Treatment for Spinal Muscular Atrophy

Policy Number: 5.01.28
Last Review: 8/1/2019
Origination: 8/2019
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Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Nusinersen for Spinal Muscular Atrophy when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered

Initial Treatment

Nusinersen may be considered medically necessary if all the following conditions are met:
1. Diagnosis of SMA confirmed by genetic testing demonstrating bi-allelic mutations in the survival motor neuron 1 (SMN1) gene (examples below):
   a. deletion of both copies of the SMN1 gene OR
   b. identification of pathogenic variant(s) in both copies of the SMN1 gene.
2. If patient is symptomatic, documentation of a genetic test confirms 2, 3 or 4 copies of the SMN2 gene; OR If patient is asymptomatic, documentation of a genetic test confirms minimum of 2 but less than 4 copies of the SMN2 gene.
3. Initial approval is for 1 year, limited to the Food and Drug Administration-approved dosing of 12 mg (5 mL) administered intrathecally per treatment with 4 loading doses; the first 3 loading doses should be administered at 14-day intervals. The fourth loading dose should be administered 30 days after the third dose. A maintenance dose should be administered once every 4 months thereafter; AND
4. The patient is not concurrently enrolled in a clinical trial for any experimental therapy for SMA.
5. Prescribed by a neurologist with expertise in treating SMA

Continuation of Treatment

Incremental reauthorization for nusinersen for 1 year may be considered medically necessary if the following conditions 1 and 2 are met:
1. The patient was previously approved for nusinersen based on criteria cited above
2. Documented evidence to support clinically meaningful improvement in motor milestones during previous treatment period.
Onasemnogene abeparvovec-xioi may be considered medically necessary if all of the following conditions are met:

1. Diagnosis of SMA confirmed by genetic testing demonstrating bi-allelic mutations in the survival motor neuron 1 (SMN1) gene (examples below):
   a. deletion of both copies of the SMN1 gene OR
   b. compound heterozygous mutations of the SMN1 gene (defined below):
      i. pathogenic variant(s) in both copies of the SMN1 gene
      ii. pathogenic variant in one copy and deletion of the second copy of the SMN1 gene.
2. Documentation of onset of symptoms consistent with clinical diagnosis of type I SMA less than 6 months of age.
3. Documentation of a genetic test confirms no more than 2 copies of the SMN2 gene.
4. Patient is less than 6 months of age at the time of infusion of onasemnogene abeparvovec-xioi.
5. Patient does not have advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence).
7. Prescribed by a neurologist with expertise in treating SMA.

When Policy Topic is not covered

Nusinersen is considered investigational for all other indications.

Repeat treatment or ante-partum use of onasemnogene abeparvovec-xioi is considered investigational.

Onasemnogene abeparvovec-xioi is considered investigational for all other indications.

Concurrent use of onasemnogene abeparvovec-xioi and nusinersen is considered investigational.

Considerations

Nusinersen

The recommended dose of nusinersen is 12 mg (5 mL) administered intrathecally. Treatment is initiated with 4 loading doses; the first 3 loading doses should be administered at 14-day intervals while the fourth loading dose is administered 30 days after the third loading dose. Maintenance doses should be administered once every 4 months thereafter.

Onasemnogene abeparvovec-xioi

The recommended dosage of onasemnogene abeparvovec-xioi is $1.1 \times 10^{14}$ vector genomes (vg) per kg of body weight. It should be administered as an intravenous infusion over 60 minutes. Systemic corticosteroids equivalent to oral prednisolone
at 1 mg/kg should be administered according to the FDA approved prescribing label.

FDA has issued a black-box warning for onasemnogene abeparvovec-xioi due to the risk of acute serious liver injury and elevated aminotransferases. Patients with pre-existing liver impairment may be at higher risk.

The FDA label states that “The safety and efficacy of ZOLGENSMA in patients with anti-AAV9 antibody titers above 1:50 have not been evaluated.” Baseline anti-AAV9 antibody testing is performed prior to infusion using. Retesting may be performed if anti-AAV9 antibody titers are reported as >1:50.

Liver function (clinical exam, AST, ALT, total bilirubin, prothrombin time), platelet counts and troponin-I levels should be monitored as per the prescribing label. Where feasible, patient’s vaccination schedule should be adjusted to accommodate concomitant corticosteroid administration prior to and following onasemnogene abeparvovec-xioi infusion.

Use of onasemnogene abeparvovec-xioi in premature neonates before reaching full term gestational age may not be recommended because concomitant treatment with corticosteroids may adversely affect neurological development.

Efficacy of onasemnogene abeparvovec-xioi in patients with c.859G>C variant in SMN2 gene has not been evaluated.

**SMN2 Copy Numbers**
For detail refer to Table 2 in the “Background” Section. Generally, the number of SMN2 gene copies is inversely related to the severity of spinal muscular atrophy. Higher numbers typically correlate with less severe disease. Among patients clinically diagnosed as type I SMA, 73% had 2 copies of SMN2, type II SMA patients 82% had 3 copies of SMN2 and type III SMA patients 51% had 3 and 46% had 4 copies of SMN2. Conversely, the probability that an unaffected child who has been tested after birth and has been found to carry a homozygous SMN1 deletion, the probability of developing type I SMA if the child has 1 or 2 copies of SMN2 is greater than 97%. Those with 3 copies of SMN2 have an 83% probability of developing type II SMA and those with 4 copies of SMN2 have an 84% probability of developing type III SMA.

Nusinersen is a modified antisense oligonucleotide that requires SMN2 gene for it to work. Efficacy of nusinersen has not been evaluated in patients with less than 2 copies of SMN2.

**Description of Procedure or Service**

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>- Who are presymptomatic with a genetic diagnosis</td>
<td>- Nusinersen</td>
<td>- Continued medical management</td>
<td>- Overall survival</td>
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<td></td>
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<td>- Change in disease</td>
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<tr>
<td>Individuals:</td>
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<tr>
<td>With type I (infantile-onset) spinal muscular atrophy</td>
<td>Nusinersen</td>
<td>Continued medical management (respiratory, digestive, and orthopedic support)</td>
<td>Overall survival, Change in disease status, Functional outcomes, Quality of life, Treatment-related mortality, Treatment-related morbidity</td>
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<tr>
<td>With types II or III spinal muscular atrophy</td>
<td>Nusinersen</td>
<td>Continued medical management (respiratory, digestive, and orthopedic support)</td>
<td>Overall survival, Change in disease status, Functional outcomes, Quality of life, Treatment-related mortality, Treatment-related morbidity</td>
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<tr>
<td>With type O spinal muscular atrophy</td>
<td>Nusinersen</td>
<td>Continued medical management (respiratory, digestive, and orthopedic support)</td>
<td>Overall survival, Change in disease status, Functional outcomes, Quality of life, Treatment-related mortality, Treatment-related morbidity</td>
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<tr>
<td>With type IV spinal muscular atrophy</td>
<td>Nusinersen</td>
<td>Continued medical management (respiratory, digestive, and orthopedic support)</td>
<td>Overall survival, Change in disease status, Functional outcomes, Quality of life, Treatment-related mortality, Treatment-related morbidity</td>
</tr>
<tr>
<td>With type I spinal muscular atrophy</td>
<td>Onasemnogene abeparvovec-xioi</td>
<td>Continued medical management (respiratory, digestive, and orthopedic support)</td>
<td>Overall survival, Change in disease status, Functional outcomes</td>
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</table>
Spinal muscular atrophy (SMA) is an inherited disorder caused by homozygous deletions or variants in the \( SMN1 \) gene. As a consequence of absent or low levels of SMN1 protein, the motor neurons in spinal cord degenerate, resulting in atrophy of the voluntary muscles of the limbs and trunk. Nusinersen is a synthetic antisense oligonucleotide designed to bind to a specific sequence in exon 7 of the SMN2 transcript causing the inclusion of exon 7 in the SMN2 transcript, leading to the production of full length functional SMN2 protein, which is very similar to SMN1. Onasemnogene abeparvovec-xioi is intended as a one-time gene replacement therapy designed to deliver a functional copy of the \( SMN1 \) gene to motor neuron cells of patients with SMA. Because motor neurons are nondividing cells, it is postulated that once the \( SMN1 \) gene is incorporated in the cells, it would be retained over time and potentially allow for long-term, sustained SMN protein expression.

**Nusinersen**

**Presymptomatic Patients with a Genetic Diagnosis of SMA and a Minimum of 2 but Less Than 4 Copies of SMN2**

For individuals who are presymptomatic with a genetic diagnosis of spinal muscular atrophy and a minimum of 2 but less than 4 copies of \( SMN2 \) who receive nusinersen, the evidence includes an open-label uncontrolled trial for which interim results have been reported. The relevant outcomes are overall survival (OS), change in disease status, morbid events, functional outcomes, quality of life.
After early initiation of nusinersen in 25 presymptomatic infantile SMA patients who were 14 months or older at the time of the analysis; 100% were alive, 100% achieved sitting without support, 88% achieved walking with assistance, and 68% achieved walking alone after 27 months of median follow-up. Early treatment resulted in the achievement of motor milestones among patients who were not likely to attain them without treatment. However, the data is limited for the durability of response and long-term evidence of safety and efficacy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Infantile-Onset or Type I SMA
For individuals who have type I (infantile-onset) SMA who receive nusinersen, the evidence includes two randomized, double-blind, controlled trial (results not yet reported for one) and a single-arm open-label study. The relevant outcomes are OS, change in disease status, morbid events, functional outcomes, QOL, and treatment-related mortality and morbidity. The largest phase 3 confirmatory, Assess the Efficacy and Safety of Nusinersen in Infants with SMA trial (n=121) showed clinically meaningful and statistically significant improvement in motor milestones, event-free survival, and OS that exceeded those seen in the control group, with an acceptable safety profile. The proportion of patients, who met the primary endpoint responder definition of achieving motor milestones, was 51% in the nusinersen arm compared with 0% in the sham-controlled arm. Further, the hazard ratio for event-free survival was 0.53 favoring nusinersen over sham-controlled. It is notable, however, that 50% of nusinersen-treated subjects did not achieve the primary endpoint motor milestone response. Only a small proportion of patients (6%) gained the ability to sit without assistance. On average, the mean motor milestone score in nusinersen-treated patients improved by three points over six months. Given the limited data on the durability of response, long-term safety, and lack of efficacy in a substantial number of patients continued risk-benefit assessment of long-term treatment with nusinersen is necessary. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Type II and III SMA
For individuals who have type II or III SMA who receive nusinersen, the evidence includes four single-arm studies and a double-blind, randomized controlled trial. The relevant outcomes are OS, change in disease status, morbid events, functional outcomes, QOL, and treatment-related mortality and morbidity. Efficacy findings from single-arm studies of type II and III SMA are difficult to interpret because these trials used a wide range of nusinersen doses and lacked control arms. The largest phase 3 confirmatory, Assess Clinical Efficacy and Safety of Nusinersen in Participants with Later-onset SMA trial (n=126) showed clinically meaningful and statistically significant improvement in motor milestones (measured using Hammersmith Functional Motor Scale–Expanded scores) that exceeded those seen in the control group (difference of 5.9 points favoring nusinersen over sham control, p<0.001). The respective proportion of patients with clinically meaningful improvements in Hammersmith scores greater than 3 points was 57% vs 26% (p<0.001). Multiple secondary endpoints also showed a consistency in treatment
effect favoring nusinersen over sham control. Given the limited data on the durability of response, long-term safety, and lack of efficacy in a substantial number of patients continued risk-benefit assessment of long-term treatment with nusinersen is necessary. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Type 0 or IV SMA
For individuals who have type 0 SMA or type IV SMA who receive nusinersen, no studies were identified. The relevant outcomes are a change in OS (type 0 only), disease status, morbid events, functional outcomes, QOL, and treatment-related mortality and morbidity. The evidence is insufficient to determine the effects of technology on health outcomes.

