpdl.org)
- Searchable site for Oregon FFS Drug Class listed at [www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	<b>Yes:</b> Go to #4	<b>No:</b> Pass to RPh. Deny; not funded by the OHP.
4. Is the medication prescribed by or in consultation with a physician who specializes in treatment of spinal muscular atrophy?	<b>Yes:</b> Go to # 5	<b>No:</b> Pass to RPh. Deny; medical appropriateness
5. Is the patient less than 2 years of age?	<b>Yes:</b> Go to # 6	<b>No:</b> Pass to RPh. Deny; medical appropriateness

## Approval Criteria

<p>6. Has the Spinal Muscular Neuropathy (SMA) diagnosis been confirmed to document the Spinal Motor Neuron (SMN)1 gene is missing or not functional by genetic documentation of :</p> <ul style="list-style-type: none"> <li>• Homozygous gene deletion or mutation of SMN1 gene (e.g., homozygous deletion of exon 7 at locus 5q13); OR</li> <li>• Compound heterozygous mutation of SMN1 gene (e.g., deletion of SMN1 exon 7 [allele 1] and mutation of SMN1 (allele 2) AND</li> <li>• Fewer than 4 copies of SMN2</li> </ul>	<p><b>Yes:</b> Go to # 7</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness</p>
<p>7. Did the SMA symptoms (hypotonia and muscles weakness) begin when the child was less than 6 months of age?</p>	<p><b>Yes:</b> Go to # 8</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness</p>
<p>8. Does the patient have advanced SMA (complete paralysis of the limbs, permanent ventilator dependence)?</p> <p>*Note FDA label states efficacy has not been established in these patients</p>	<p><b>Yes:</b> Pass to RPh. Deny; medical appropriateness</p>	<p><b>No:</b> Go to # 9</p>
<p>9. Has baseline motor ability been documented via:</p> <ul style="list-style-type: none"> <li>• Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) OR</li> <li>• Assessment of motor function developmental milestones by physical therapist OR</li> <li>• Hammersmith Infant Neurological Examination (HINE) Section 2 motor milestone score</li> <li>• Gross Motor Function Measure OR</li> <li>• Hammersmith Functional Motor Scale (HFMS) OR</li> <li>• Modified/Expanded Hammersmith Functional Motor Scale</li> </ul>	<p><b>Yes:</b> Go to # 10</p>	<p><b>No:</b> Pass to RPh. Deny; medical appropriateness</p>

<b>Approval Criteria</b>		
10. Has the child been screened for viral infection?	<b>Yes:</b> Go to # 11	<b>No:</b> Pass to RPh. Deny; medical appropriateness
11. Is the baseline adeno-associate virus vector (AAV) 9 antibody titer < 1:50?  Note: Efficacy has not been established in this population and high anti-AAV9 antibody titers are expected to limit efficacy of therapy.	<b>Yes:</b> Go to # 12	<b>No:</b> Pass to RPh. Deny; medical appropriateness
12. Has a baseline platelet count been obtained?	<b>Yes:</b> Go to # 13	<b>No:</b> Pass to RPh. Deny; medical appropriateness
13. Have baseline liver function tests (AST, ALT, total bilirubin, and PT) been obtained?	<b>Yes:</b> Go to # 14	<b>No:</b> Pass to RPh. Deny; medical appropriateness
14. Has baseline troponin-I been obtained?	<b>Yes:</b> Go to # 15	<b>No:</b> Pass to RPh. Deny; medical appropriateness
15. Does the patient has a prescription on file for 30 days of on oral corticosteroid to begin one day before infusion of onasemnogene abeparvovec?	<b>Yes:</b> Go to # 16	<b>No:</b> Pass to RPh. Deny; medical appropriateness
16. Has the patient received nusinersen?	<b>Yes:</b> Pass to RPh. Deny; medical appropriateness	<b>Yes:</b> Go to # 17

## Approval Criteria

17. Is there attestation that the patient and provider will comply with case management required by the Oregon Health Authority?

Case management includes follow-up assessment to assess treatment success, monitoring, and adverse events.

**Yes:** Approve for one time infusion

**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 9/19 (DM)  
Implementation: TBD

## Nusinersen

### **Goal(s):**

- Approve nusinersen for funded OHP conditions supported by evidence of benefit (e.g. Spinal Muscular Atrophy)

### **Length of Authorization:**

- Up to 8 months for initial approval and up to 12 months for renewal.

### **Requires PA:**

- Nusinersen (billed as a pharmacy or physician administered claim)

### **Covered Alternatives:**

- Current PMPDP preferred drug list per OAR 410-121-0030 at [www.orpdl.org](http://www.orpdl.org)
- Searchable site for Oregon FFS Drug Class listed at [www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

## Approval Criteria

1. What diagnosis is being treated?

Record ICD-10 code. Go to #2

Approval Criteria		
2. Is this a request for continuation of therapy?	<b>Yes:</b> Go to <b>Renewal Criteria</b>	<b>No:</b> Go to #3
3. Does the patient have type 1, 2 or 3 Spinal Muscular Atrophy documented by genetic testing and at least 2 copies of the SMN2 gene?	<b>Yes:</b> Go to #4	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
4. Is a baseline motor assessment available such as one of the following functional assessment tools: <ul style="list-style-type: none"> <li>• Hammersmith Infant Neurological Examination (HINE-2)</li> <li>• Hammersmith Functional Motor Scale (HFSME)</li> <li>• Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND)</li> <li>• Upper Limb Module (ULM)</li> <li>• 6-Minute Walk Test</li> </ul>	<b>Yes:</b> Go to #5	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
5. Is the patient ventilator dependent (using at least 16 hours per day on at least 21 of the last 30 days)?  Note: This assessment does not apply to patients who require ventilator assistance	<b>Yes:</b> Pass to RPh. Deny; medical appropriateness.	<b>No:</b> Go to #6.
<u>6. Has the patient received onasemnogene abeparvovec (Zolgensma)?</u>	<u><b>Yes:</b> Pass to RPh. Deny; medical appropriateness.</u>	<u><b>No:</b> Go to #7.</u>

## Approval Criteria

7. Is the drug being prescribed by a pediatric neurologist or a provider with experience treating spinal muscular atrophy?

**Yes:** For initial approval, approve 5 doses over 8 months.

**No:** Pass to RPh. Deny; medical appropriateness.

## Renewal Criteria

1. Has the patient's motor function improved as demonstrated by:

- Improvement from baseline motor function score documented within one month of renewal request AND
- More areas of motor function improved than worsened

**Yes:** Approve for 12 months

**No:** Pass to RPh; Deny; medical appropriateness.

P&T Review: [9/19 \(DM\)](#); [7/17 \(DM\)](#); [3/17](#)  
Implementation: [TBD](#); [9/1/17](#); [5/17](#)