Onasemnogene Abeparvovec-Xioi

Infantile-Onset or SMA Type I
For individuals who have SMA type I (infantile-onset) who receive onasemnogene abeparvovec-xioi, the evidence includes a prospective cohort of 15 patients followed for 2 years. Relevant outcomes are overall survival, change in disease status, functional outcomes, quality of life, and treatment-related mortality and morbidity. In this single phase 1 study of symptomatic infants with 2 copies of SMN2 gene, 12 of 15 infants received the proposed therapeutic dose while 3 received the minimally effective dose. At the end of the 2-year follow-up, all 15 infants survived and none of the 12 patients who received the proposed therapeutic dose required permanent ventilation. All 12 patients also achieved at least 1 motor milestone, with 92% of those achieving scores greater than 40 on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (a score $>40$ is a favorable outcome). The FDA approval was based on a pooled analysis of 21 patients from the pivotal phase I and ongoing confirmatory phase III STRIVE-US trial. The observed treatment effect on survival, event-free survival and achievement of motor functions is beyond what is typical based on the known natural history of patients with SMA type I with two copies of SMN2. The available published data support a clinically meaningful durable treatment effect through 2 years. However, there is limited data to assess the long-term durability of treatment effect as well as safety related to adverse events that are rare or have delayed onset. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Presymptomatic Patients with a Diagnosis of SMA and Less Than 3 Copies of SMN2
For individuals who are presymptomatic with a genetic diagnosis of SMA and less than 3 copies of SMN2 who receive onasemnogene abeparvovec-xioi, the evidence includes a prospective cohort with a planned enrollment of 44 patients and a planned follow-up of 18 to 24 months. Relevant outcomes are overall survival, change in disease status, functional outcomes, quality of life, and treatment-related mortality and morbidity. The single prospective cohort study (SPRINT) is currently ongoing. As of March, 2019, 18 patients have been treated. The median
follow-up after treatment was 2.9 months (range 0.4 to 8.7). All 18 children were alive and “event free.” Among 8 patients with two copies of SMN2, all reportedly achieved age-appropriate motor milestones including 4 who could sit without support and 1 who could stand with assistance. Data was much more limited for patients with 3 copies of SMN2. However, early increases in mean Bayley-III Gross Motor score were observed. The evidence for presymptomatic SMA patients is currently evolving. The evidence is insufficient to determine the effects of technology on health outcomes.

**SMA Type II**
For individuals with SMA type II who receive intrathecal onasemnogene abeparvovec-xioi, the evidence includes a single prospective cohort study with a planned enrollment of 27 patients who are up to 60 months old. Relevant outcomes are overall survival, change in disease status, functional outcomes, quality of life, and treatment-related mortality and morbidity. The single prospective cohort study (STRONG) evaluating use of intrathecal onasemnogene abeparvovec-xioi administration in patients with age of symptom onset up to 60 months is currently ongoing. The data is premature but suggests some benefit as a number of patients achieved new motor milestones. The evidence is insufficient to determine the effects of technology on health outcomes.

**Background**
**Spinal Muscular Atrophy**
SMA is a rare autosomal recessive genetic disorder caused by homozygous deletions or variants in the *SMN1* gene located on chromosome 5. This gene produces the “survival of motor neuron” protein (SMN1), which is essential for motor neuron functioning. In 95% of cases of SMA, there is a homozygous deletion of exon 7 in the *SMN1* gene. The remaining 5% of cases are compound heterozygotes for *SMN1* exon 7 deletions and small intragenic variants. Due to absent or low levels of the SMN1 protein, motor neurons in the spinal cord degenerate, resulting in atrophy of the voluntary muscles of the limbs and trunk affecting the ability to crawl, walk, sit up, and control head. In more severe cases, feeding, swallowing, and breathing are affected as well. The exact role of the SMN protein in motor neurons has not been completely elucidated, and levels of the SMN protein required for optimal functioning are unknown.

There is wide phenotypic heterogeneity in SMA, as summarized in Table 1. This is due to the presence of *SMN2*, a modifying/backup gene, also located on chromosome 5, which is 99% identical to *SMN1*. However, 70% to 90% of the SMN2 compensatory protein produced by this gene is defective and unstable due to the lack of exon 7. The number of copies of the *SMN2* gene varies widely (range, 0-6), resulting in a less severe form of SMA among those with more copies of the *SMN2* gene and vice-versa. The relation between the *SMN2* copy number and SMA phenotype is summarized in Table 2. These data were generated from DNA samples of 375 patients with SMA who previously had been classified as follows: 188 with SMA type I, 110 with SMA type II, and 77 with SMA type III.
Table 1. Characteristics and Subtypes of SMA

<table>
<thead>
<tr>
<th>Type of SMA</th>
<th>Age at Symptoms Onset</th>
<th>Life Span</th>
<th>Highest Motor Milestone Achieved</th>
<th>SMN2 Copy Number&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 0 (antenatal-onset SMA)</td>
<td>Prenatal</td>
<td>&lt;6 mo</td>
<td>Little ability to move and may be unable to breathe and swallow independently.</td>
<td>1</td>
</tr>
<tr>
<td>Type I (infantile SMA or Werdnig-Hoffman disease)</td>
<td>0-6 mo</td>
<td>&lt;2 y without respiratory support</td>
<td>Never rolls or sits unsupported</td>
<td>2</td>
</tr>
<tr>
<td>Type II (intermediate SMA or Dubowitz disease)</td>
<td>&lt;18 mo</td>
<td>&gt;2 y; &gt;70% alive at 25 y of age</td>
<td>Sits independently once properly positioned; sometimes stands but never able to walk</td>
<td>3 or 4</td>
</tr>
<tr>
<td>Type III (Kugelberg-Welander disease)</td>
<td>&gt;18 mo to 3 y</td>
<td>Similar to that of the general population</td>
<td>Sits, stands, and walks independently until puberty; many no longer walk after puberty. Never runs or jumps well</td>
<td>3 or 4</td>
</tr>
<tr>
<td>Subtype IIIa</td>
<td>&gt;3 y</td>
<td>Similar to that of the general population</td>
<td>Sits, stands, and walks independently until puberty; many no longer walk after puberty. Walks, runs, jumps, and can participate in sports.</td>
<td>4</td>
</tr>
<tr>
<td>Type IV (adult-onset SMA)</td>
<td>&gt;21 y</td>
<td>Similar to that of the general population</td>
<td>Similar to that of the general population</td>
<td>4-8</td>
</tr>
</tbody>
</table>


<sup>a</sup> Quantitative analysis of SMN2 copies in 375 patients showed that 80% of SMA type I carry 1 or 2 SMN2 copies, 82% with SMA type II carry 3 SMN2 copies, and 96% with SMA type III carry 3 or 4 SMN2 copies. Among 113 patients with SMA type I, 9 with 1 SMN2 copy lived <11 months, 88 of 94 with 2 SMN2 copies lived <21 months, and 8 of 10 with 3 SMN2 copies lived 33 to 66 months.

Table 2. Relation Between SMN2 Copy Numbers and SMA Phenotype

<table>
<thead>
<tr>
<th>Type of SMA</th>
<th>Percent With 1 SMN2 Copy</th>
<th>Percent With 2 SMN2 Copies</th>
<th>Percent With 3 SMN2 Copies</th>
<th>Percent With 4 SMN2 Copies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>6.9</td>
<td>73.4</td>
<td>19.7</td>
<td>0</td>
</tr>
<tr>
<td>Type II</td>
<td>0</td>
<td>10.9</td>
<td>81.8</td>
<td>7.3</td>
</tr>
<tr>
<td>Type III</td>
<td>0</td>
<td>3.9</td>
<td>50.6</td>
<td>45.5</td>
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</table>

<table>
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<tr>
<th>Probability&lt;sup&gt;a&lt;/sup&gt; of SMA Type</th>
<th>Probability&lt;sup&gt;a&lt;/sup&gt; of SMA Type</th>
<th>Probability&lt;sup&gt;a&lt;/sup&gt; of SMA Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 SMN2 copy</td>
<td>99.9</td>
<td>0</td>
</tr>
<tr>
<td>2 SMN2 copies</td>
<td>97.3</td>
<td>2.7</td>
</tr>
<tr>
<td>3 SMN2 copies</td>
<td>7.2</td>
<td>82.8</td>
</tr>
<tr>
<td>4 SMN2 copies</td>
<td>1.6</td>
<td>14.8</td>
</tr>
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</table>

Adapted from Feldkotter et al (2002). SMA: spinal muscular atrophy.

<sup>a</sup> Probability that an unaffected child who has been tested after birth and has been found to carry a homozygous SMN1 deletion will develop SMA type.
**Diagnosis**

SMA can be diagnosed using multiple molecular genetic testing techniques such as multiplex ligation-dependent probe amplification or quantitative polymerase chain reaction or a comprehensive next-generation sequencing-based approach. Individuals are classified as having SMA if they have a homozygous deletion of the *SMN1* gene or a homozygous absence of the *SMN1* gene due to gene conversion (ie, *SMN1* gene conversion to *SMN2* gene) or a compound heterozygote variant in the *SMN1* gene. Individuals are defined as carriers if they have one copy of the *SMN1* gene on one chromosome and no copies on the other or two copies of the *SMN1* gene on one chromosome and no copies on the other.

Assessing *SMN2* copy numbers as part of a diagnostic workup is important because it can provide critical information on disease progression and assist in possible clinical trial enrollment or treatment.

Because SMA symptom onset may occur shortly after birth to months to years later, estimating the incidence and prevalence of SMA subtypes is difficult. The incidence, as reported in the literature, is more precisely a birth prevalence rate, which is estimated between 9.1 and 10 per 100000 live births, which translates to 500 new SMA cases annually.

**Treatment**

Medical management of SMA patients includes respiratory, nutritional, and musculoskeletal supportive care. Respiratory management includes airway clearance, antibiotic treatment of infections, noninvasive and invasive ventilation. Nutritional management includes changing food consistency, gastrostomy tube feeding, and dietician assessment. Musculoskeletal supportive care includes a variety of intervention such as equipment for mobility, teaching self-care and function, physiotherapy, spinal surgery, posture and pain management, regular exercise, and scoliosis surgery. The type and extent of supportive care can affect survival in infant-onset disease (eg, gastrostomy feeding and noninvasive/invasive ventilation).

Nusinersen is a modified antisense oligonucleotide (a synthetic genetic material) that binds to a specific sequence in the intron downstream of exon 7 of the *SMN2* transcript; nusinersen causes the inclusion of exon 7 in the *SMN2* transcript, leading to the production of full length functional *SMN2* protein. Prior to approval of nusinersen, there were no treatments approved by the Food and Drug Administration for SMA.

Onasemnogene abeparvovec-xioi, a one-time gene replacement therapy is intended as an intravenous infusion for patients with SMA type I and an intrathecal infusion for SMA type II. There are four major components of this technology—the vector, the *SMN* transgene, the self-complementary DNA technology, and the promoter. A brief description of each component is provided below.

- Vector: Nonreplicating adeno-associated virus serotype 9 that easily crosses the blood-brain barrier.
Transgene: Nonintegrating copy of a stable and fully functioning human \textit{SMN} gene that is introduced into the motor neuron cells. The gene is designed to stay in the nucleus and does not alter the patient’s genome.

Self-complementary adeno-associated virus Inverted Terminal Repeats: Use of self-complementary adeno-associated virus inverted terminal repeats obviates the dependence of the transgene on the patient’s motor neuron-mediated synthesis of a complementary DNA strand to form the double-stranded DNA. Instead, the transgene is self-complementary, enabling rapid onset of effect.

Promoter: The technology uses a chicken beta-actin hybrid promoter, which functions as a continuous promoter allowing for sustained expression of the SMN protein.

Because motor neurons are nondividing cells, it is has been suggested that once the \textit{SMN} gene is incorporated in the cells, it would be retained over time and potentially allow for long-term, sustained SMN protein expression with a one-time dose, and provide a durable therapeutic effect based on studies in animal models.\textsuperscript{15,16,17,18}

Regulatory Status
On December 23, 2016, nusinersen (Spinraza\textsuperscript{™}; Biogen) was approved by the U.S. Food and Drug Administration for treatment of pediatric and adult patients with SMA.

On May 24, 2019, onasemnogene abeparvovec-xioi (Zolgensma®; Avexis) was approved by the U.S. Food and Drug Administration for treatment of pediatric patients less than 2 years of age with spinal muscular atrophy with bi-allelic mutations in the survival motor neuron 1 gene.

Rationale
This evidence review was created in February 2017 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through May 24, 2019.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function\textsuperscript{34}including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some
conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, non-randomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

**Nusinersen**

**Clinical Context and Therapy Purpose**
The purpose of nusinersen in pediatric and adult patients who have spinal muscular atrophy (SMA) is to provide a treatment option that is an improvement on existing therapies. Potential benefits of this therapy may include the following:

- Treatment offers a novel mechanism of action or approach that may allow successful treatment of many patients for whom other available treatments are not available.

The question addressed in this evidence review is: Does treatment with nusinersen improve the net health outcome in pediatric and adult patients with a genetic diagnosis of SMA?

The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest are individuals who are presymptomatic with a genetic diagnosis of spinal muscular atrophy and a minimum of 2 but less than 4 copies of SMN2.

**Interventions**
The therapy being considered is nusinersen.

**Comparators**
Prior to the availability of nusinersen, there was no Food and Drug Administration (FDA) approved treatment for SMA. Medical management includes respiratory, nutritional, and musculoskeletal supportive care.

**Outcomes**
The general outcomes of interest are survival, functional ability, quality of life, and treatment-related mortality and morbidity. Because SMA is a heterogeneous disease, measuring the impact of the intervention depends on the subtype of SMA. For example, in infantile-onset SMA (type I), comparing the achievement of motor milestones with the known natural history of SMA is relevant but the same may not be applicable for patients with late-onset SMA (type III) in whom normal motor milestones may be delayed but nevertheless achieved or achieved but lost
later. Age- and ability-appropriate motor function scales as they relate to the natural progression of SMA are summarized in Table 3.

### Table 3. Health Outcome Measures Relevant to SMA

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Description</th>
<th>Relevance</th>
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</table>
| **HINE Section 2** | Motor milestones includes 8 items scored on a 5-point scale with 0 as the absence of activity, and a maximum score of 4 points | - Appropriate for infants 2-24 mo  
- Infants with the most severe symptoms of SMA (early onset) may show a score of 0 on all 8 items of the HINE Section 219. |
| **CHOP INTEND** | Motor skills includes 16 items scored on a scale of 0 (no response) to 4 (complete response) and total score ranges from 0 to 6414,NA20. | - Appropriate for 3.8 mo to >4 y  
- Score >40 rare in SMA type I with 2SMN2gene copies21.  
- Mean CHOP INTEND score in healthy infants (n=14; age, 3.3 mo) was 501.1 vs 20.2 in SMA type I (n=16; age, 3.7 mo) |
| **HFMSE** | Motor function includes 33 items from the Gross Motor Function Measure related to lying/rolling, crawling, crawling/kneeling, standing, and walking/running/jumping that are scored on a scale of 0 to 2, with a total score that ranges from 0 to 66, where lower scores indicate poorer motor function. On average, it can be conducted in 12 min. | - Appropriate for individuals with SMA types II and III22.  
- Multiple studies have shown that HFMSE scores decline progressively in patients with SMA type II or III. However, there is conflicting data on whether such declines are linear,23,NA24. |
| **Natural history with and without SMA** | Infants without SMA at 1 y25:  
- 90% able to maintain head control, turn in sitting position (pivot), form a pincer grasp, play with feet, roll from prone to supine (and back), crawl on hands and knees  
- 79% able to stand unaided  
- 51% able to walk  
At 18 mo:  
- 90% stand/walk unaided  
Event-free survival rates in infants with SMA type I9,NA26:  
- 50% by 8-10.5 mo  
- 25% by 13.6 mo  
- 8% by 20 mo | - With the availability of nusinersen, conducting placebo-controlled trials in patients with SMA type I who face near-term mortality would be unethical. Therefore, good quality natural history data from SMA and non-SMA populations using validated cohorts are essential to assess relative health benefit over short- and long-term. |

**CHOP INTEND**: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; **HFMSE**: Expanded Hammersmith Functional Motor Scale; **HINE**: Hammersmith Infant Neurological Examination; **SMA**: spinal muscular atrophy.

### Timing

Given the heterogeneity and varying life expectancies among patients with different SMA subtypes, the timing of follow-up of studies to reasonably assess whether nusinersen offers a net health benefit will differ by SMA subtypes as well as by the timing of treatment initiation relative to symptom onset. Given the significant uncertainty about the durability of the long-term benefits and safety of therapies, long-term data in an observational setting are also a requirement. The timing of outcomes measures relevant to SMA subtypes is summarized in Table 4.
Table 4. Timing of Outcome Measures Relevant to SMA

<table>
<thead>
<tr>
<th>SMA Subtype</th>
<th>Purpose</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presymptomatic with a genetic diagnosis of SMA and less than 3 copies of SMN2</td>
<td>To assess short-term benefit (efficacy &amp; safety)</td>
<td>6 mo to 1 y may be sufficient</td>
</tr>
<tr>
<td>Types I to III</td>
<td>To assess short-term benefit (efficacy and safety)</td>
<td>1-2 y may be sufficient</td>
</tr>
<tr>
<td>Types I to III</td>
<td>To assess durability of benefit and delayed/rare adverse events</td>
<td>10-15 y (survival, comparative development milestones vs natural history of SMA and non-SMA patients, safety)</td>
</tr>
</tbody>
</table>

SMA: spinal muscular atrophy.

Setting
Nusinersen is given as an intrathecal injection in an outpatient hospital setting by specialized trained staff.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for randomized controlled trials;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Presymptomatic Patients with a Genetic Diagnosis of SMA and 2 But Less Than 4 copies of SMN2

Non-Randomized Studies
In a multicenter, single-arm, open-label trial, Multiple Doses of Nusinersen Delivered to Infants with Genetically Diagnosed and Presymptomatic SMA (NURTURE; NCT02386553), 25 infants documented to have 5q SMA homozygous gene deletion, homozygous variant or compound heterozygote variant, and deemed likely to develop type I or II spinal muscular atrophy (SMA; based on number of SMN2 copies) received nusinersen. Of the 25 infants, 15 had 2 copies of SMN2 (most likely to develop type 1 SMA) and 10 had 3 copies of SMN2 (most likely to develop type II SMA). Infants’ age at first dose ranged from 8 to 41 days (≤14 days, n=9; >14 to ≤28 days, n=12; >28 days, n=4). Patients will be followed through January 2022 to evaluate the primary outcome of time to death or respiratory intervention (invasive or noninvasive ventilation for >6 h/d continuously over for ≥7 days or tracheostomy). Multiple secondary endpoints related to motor improvement, growth, survival, need for ventilation, and electrophysiology were also assessed. See Table 5 for study key characteristics summary.
Results are summarized in Table 6. Data reported from July 2017 assessed whether children developed any protocol-defined symptoms of SMA by 13 months of age. Of the 17 children with analyzable data, 67% (8/12) and 20% (1/5) with two and three SMN2 copies, respectively, developed one or more SMA symptoms. None of these nine children achieved hands and knees crawling (average age of attainment: 8.5 months). Five of 12 (42%) children with two SMN2 copies were unable to stand with assistance (average age of attainment: 9.2 months). By the May 2018 interim analysis, caregivers reported all 25 (100%) children had achieved sitting without support, 22/25 (88%) of children had achieved walking with assistance, and 17/25 (68%) had achieved walking alone. Four children each achieved sitting unsupported and walking alone later than expected in healthy children, and seven children were able to walk with assistance later than expected. At the most recent study visit, the mean (range) CHOP INTEND scores for children with two and three copies were similar and reflected near maximal motor function (two copies: 61.0 [46 to 64]; three copies: 62.6 [8 to 64]). All 25 children were alive at the May 2018 interim analysis and 16% (4/25) children met the primary outcome of required respiratory intervention; all 4 children had 2 SMN2 copies. All of these infants received respiratory intervention during an acute, reversible illness, and none required permanent ventilation or tracheostomy. While the FDA label has not been updated, the FDA agreed with sponsor findings that the open-label uncontrolled trials such as NURTURE were consistent with the results of the pivotal RCT and the FDA supported the efficacy of nusinersen in infantile SMA, including when given to presymptomatic patients. The prescribing label states: “some patients achieved milestones such as ability to sit unassisted, stand, or walk when they would otherwise be unexpected to do so, maintained milestones at ages when they would be expected to be lost, and survived to ages unexpected considering the number of SMN2 gene copies of patients enrolled in the studies.”

The purpose of study limitations tables (see Tables 7 and 8) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table. Notable study limitations include a relatively short follow-up, which is inadequate to assess the durability of the treatment effect or safety, especially those that are potentially rare or have delayed onset.

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Country</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Vivo et al (2018); NURTURE</td>
<td>U.S., EU, Asia</td>
<td>15</td>
<td>2015-ongoing</td>
<td>Presymptomatic infants (n=25) likely to develop SMA type I (n=15) or II (n=10)</td>
<td>Nusinersen at FDA-approved dose</td>
<td>Analysis May 2018: median age 26.0 months (range: 14.0 to 34.3), and median time on treatment 27.1 months</td>
</tr>
</tbody>
</table>
EU: European Union; FDA: Food and Drug Administration; SMA: spinal muscular atrophy.

Table 6. Summary of Results of NURTURE Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Independent Sitting</th>
<th>Walking with Assistance</th>
<th>Walking Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Vivo et al (2018); NURTURE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>17</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Nusinersen (July 2017)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 SMN2 copies</td>
<td>93% (14)</td>
<td>33% (5)</td>
<td>20% (3)</td>
</tr>
<tr>
<td>3 SMN2 copies</td>
<td>80% (8)</td>
<td>70% (7)</td>
<td>50% (5)</td>
</tr>
<tr>
<td>Swoboda et al (2018); NURTURE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Nusinersen (May 2018)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 SMN2 copies</td>
<td>100% (15)</td>
<td>80% (12)</td>
<td>53% (8)</td>
</tr>
<tr>
<td>3 SMN2 copies</td>
<td>100% (10)</td>
<td>100% (10)</td>
<td>90% (9)</td>
</tr>
</tbody>
</table>

Expected Age Range of Attainment in Healthy Children (months)

<table>
<thead>
<tr>
<th>Study</th>
<th>Expected Age Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Vivo et al (2018); NURTURE</td>
<td>3.8 to 9.2</td>
</tr>
<tr>
<td>Swoboda et al (2018); NURTURE</td>
<td>5.9 to 13.7</td>
</tr>
<tr>
<td>Nusinersen (July 2017)</td>
<td>8.2 to 17.6</td>
</tr>
<tr>
<td>Nusinersen (May 2018)</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from ICER Report on SMA (2018)
Range defined by 1st -99th percentile for the windows of milestone achievement

Table 7. Relevance Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Vivo et al (2018); NURTURE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1. Not sufficient duration for benefit</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2. Not sufficient duration for harms</td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.


Table 8. Study Design and Conduct Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation</th>
<th>Blinding</th>
<th>Selective Reporting</th>
<th>Data Completeness</th>
<th>Power</th>
<th>Statistical</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Vivo et al (2018); NURTURE</td>
<td>1. Participants not randomly allocated</td>
<td></td>
<td>3. Outcome assessed by treating physician</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Presymptomatic Patients with a Genetic Diagnosis of SMA and a Minimum of 2 But Less Than 4 Copies of SMN2
The evidence for use of nusinersen for presymptomatic type I (infantile-onset) SMA consists of interim reporting on a single-arm study. After a median follow-up of 27.1 months, early initiation of nusinersen in 25 presymptomatic infantile SMA patients who were 14 months or older at the time of the analysis, 100% were alive, 100% achieved sitting without support, 88% achieved walking with assistance, and 68% achieved walking alone. All of these infants received respiratory intervention during an acute, reversible illness, and none required permanent ventilation or tracheostomy. These results demonstrate that early treatment resulted in the achievement of motor milestones among patients who are not likely to attain them without treatment. However, the data is limited for the durability of response and long-term data documenting safety and efficacy are needed.

TYPE I (Infantile-Onset) SMA
The evidence base for infantile-onset or type I SMA is summarized in Table 9. This evidence base consists of two RCTs and an early-phase open-labeled study. Results of a phase 2 RCT trial, Assess the Safety and Tolerability of Nusinersen in Participants with SMA (EMBRACE) are not available and not discussed further.

Table 9. Summary of Key Clinical Trial in Infantile-Onset or Type I SMA Patients

<table>
<thead>
<tr>
<th>Study (Trial)</th>
<th>Trial Name</th>
<th>Design</th>
<th>Dates</th>
<th>Patients (N)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unpublished* (NCT02462759)</td>
<td>EMBRACE</td>
<td>RCT</td>
<td>Aug 2015</td>
<td>Symptomatic 21</td>
<td>Safety, tolerability</td>
</tr>
</tbody>
</table>

PK: pharmacokinetics; RCT: randomized controlled trial; SMA: spinal muscular atrophy.

* Available as abstract only.
Randomized Studies
The pivotal trial was a multicenter randomized, double-blind trial, Assess the Efficacy and Safety of Nusinersen in Infants with SMA (ENDEAR; NCT02193074) in which 121 infants with a documented genetic diagnosis of SMA with symptom onset before 6 months of age were randomized 2:1 to nusinersen (n=80) or to sham injection (n=41). Nusinersen was approved on the basis of planned interim analysis of 82 patients who completed at least 183 days of treatment or died or withdrew. Patients’ demographics at baseline were 44% male, and 87% white, with a median length of treatment of 261 days (range, 6-442 days). The primary endpoint was the proportion of motor milestone responders. See Table 10 for the study summary.

Results are summarized in Table 11. The trial met its coprimary endpoints, with nusinersen showing clinically meaningful improvement in motor milestones and probability of surviving or receiving permanent-assisted ventilation compared with sham control. The median time to death or the use of permanent-assisted ventilation was 22.6 weeks in the control group and was not reached in the nusinersen group. Multiple secondary endpoints showed a consistency in treatment effect favoring nusinersen over sham control. It is notable that half of the nusinersen-treated subjects did not achieve the primary endpoint, motor milestone response. The FDA (based on interim analysis) reported “although the response was clearly important, perhaps life-changing in few cases (6% of patients gained the ability to sit without assistance, a feat that almost never occurs in individuals with only 2 copies of the SMN2 gene), the majority of patients had a modest response or no response at all.” Further, the FDA noted that 94% of patients were not able to sit, no patient was able to stand unassisted, and no patient progressed to walking. On the motor response rate (using the HINE), the FDA concluded that, on average, mean motor milestone scores in nusinersen-treated patients improved from approximately 1 point (before treatment) to approximately 4 points at 12 months—a difference of 3 points over 6 months. At 12 months, a healthy baby would achieve a motor milestone score of 22. Thus, nusinersen is a disease-modifying treatment and not a cure. While no irreversible harms were observed in the preliminary clinical data analyzed by the FDA before drug approval, the FDA noted that such harms could not be ruled out based on animal toxicity data (potential of neurotoxicity) and class effects of antisense oligonucleotides (coagulation abnormalities, thrombocytopenia, renal toxicity). Given the limited data on the durability of response, long-term data documenting safety and efficacy is needed.

The purpose of the study limitations table (see Table 12) is to display notable limitations identified in a study. This information is synthesized as a summary of the body of evidence following each table. No study design and conduct gaps were identified. Notable study limitations include a relatively short follow-up, which is inadequate to assess the durability of the treatment effect or safety, especially those that are potentially rare or have delayed onset. In addition to the gaps identified in the tables, the two treatment groups were not balanced with respect to age at symptom onset, use of ventilatory support, and the presence of
symptoms specific to SMA. These were higher in the nusinersen group than the control group. None of these differences were tested for statistical significance.

Table 10. Summary of Key ENDEAR Trial

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>Country</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nusinersen</td>
<td>DB-RCT</td>
<td>U.S., EU, Asia</td>
<td>31</td>
<td>2014-2016</td>
<td>SMA type I with symptom onset before 6 mo (n=121)</td>
<td>Nusinersen at FDA-approved dose (n=80)</td>
<td>Placebo (n=41)</td>
</tr>
</tbody>
</table>

DB-RCT: double-blind randomized controlled trial; EU: European Union; FDA: Food and Drug Administration; SMA: spinal muscular atrophy.

Table 11. Summary of Results of ENDEAR Trial

<table>
<thead>
<tr>
<th>Study</th>
<th>Percent motor milestone response (HINE section 2)a</th>
<th>No death or use of permanent-assisted ventilationb</th>
<th>≥4-point improvement in CHOP INTEND scorec</th>
<th>No death</th>
<th>No use of permanent-assisted ventilationb</th>
<th>CMAP responsed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finkel et al (2017); ENDEAR29</td>
<td>37/73 (51)</td>
<td>49/80 (61)</td>
<td>52/73 (71)</td>
<td>67/80 (84)</td>
<td>62/80 (78)</td>
<td>26/73 (36)</td>
</tr>
<tr>
<td>Nusinersen</td>
<td>0/37 (0)</td>
<td>13/41 (32)</td>
<td>1/37 (3)</td>
<td>25/41 (61)</td>
<td>28/41 (68)</td>
<td>2/37 (5)</td>
</tr>
<tr>
<td>Sham</td>
<td>121</td>
<td>121</td>
<td>121</td>
<td>121</td>
<td>121</td>
<td>121</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.53 (0.32 to 0.89)</td>
<td>-</td>
<td>0.37 (0.18 to 0.77)</td>
<td>0.66 (0.32 to 1.37)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>0.005</td>
<td>&lt;0.001</td>
<td>0.004</td>
<td>0.13</td>
<td>-</td>
</tr>
</tbody>
</table>

Adapted from Finkel et al (2017).29 Values are percent or n (%) or as otherwise indicated. Final analysis conducted on November 21, 2016 included 121 data from infants who had undergone randomization and the assigned procedure at least once.

CI: confidence interval; CMAP: compound muscle action potential; CHOP INTEND: Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE: Hammersmith Infant Neurologic Exam; HR: hazard ratio.

a Motor milestone response was defined according to scores on the HINE-2, which assesses the development of motor function through the achievement of motor milestones; in this trial, the scores accounted for 7 of the 8 motor milestone categories, excluding voluntary grasp. Infants were considered to have a motor milestone response if they met the following 2 criteria: improvement in at least 1 category (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 more categories with improvement than categories with worsening (ie, a decrease in the score for head control, rolling, sitting, crawling, standing, or walking of ≥1 point or a decrease in the score for kicking of ≥2 points).

b Permanent-assisted ventilation was defined as tracheostomy or ventilatory support for at least 16 h/d for more than 21 continuous days in the absence of an acute reversible event, as determined by an independent endpoint adjudication committee.

c A CHOP INTEND response was defined as an increase of at least 4 points from baseline in CHOP INTEND score at the end-of-trial visit (day 183, 302, or 394).

d A CMAP response was defined as an increase in the peroneal CMAP amplitude to at least 1 mV (or maintenance of an amplitude of ≥1 mV) at the end-of-trial visit (day 183, 302, or 394).
Table 12. Relevance Study Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Populationa</th>
<th>Interventionb</th>
<th>Comparatorc</th>
<th>Outcomesd</th>
<th>Follow-Up²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finkel et al (2017); ENDEAR⁹⁹</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
² Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Non-Randomized Studies
Supportive evidence also includes a published phase 2, open-labeled proof-of-concept study (NCT01839656) in which 20 patients with type I SMA with the onset of symptoms before 6 months of age were randomized to 2 doses of nusinersen (6 mg [n=4], 12 mg [n=16]). The study was completed in 2017 and the results of the interim analysis done in January 2016 were published. Incremental improvements in motor milestones on the HINE-2 were observed in 84% (16/19) of patients at the last visit compared with baseline. Improvements of 2 points or more per motor milestone category for at least 1 category were observed in 68% (13/19) of patients. Mean increase in CHOP INTEND scores was 11. 5 points from baseline to the last visit, with 78% (14/18) showing an improvement. Additional data from this study were suggestive of improvement in survival, permanent ventilation independence, and neuromuscular electrophysiology. Small sample size, short follow-up (2-32 months), and lack of a control group limit the interpretation of study results. Nevertheless, the data are indicative of the potential benefit of nusinersen in type I SMA.

Section Summary: Type I (Infantile-Onset) SMA
The evidence for use of nusinersen for symptomatic type I (infantile-onset) SMA consists of two double-blind RCTs and a single-arm study. The largest phase 3 confirmatory ENDEAR trial (n=121) showed clinically meaningful and statistically significant improvement in motor milestones and event-free survival that exceeded those seen in the control group. However, most patients had a modest response or no response, and only a small proportion of patients (6%) gained the ability to sit without assistance. On average, the mean motor milestone score in nusinersen-treated patients improved by three points over six months. Given the limited data on the durability of response, long-term data documenting safety and efficacy are needed.
Type II or III SMA
The evidence base for patients with type II or III SMA is summarized in Table 13.

Table 13. Summary of Key Trial Characteristics in Type II and III SMA Patients

<table>
<thead>
<tr>
<th>Study (Trial)</th>
<th>Trial Name</th>
<th>Design</th>
<th>Dates</th>
<th>N</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiriboga et al (2016)</td>
<td>CS1</td>
<td>1 arm</td>
<td>Nov 2011</td>
<td>28</td>
<td>Safety and tolerability</td>
</tr>
<tr>
<td>Chiriboga et al (2016)</td>
<td>CS10</td>
<td>1 arm</td>
<td>Jan 2013</td>
<td>18</td>
<td>Safety and tolerability</td>
</tr>
<tr>
<td>Unpublished (NCT01703988)</td>
<td>CS2</td>
<td>1 arm</td>
<td>Oct 2012</td>
<td>34</td>
<td>Safety and tolerability</td>
</tr>
<tr>
<td>Unpublished (NCT02052791)</td>
<td>CS12</td>
<td>1 arm</td>
<td>Jan 2014</td>
<td>47</td>
<td>Safety and tolerability</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial; SMA: spinal muscular atrophy.

The evidence base for patients with type II and III SMA consists of four early-phase, open-labeled studies and a double-blind phase 3 RCT. Of these, results of two early-phase 1 studies and one double-blind phase 3 RCT have been published. However, data from phase 1 studies are not reviewed because they were early dose-finding and proof-of-concept studies. The remaining 2 studies have not been published yet but data were sourced from the Academy of Managed Care Pharmacy dossier supplied by Biogen (2016) and only summarized at the end of this section.

Randomized Studies
Similar to ENDEAR, Assess Clinical Efficacy and Safety of Nusinersen in Participants with Later-onset SMA (CHERISH) was also designed as a multicenter, randomized, double-blind trial that evaluated 126 nonambulatory patients with genetic documentation of 5q SMA (a homozygous deletion, variant, or compound heterozygote in SMN1) with the onset of signs and symptoms at more than 6 months and between ages 2 and 12 years at screening as well as the presence of the following features at screening: the ability to sit independently, no history of the ability to walk independently (defined as the ability to walk ≥15 feet unaided), and a Hammersmith Functional Motor Scale–Expanded (HFMSE) score between 10 and 54. Children were excluded if they had a severe contracture, evidence of severe scoliosis on radiography, respiratory insufficiency, or a gastric tube placed to provide adequate nutrition. Because of the strict inclusion and exclusion criteria to enroll a homogenous and younger patient population (median age from four to three years in treatment and control group, respectively), the results from this trial have limited generalizability to type II and III SMA patients generally seen in clinical practice. See Table 14 for study summary.

The primary endpoint was change in HFMSE score compared with baseline. HFMSE scores range from 0 to 66, with higher scores indicating better motor function. Results are summarized in Table 15. The trial met its primary endpoints with nusinersen showing clinically meaningful improvement in mean HFMSE scores.
compared with sham control. In terms of responder analysis, a higher percentage of children in the nusinersen group (57%) than in the control group (26%; p<0.001) had an increase from baseline to month 15 in the HFMSE score of at least 3 points, which was considered meaningful. Multiple secondary endpoints summarized in Table 15 showed a consistency in treatment effect favoring nusinersen compared with sham control. Approximately a quarter of placebo patients reported clinically meaningful improvements in HFMSE scores at 15 months, which is most likely a combination of the placebo effect, the learning curve for the assessment of the HFMSE and Revised Upper Limb Module (RULM) scores, and initial developmental gains, particularly in younger children. Mean HFMSE score plotted over time (data not shown) show that the initial improvement in HFMSE scores in the placebo arm was short-lived and showed a declining trend starting at 6 months and continuing to the end of the trial (ie, 15 months). Analyses of the magnitude of change in the HFMSE score stratified by age and disease duration (data not shown) revealed greater, improvements in younger children and in those who received treatment earlier in their disease course, respectively. The overall incidences of adverse events and moderate and serious adverse events were similar for the nusinersen group and the control group (93% and 100% vs 46% and 55%, respectively). Adverse events with an incidence of five or more percentage points higher in the nusinersen group than in the control group were pyrexia, headache, vomiting, back pain, and epistaxis. Given the limited data on the durability of response, long-term data documenting safety and efficacy are needed.

Similar to ENDEAR trial, the confirmatory phase 3 CHERISH trial was terminated early because the results of a preplanned interim analysis met the primary endpoint of efficacy. However, in the prespecified interim analysis, data for the 15-month time-point for HFMSE score were missing in 58% (49/84) and 55% (23/42) patients in the nusinersen and control group, respectively, and was imputed using the use of a multiple imputation method to conduct an intention-to-treat analysis. The missing data were largely due to patients who had not completed their 15-month visit at the time of analysis. In the final analysis, the proportions of missing data for HFMSE and RULM scores were imputed for 21% (18/84) and 19% (8/42) patients in the nusinersen and control group, respectively, and imputed using multiple imputation method to conduct an intention-to-treat analysis. For all other outcomes, only the observed data were included. The authors conducted multiple sensitivity analyses including (1) multiple imputations using mixed-effects model for repeated measures, (2) only completers (per protocol), (3) last observation carried forward approach, and (4) for children who had a missing 15-month assessment and discontinued due to treatment failure or death, the worst of the last observed value or the baseline value was imputed. The intergroup difference between the least-squares mean change from baseline to month 15 remained statistically significant in favor of nusinersen in all 4 scenarios with highest treatment effect (change, 5.2) in the “completers only analysis.”

The purpose of the study limitations table (see Table 16) is to display notable limitations identified in a study. This information is synthesized as a summary of
the body of evidence following each table. No study design and conduct gaps were identified. Notable limitations include a relatively short follow-up, which is inadequate to assess the durability of the treatment effect or safety, especially those that are potentially rare or have delayed onset. In addition, survival, ventilation, and event-free survival were not evaluated in CHERISH.

Table 14. Summary of Key Characteristics of CHERISH Trial

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Country</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nusinersen</td>
<td>U.S., EU, Asia</td>
<td>24</td>
<td>2014-2017</td>
<td>SMA type II with symptom onset after 6 mo (n=126)</td>
<td>Nusinersen at FDA-approved dose (n=84)</td>
<td>Prespecified interim analysis when all children followed for minimum of six months and 39 or more children had completed 15-month evaluations</td>
</tr>
</tbody>
</table>

DB-RCT; double-blind randomized controlled trial; EU: European Union; FDA: Food and Drug Administration; SMA: spinal muscular atrophy.

Table 15. Summary of Results of CHERISH Trial

<table>
<thead>
<tr>
<th>Study</th>
<th>D in HFMSE score from baseline, LSM (95% CI)</th>
<th>Patients with D in HFMSE score ≥3 points, Percent (95% CI)</th>
<th>Patients who achieved ≥1 new WHO motor milestone, Percent (95% CI)</th>
<th>D from baseline in RULM score, LSM (95% CI)</th>
<th>Patients who achieved ability to stand alone, Percent (95% CI)</th>
<th>Patients who achieved ability to walk with assistance, Percent (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nusinersen</td>
<td>3.9 (3.0 to 4.9)</td>
<td>57 (46 to 68)</td>
<td>20 (11 to 31)</td>
<td>0.2 (0.1 to 0.3)</td>
<td>4.2 (3.4 to 5.0)</td>
<td>2 (0 to 8)</td>
</tr>
<tr>
<td>Sham</td>
<td>-1.0 (-2.5 to 0.5)</td>
<td>26 (12 to 40)</td>
<td>6 (1 to 20)</td>
<td>-0.2 (-0.4 to 0)</td>
<td>0.5 (-0.6 to 1.6)</td>
<td>3 (0 to 15)</td>
</tr>
<tr>
<td>Difference (95% CI)</td>
<td>4.9 (3.1 to 6.7)</td>
<td>30.5 (12.7 to 48.3)</td>
<td>14 (-7 to 34)</td>
<td>0.4 (0.2 to 0.7)</td>
<td>3.7 (2.3 to 5.0)</td>
<td>-1 (-22 to 19)</td>
</tr>
<tr>
<td>Odds ratio (95% CI)b</td>
<td>-</td>
<td>6 (2 to 15)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001c</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Adapted from Mercuri et al (2018).31

Outcomes assessed at 15 Months. In the final analysis, the multiple imputation method was used for missing data to assess changes from baseline in the HFMSE score, percentage of children with a change in HFMSE score of at least 3 points, and change from baseline in the RULM score. The proportion of missing data for 15-month time-point for HFMSE score were 21% (18/84) and 19% (8/42) in the nusinersen and control group, respectively, and imputed using a multiple imputation method to conduct an intention-to-treat analysis.

a LSM change and LSM difference in change between groups were based on analysis of covariance with group assignment as a fixed effect and with adjustment for each child’s age at screening and the value at baseline.

bThis value is an odds ratio rather than a difference. The odds ratio for nusinersen vs control was based on logistic regression, with group assignment as a fixed effect and with adjustment for each child’s age at screening and the HFMSE score at baseline.

cBecause the p-value for the primary endpoint was significant in the interim analysis, this endpoint was not formally tested for significance in the final analysis.

Table 16. Relevance Study Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Population&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Intervention&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Comparator&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Outcomes&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Follow-Up&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mercuri et al (2018); CHERISH&lt;sup&gt;31&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>1. Key health outcomes not addressed;</td>
<td>1. Not sufficient duration for benefit 2. Not sufficient duration for harms</td>
<td></td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Non-Randomized Studies

CS2 is phase 1/2, single-arm study that was completed in January 2015.<sup>32</sup> It included 34 patients between the ages of 2 and 15 with a documented genetic diagnosis of 5q SMA and clinical signs and symptoms attributed to SMA. Patients received various doses of nusinersen, ranging from 3 to 12 mg, with an average 8-month follow-up. The primary endpoint was safety, and the secondary endpoint was pharmacokinetic parameters. Multiple exploratory endpoints related to motor function were assessed including a change in HFMSE score. CS12 was a long-term extension study that included patients from CS2 and other studies. In the 6 patients with type II SMA, the mean change in HFMSE score after 1050 days of treatment was 12.3. In the 7 patients with type III SMA, the mean change in HFMSE score after 1050 days of treatment was 1.6.

Section Summary: Type II or III SMA

The evidence for the use of nusinersen for patients with type II or III SMA consists of four single-arm studies and a double-blind RCT. The small single-arm studies employed multiple doses of nusinersen, ranging from 6 to 12 mg in patients with type II and III SMA. The available results did not stratify outcomes by dose or type of SMA, and therefore it is difficult to interpret the data from these studies. The largest phase 3 confirmatory CHERISH trial (126 patients) showed clinically meaningful and statistically significant improvement in motor milestones that
exceeded those seen in the control group. Multiple secondary endpoints showed a consistency in treatment effect favoring nusinersen over sham control. The treatment effect was greater in younger children and in those who received treatment earlier in their disease course. Given the limited data on the durability of response, long-term data documenting safety and efficacy are needed.

**Type 0 or IV SMA**
There are currently no studies assessing the efficacy and safety of nusinersen in patients with type 0 or IV SMA.

**Safety: Nusinersen**
As per the prescribing label, thrombocytopenia (including acute, severe thrombocytopenia) and renal toxicity (including potentially fatal glomerulonephritis) have been observed with antisense oligonucleotides. In the controlled ENDEAR trial, the most common adverse events that occurred in at least 20% of nusinersen-treated patients and occurred at least 5% more frequently than in sham-controlled patients were a lower respiratory infection, upper respiratory infection, and constipation. Atelectasis (a serious adverse event) was more frequent in nusinersen-treated patients (14%) than in sham control (5%). Adverse events reported verbally were not assessable in the sham-controlled trial because patients were infants. In the open-labeled studies of patients with type II or III SMA, the most common adverse events were a headache (50%), back pain (41%), and post-lumbar puncture syndrome (41%), which occurred within 5 days of lumbar puncture. Other adverse events in these patients were consistent with reactions observed in the controlled study. Also, 1 case of severe hyponatremia in an infant that required salt supplementation for 14 months and 2 cases of rash were reported. Both patients with rash continued to receive nusinersen and had a spontaneous rash resolution.

Development of anti-nusinersen antibodies was assessed in 126 patients of whom 5 (4%) developed treatment-emergent antidrug antibodies, of which 3 were transient, and 2 were persistent. There are insufficient data to evaluate the effect of antidrug antibodies on clinical response, adverse events, or the pharmacokinetic profile of nusinersen.

**Onasemnogene abeparvovec-xioi**

**Clinical Context and Therapy Purpose**
The purpose of onasemnogene abeparvovec-xioi in patients who have SMA type I is to provide a treatment option that is an improvement on existing therapies. Potential benefits of this gene therapy may include the following:

- Treatment offers a novel mechanism of action or approach that may allow successful treatment of many patients for whom other available treatments have failed.
- Treatment reduces complexity in administration (avoidance of repeated intrathecal injections) that may significantly improve patient outcomes.
• Treatment reduces caregiver or broader family burden.
• Treatment reduces important health disparities across racial, ethnic, gender, socioeconomic, or regional categories.

The question addressed in this evidence review is: Does treatment with onasemnogene abeparvovec-xioi improve the net health outcome in individuals with a genetic diagnosis of SMA?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest is individuals who are symptomatic infants diagnosed with type 1 SMA type, type II SMA and presymptomatic infants with a genetic diagnosis of SMA.

Interventions
The therapy being considered is onasemnogene abeparvovec-xioi.

Comparators
The relevant comparators are continued medical management (respiratory, digestive, and orthopedic support) and nusinersen.

Outcomes
The general outcomes of interest are survival, functional ability, quality of life, and treatment-related mortality and morbidity. For details, see Table 4.

Timing
Given the heterogeneity and varying life expectancies among patients with different SMA subtypes, the timing of follow-up of studies to reasonably assess whether onasemnogene abeparvovec-xioi offers a net health benefit will differ by SMA subtypes as well as by the timing of treatment initiation relative to symptom onset. For details, see Table 5.

Setting
Administration of gene therapy is likely to be provided in an outpatient hospital setting by specialized staff equipped to handle any unplanned emergencies that may arise from administration.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

• To assess efficacy outcomes, comparative controlled prospective trials were sought, with preference for randomized controlled trials;
• In the absence of such trials, comparative observational studies were sought, with preference for prospective studies.
• To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
• Studies with duplicative or overlapping populations were excluded.
Non Randomized Studies
The clinical development program for onasemnogene abeparvovec-xioi is summarized in Table 17.

Table 17. Summary of the Clinical Development Program for Onasemnogene Abeparvovec-xioi

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>N</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants under 6 wk (presymptomatic with a genetic diagnosis of SMA and less than 3 copies of SMN2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPR1NT (NCT03505099) 34</td>
<td>3</td>
<td>44</td>
<td>Ongoing; estimated completion: Nov 2020</td>
</tr>
<tr>
<td>Children &lt;6 mo of age (SMA type I)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pivotal (NCT02122952) 35, NA 36</td>
<td>1</td>
<td>15</td>
<td>Completed</td>
</tr>
<tr>
<td>STR1VE U.S. trial (NCT03306277) 37</td>
<td>3</td>
<td>20</td>
<td>Ongoing; estimated completion: Mar 2020</td>
</tr>
<tr>
<td>STR1VE E.U. trial (NCT03461289)</td>
<td>3</td>
<td>30</td>
<td>Ongoing; estimated completion: Nov 2020</td>
</tr>
<tr>
<td>START (NCT03421977) 30</td>
<td>4</td>
<td>15</td>
<td>Ongoing; estimated completion: Dec 2033</td>
</tr>
<tr>
<td>Children up to 60 mo of age (SMA type II)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STRONG (NCT03381729) 1</td>
<td>1</td>
<td>27</td>
<td>Ongoing; estimated completion: Nov 2019</td>
</tr>
<tr>
<td>Patients between 6 mo and 18 y who are ineligible for the other studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REACH (yet to register)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SMA: spinal muscular atrophy.

a Long-term, safety follow-up study of patients enrolled in NCT02122952.

Symptomatic Spinal Muscular Atrophy TYPE I (Infantile-Onset)
The clinical development program of onasemnogene abeparvovec-xioi for patients with symptomatic SMA type I includes four prospective cohort studies; one dose-finding study, two phase 3 confirmatory studies (STRIVE-US and -EU), and one long-term follow-up study (START). These trials will enroll a total of 65 patients with symptomatic SMA type I. Of these four trials, only the dose-finding phase 1 study has been completed and has reported two-year follow-up data.36 The study characteristics and results are summarized in Tables 18 and 19.

In the phase 1 study, 12 of 15 infants received the proposed therapeutic dose while 3 received a minimally effective dose. At a median follow-up ranging from 30.7 to 27.8 months (based on 2 dose cohorts), all 15 patients survived and none of the 12 patients who received the proposed therapeutic dose required permanent ventilation at the 2-year follow-up. Based on the known natural history of patients with SMA type I with two copies of the SMN2 gene, 8% of patients are expected to survive beyond two years without ventilation. In terms of motor functions, all 12 patients achieved at least 1 motor milestone, with 92% of those achieving scores greater than 40 on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND). Compared with the known natural history, attaining a CHOP INTEND score greater than 40 is rare21, and patients experience a 10.7-point drop in CHOP INTEND scores between 6 to 12 months of age. Treatment-related asymptomatic transient elevated liver function enzymes
(categorized as serious adverse events) were reported in two patients. The early data in a small number of patients diagnosed with SMA type I is indicative of positive impact on survival and motor functions that are durable up to two years.

The FDA approval was based on a pooled analysis of 21 patients with 2 copies of SMN2 from the pivotal phase I and STRIVE-US trial with a data analysis cut off of March 2019. Efficacy was established on the basis of survival, and achievement of developmental motor milestones such as sitting without support. Comparison of the results of the ongoing clinical trial to available natural history data of patients with infantile-onset SMA was the primary evidence for effectiveness of onasemnogene abeparvovec-xioi. The FDA analysis is summarized in Table 19.

While the current evidence for symptomatic type I SMA patients is limited to patients with 2 copies of SMN2, approximately 20% of type I SMA patients may have 3 copies of SMN2. Given the treatment effect observed in symptomatic patients, it is possible that patients with 3 copies of SMN2 may experience a clinically meaningful benefit. However, there is no published evidence to support such a hypothesis. Further, there is no published data that supports clinical benefit in Type I SMA patients who are administered onasemnogene abeparvovec-xioi after 6 months of age.

The purpose of study limitations tables (see Tables 20 and 21) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following each table. Due to strict inclusion criteria, the patient population included in the trial was more homogeneous (eg, SMN2 copy number differences), younger, and treated earlier from the time of onset of symptoms than patients in routine clinical practice. For example, the weighted mean (standard deviation) age of symptom onset and age of confirmed genetic diagnosis in SMA type I patients were 2.5 (0.6) and 6.3 (2.2) months, respectively, based on a systematic literature review of studies published between 2000 and 2014. The weighted diagnostic delay in this systematic review was 3.6 months. In the onasemnogene abeparvovec-xioiphase I study, the age of symptom onset and age of confirmed genetic diagnosis were 1.4 months (range, 0-3 months) and 2 months (range, 0-4.5 months), respectively. Therefore, the benefits observed in this study setting might not translate to patients in a real-world setting. However, with increasing efforts toward newborn screening for SMA, it is possible that the delay in diagnosis of SMA may be shortened.

Other notable limitations include a relatively short follow-up of two years, which may be adequate to demonstrate if a clinically meaningful improvement in health outcomes but inadequate to assess fully the long-term durability of the treatment effect or safety, especially those that are potentially rare or have delayed onset. Although the sponsor, AveXis, is planning to create a prospective, long-term registry of at least 500 SMA patients with a diagnosis over a 5-year period (2018 to 2023), this is a disease-specific registry and may include a mix of patients treated and not treated with onasemnogene abeparvovec-xioi. The primary objective is to assess treatment effectiveness, long-term safety, and overall survival. Secondary objectives include an assessment of health care resource
utilization, caregiver burden, and patient functional independence. AveXis also plans to follow patients for 15 years from the pivotal trials, but enrollment is optional. To address the lack of evidence on long-term efficacy and safety (beyond two years), such registries or long-term follow-up should universally enroll all patients that receive onasemnogene abeparvovec-xioi. Optional enrollment is prone to selection bias.

Table 18. Summary of Key Characteristics of Nonrandomized Trials

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Country</th>
<th>Dates</th>
<th>Participants</th>
<th>Treatment</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mendell et al (2017&lt;sup&gt;35&lt;/sup&gt;, 2018&lt;sup&gt;36&lt;/sup&gt;)</td>
<td>U.S.</td>
<td>2014-2018</td>
<td>Infants &lt;9 months&lt;sup&gt;a&lt;/sup&gt; with biallelic SMN1 deletions or variants with 2 copies of SMN2 (n=15). Patients with c.859G&gt;C variant in SMN2 exon 7 were excluded from the study.&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Onasemnogene abeparvovec-xioi (3 minimally effectivedose&lt;sup&gt;c&lt;/sup&gt;; 12 proposed therapeutic dose&lt;sup&gt;d&lt;/sup&gt;)</td>
<td>Median, 30.7&lt;sup&gt;e&lt;/sup&gt; and 27.8&lt;sup&gt;e&lt;/sup&gt; months&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Protocol was amended to lower the age to 6 months of age or younger.
<sup>b</sup>c.859G>C substitution is a positive modifier and has been shown to results in a mild SMA phenotype.<sup>39</sup>
<sup>c</sup>At 6.7×10<sup>13</sup>mg/kg.
<sup>d</sup>At 2.0×10<sup>14</sup>mg/kg.
<sup>e</sup>The oldest patients is 46.2 months of age, with 40.6 months of follow-up.

Table 19. Summary of Key Results of Nonrandomized Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Survival</th>
<th>Change in Mean CHOP INTEND Score</th>
<th>Patients With CHOP INTEND Score &gt;40, n (%)</th>
<th>Others</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mendell et al (2018)&lt;sup&gt;34&lt;/sup&gt;</td>
<td>N</td>
<td>15</td>
<td>15</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Onasemnogene abeparvovec-xioi</td>
<td>100%</td>
<td>+7.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11 (92%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Among Cohort 2&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Historical cohort (PNCR&lt;sup&gt;9&lt;/sup&gt;, NeuroNEXT&lt;sup&gt;26&lt;/sup&gt;, and De Sanctis&lt;sup&gt;19&lt;/sup&gt;)</td>
<td>»20%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>10 points between 6 and 12 mo</td>
<td>Rare</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Brings hand to mouth: 100%
<sup>b</sup>Controls head: 92%
<sup>c</sup>Rollover: 75%
<sup>d</sup>Sits with assistance: 92%
<sup>e</sup>Sits unassisted (≥5 s): 92%
<sup>f</sup>Sits unassisted (≥10 s): 83%
<sup>g</sup>Sits unassisted (≥30 s): 75%
<sup>h</sup>Speaks: 92%
<sup>i</sup>Swallows: 92%
<sup>j</sup>No NIV use: 58%
<sup>k</sup>No nutritional support: 50%

SAE (2 experienced by 2 patients)<sup>c</sup>
AEs (3 experienced by 2 patients)<sup>c</sup>
- Sits with assistance: 0
- Sits unassisted (≥5 s): 0
- Sits unassisted (≥10 s): 0
- Sits unassisted (≥30 s): 0
- Speaks: Not available
- Swallows: Not available
- No NIV use: Not available
- No nutritional support: 8 by 20 months

FDA Label (as of the March 2019 data cutoff)  

<table>
<thead>
<tr>
<th>N</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onasemnogene abeparvovec-xioi</td>
<td>90.5%</td>
</tr>
</tbody>
</table>

- One patient died at age 7.8 months due to disease progression
- One patient withdrew from the study at age 11.9 months.
- 68% (13 of the 19) patients continuing in the trial reached 14 months of age without permanent ventilation
- 47.6% (10 of 21) sit without support for ≥ 30 seconds between 9.2 and 16.9 months of age (mean age 12.1 months).
- 84% (16 of 19) did not require daily non-invasive ventilator use.

Elevated ALT/AST(>ULN): 12 (27.3%)
Vomiting: 3 (6.8%)

AE: adverse events; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CHOP INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; NA: not applicable; SAE: serious adverse event; ULN: upper limit of normal.

a Cohort 1 (lower dose)
b Cohort 2 (proposed/higher dose)
c Clinically asymptomatic transient elevated liver function enzymes on the basis of laboratory values and resolved with prednisolone treatment. No drug-induced liver injury as per Hy’s law.
d In the completed clinical trial, one patient (the first patient infused in that study) was enrolled prior to the protocol amendment instituting administration of prednisolone before and after infusion.

table 20. Relevance Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Populationa</th>
<th>Interventionb</th>
<th>Comparatorc</th>
<th>Outcomess</th>
<th>Follow-Upc</th>
</tr>
</thead>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
Table 21. Study Design and Conduct Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation</th>
<th>Blinding</th>
<th>Selective Reporting</th>
<th>Data Completeness</th>
<th>Power</th>
<th>Statistical</th>
</tr>
</thead>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

The phase 3 confirmatory study (STRIVE-US) was initiated in September 2017.37 The inclusion and exclusion criteria are same as the phase 1 dose-finding study. The co-primary efficacy outcomes are functional independent sitting for 30 or more seconds at 18 months of age and event-free survival at 14 months of age (defined as avoidance of either death or need for tracheostomy or ventilation ≥16 hours/day for ≥2 consecutive weeks). Secondary efficacy outcomes are the ability to thrive at 18 months of age, including not receiving nutrition through mechanical support or other nonoral methods, ability to tolerate thin liquids (formal swallowing test), and maintaining weight (>3rd percentile for age and sex) and ability to remain independent of ventilatory support at 18 months of age. Results of this trial have not been published in a peer-reviewed journal yet. However, data has been presented at multiple cutoffs (Sep 27, 2018, Dec 31, 2018 and March 8, 2019) with most recent presentation at American Academy of Neurology (AAN) 2019 annual meeting with a median duration of follow-up of 10.2 months (15 out of 22 have been followed up for more than 1 year).41 The results are not summarized in detail but early data are largely consistent with previously available
findings. Briefly, 21 of 22 infants were alive with a median age of 14.4 months. There was one death and it was deemed not related to treatment. Five months after treatment, CHOP-INTEND scores increased by an average of 14.3 points, which was similar to the results from the pivotal Phase II trial.

**Section Summary: Symptomatic SMA Type I (Infantile-Onset)**

The evidence for use of onasemnogene abeparvovec-xioi for symptomatic SMA type I (infantile-onset) consists of a single, phase 1 study in which 12 of 15 infants with 2 copies of *SMN2* gene received the proposed therapeutic dose while 3 received a minimally effective dose. At the end of the 2-year follow-up, all 15 infants survived and none of the 12 patients who received the proposed therapeutic dose required permanent ventilation. All 12 patients also achieved at least 1 motor milestone, with 92% of those achieving CHOP INTEND scores greater than 40. The FDA approval was based on a pooled analysis of 21 patients from the pivotal phase I and ongoing confirmatory phase III STRIVE-US trial. The observed treatment effect on survival, event-free survival and achievement of motor functions is beyond what is typical based on the known natural history of patients with SMA type I with two copies of *SMN2*. The available published data support a durable treatment effect through 2 years. However, there is limited data to assess the long-term durability of treatment effect or safety, especially those adverse events that are potentially rare or have delayed onset.

**Presymptomatic Infants with a Genetic Diagnosis of SMA and Less Than 3 Copies of SMN2**

The clinical development program of onasemnogene abeparvovec-xioi for presymptomatic infants with a genetic diagnosis SMA and less than 3 copies of SMN2 includes a single prospective cohort study (SPRINT). The study characteristics are summarized in Table 23. This study plans to enroll 44 infants with biallelic *SMN1* deletion and 2 or 3 copies of *SMN2*. The primary endpoint among infants with 2 copies of *SMN2* is the proportion of patients with functional independent sitting for 30 or more seconds by 18 months of age and among those with 3 copies of *SMN2* is the proportion of patients able to stand without support for 3 or more seconds up to 24 months of age. Data has been presented at multiple cutoffs with most recent presentation at American Academy of Neurology (AAN) 2019 annual meeting. From April 10, 2018, to March 8, 2019, 18 patients with SMA have been dosed. All 18 patients had biallelic SMN1 deletions; 8 (44%) had 2 copies of SMN2, 9 (50%) had 3 copies of SMN2, and 1 (6%) had 4 copies of SMN2. The median treatment duration was 2.9 months (range 0.4 to 8.7) for all patients, 5.4 (range 1.1 to 8.7) for 8 patients with 2 copies of SMN2 and 2.2 months (0.4 to 4.8) for 9 patients with 3 copies of SMN2. At the data cutoff of March 8, 2019, all 18 children were alive and “event free.” Among 8 patients with two copies of SMN2, all reportedly achieved age-appropriate motor milestones including 4 who could sit without support and 1 who could stand with assistance. Data was much more limited for patients with 3 copies of SMN2. However, early increases in mean Bayley-III Gross Motor score were observed. Because only sparse data are available based on abstract/poster presentations to date, and the study has not been completed yet, summarizing study strengths and limitations would be premature. Further, the limited data is
inadequate to assess the durability of treatment effect or safety, especially those adverse events that are potentially rare or have delayed onset.

### Table 22. Summary of Key Nonrandomized Trials

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Country</th>
<th>Dates</th>
<th>Participants</th>
<th>Treatment</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort</td>
<td>U.S., Europe, Asia</td>
<td>2018-ongoing</td>
<td>Presymptomatic infants with biallelic deletions of SMN1 and 2 or 3 copies of SMN2 (n=44)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Onasemnogene abeparvovec-xioi (therapeutic dose)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Planned for 2 y</td>
</tr>
</tbody>
</table>

<sup>a</sup> As of August 22, 2018, 3 infants have been treated with onasemnogene abeparvovec-xioi.

<sup>b</sup> 1.1×10<sup>14</sup> mg/kg.

### Symptomatic SMA Type II

The clinical development program of intrathecal administration of onasemnogene abeparvovec-xioi for patients with SMA type II includes a single prospective cohort study (STRONG) that will enroll 27 patients up to 60 months (1800 days) of age at the time of dosing. The study inclusion criteria include genetic confirmation of SMA (biallelic SMN1 gene variants or deletions) with exactly three copies of SMN2. Children will be enrolled in the study if they demonstrate the ability to sit unassisted for ten or more seconds but cannot stand or walk. The study will evaluate the efficacy and safety of two doses given intrathecally (6.0´10<sup>[13]</sup>mg/kg and 1.2´10<sup>14</sup> mg/kg) in multiple cohorts. As of March 8, 2019, 30 patients have been enrolled.

The median duration of follow-up was 6 months (range 5 to 12) and 7 months (range 5 to 9) in cohorts of 16 patients with symptom onset between age ≥6 to <24 months and 12 patients with symptom onset between age ≥24 to <60 months. In the limited follow-up, no motor milestones achieved at baseline were subsequently lost. Among patients aged ≥6 to <24 months at baseline, 7 of 16 gained motor milestones following treatment. Among patients aged ≥24 to <60 months at baseline, 3 of 12 patients gained motor milestones following treatment. Use of intrathecal onasemnogene abeparvovec-xioi was not part of the original biologics license application filed by AveXis.<sup>43</sup>

### Summary of Evidence

Spinal muscular atrophy is an inherited disorder caused by homozygous deletions or variants in the SMN1 gene. As a consequence of absent or low levels of SMN1 protein, the motor neurons in spinal cord degenerate, resulting in atrophy of the voluntary muscles of the limbs and trunk. Nusinersen is a synthetic antisense oligonucleotide designed to bind to a specific sequence in exon 7 of the SMN2 transcript causing the inclusion of exon 7 in the SMN2 transcript, leading to the production of full length functional SMN2 protein, which is very similar to SMN1. Onasemnogene abeparvovec-xioi is intended as a one-time gene replacement therapy designed to deliver a functional copy of the SMN1 gene to motor neuron cells of patients with SMA. Because motor neurons are nondividing cells, it is postulated that once the SMN1 gene is incorporated in the cells, it would be retained over time and potentially allow for long-term, sustained SMN protein expression.
SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Institute for Health and Care Excellence
The National Institute for Health and Care Excellence (2018) issued a provisional recommendation against the use of nusinersen for the treatment for spinal muscular atrophy (SMA) due to the lack of long-term evidence, and the subsequent uncertainty surrounding long-term benefits. Additionally, the National Institute for Health Care and Excellence also concluded that there were uncertainties in the economic evidence and it was not deemed cost effective. The Institute was expected to release the Report in November 2018 but a final Report has not been released at the time of the last update of this Medical Policy.

Institute for Clinical and Economic Review
The Institute for Clinical and Economic Review published a final Report on comparative effectiveness and value of nusinersen and onasemnogene abeparvovec-xioi for SMA on April 3, 2019 and subsequently on May 24, 2019 published an update following FDA approval of onasemnogene abeparvovec-xioi.33

Nusinersen
Based on the lack of relevant data, the Report concluded that the evidence for nusinersen was insufficient for type 0 and IV SMA.

For infantile-onset SMA, the Report concluded with high certainty that nusinersen provides a substantial net health benefit, and rate the evidence base as “superior” to standard care (A). Limitations included potentially limited generalizability, as Type I SMA patients with more severe disease were underrepresented in the trials and may not adequately reflect the “real-world” patient population.”

For later-onset SMA, the Report concluded with moderate certainty that nusinersen provides a small or substantial net health benefit with a high certainty of at least a small net health benefit and rate the evidence as “incremental or better” (B+). Limitations included potentially limited generalizability (trial population may not reflect the true patient population) lack of data on survival, ventilation, and event-free survival and long-term safety and durability of clinical benefit.

For presymptomatic SMA, the Report concluded with moderate certainty of a small or substantial net health benefit with a high certainty of at least a small net health benefit and rate the evidence as “incremental or better” (B+).

Onasemnogene Abeparvovec-xioi
The Report only included and appraised the published evidence from the Phase II one dose-finding study of onasemnogene abeparvovec-xioi. The authors did not rate the quality of this study because they do not conduct quality assessment of non-comparative studies.
For type 0, later-onset (types II and III), type IV and presymptomatic SMA, the Report concluded that the evidence for onasemnogene abeparvovec-xioi was insufficient due to lack of relevant data. The Report also rated the evidence to be insufficient for comparison of onasemnogene abeparvovec-xioi versus nusinersen for infantile-onset SMA due to lack of evidence.

For infantile-onset SMA, the Report concluded with high certainty that onasemnogene abeparvovec-xioi provides a substantial net health benefit, and rate the evidence base as “superior” to standard care (A).

In summarizing the uncertainties of the clinical evidence, the ICER Report noted considerable uncertainty in the generalizability of the results and in the long-term durability and tolerability of treatment. Further, the Report notes additional uncertainty related to the possibility of loss of transgene expression over time and subsequent treatment pathway. The Report also noted that some patients in the pivotal trial subsequently received nusinersen, but the effects of combination or sequential therapies have not been well studied.

Subsequent to the FDA approval of onasemnogene abeparvovec-xioi, ICER issued an update with a brief discussion of additional data/interim analyses from ongoing trials that were presented at the Muscular Dystrophy Association Clinical and Scientific Conference April 13-17, 2019 and American Academy of Neurology Annual Meeting May 4-10, 2019) and manufacturer press releases. In summary, ICER noted that the updated data are largely consistent with previously available findings and as the data evolves and confirm the initial findings, the evidence rating may be revised.

**U.S. Preventive Services Task Force Recommendations**
Not applicable

**Medicare National Coverage**
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 23.

**Table 23. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing (Nusinersen)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02594124*</td>
<td>An Open-Label Study (SHINE) for Patients With Spinal Muscular Atrophy (SMA) Who Participated in Studies With IONIS-SMNRx</td>
<td>271</td>
<td>Feb 2020</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ongoing (Onasemnogene abeparvovec)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT</td>
<td>Title</td>
<td>Phase</td>
</tr>
<tr>
<td>-----</td>
<td>----------------------------------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>NCT03381729</td>
<td>Study of Intrathecal Administration of AVXS-101 for SMA</td>
<td>27</td>
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<tr>
<td>NCT03306277</td>
<td>Gene Replacement Therapy Clinical Trial for Patients With SMA Type 1</td>
<td>20</td>
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<tr>
<td>NCT03461289</td>
<td>Single-Dose Gene Replacement Therapy Clinical Trial for Patients With SMA Type 1</td>
<td>30</td>
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<tr>
<td>NCT03505099</td>
<td>Pre-Symptomatic Study of Intravenous AVXS-101 in SMA for Patients With Multiple Copies of SMN2</td>
<td>44</td>
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<tr>
<td>NCT03421977</td>
<td>Long-Term Follow-up Study for Patients From AVXS-101-CL-101</td>
<td>15</td>
</tr>
<tr>
<td>REACH (yet to register)</td>
<td>Information not available</td>
<td>Information not available</td>
</tr>
<tr>
<td>Ongoing (Onasemnogene abeparvovec)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

REFERENCES
Type 1: 24-Month Event-Free Survival and Achievement of Developmental Milestones (P.177). The 23rd International Annual Congress of the World Muscle Society; October 2-6, 2018; Mendoza, Argentina.


**Billing Coding/Physician Documentation Information**

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<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>96450</td>
<td>Chemotherapy administration, into CNS (eg, intrathecal), requiring and including spinal puncture</td>
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<tr>
<td>J2326</td>
<td>Injection, nusinersen, 0.1 mg (effective 01/01/18)</td>
</tr>
<tr>
<td>C9489</td>
<td>Injection, nusinersen, 0.1 mg (effective 07/01/17-12/31/17)</td>
</tr>
</tbody>
</table>

**ICD-10 Codes**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G12.0</td>
<td>Infantile spinal muscular atrophy, type I [Werdnig-Hoffman]</td>
</tr>
<tr>
<td>G12.1</td>
<td>Other inherited spinal muscular atrophy</td>
</tr>
</tbody>
</table>

**Additional Policy Key Words**

N/A

**Policy Implementation/Update Information**

8/1/19 New Policy. Considered Medically Necessary when criteria is met.

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational
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