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Professional	Institutional
Original Effective Date: August 25, 2022	Original Effective Date: August 25, 2022
Revision Date(s): October 13, 2022; February 9, 2023	Revision Date(s): October 13, 2022; February 9, 2023
Current Effective Date: February 9, 2023	Current Effective Date: February 9, 2023

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Populations	Interventions	Comparators	Outcomes
Individuals: • With type I spinal muscular atrophy	**Interventions of interest are:** • Onasemnogene abeparvovec-xioi	**Comparators of interest are:** • Continued medical management (respiratory, digestive, and orthopedic support) • Nusinersen	**Relevant outcomes include:** • Overall survival • Change in disease status • Functional outcomes • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • Who are presymptomatic with a genetic diagnosis	**Interventions of interest are:** • Onasemnogene abeparvovec-xioi	**Comparators of interest are:** • Nusinersen	**Relevant outcomes include:** • Overall survival

Populations	Interventions	Comparators	Outcomes
of spinal muscular atrophy and less than 4 copies of *SMN2*			• Change in disease status • Functional outcomes • Quality of life • Treatment-related mortality • Treatment-related morbidity
Individuals: • With type II spinal muscular atrophy	**Interventions of interest are:** • Intrathecal onasemnogene abeparvovec-xioi	**Comparators of interest are:** • Continued medical management (respiratory, digestive, and orthopedic support) • Nusinersen	**Relevant outcomes include:** • Overall survival • Change in disease status • Functional outcomes • Quality of life • Treatment-related mortality • Treatment-related morbidity

DESCRIPTION

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 survival motor neuron 1 protein, the motor neurons in the spinal cord degenerate, resulting in atrophy of the voluntary muscles of the limbs and trunk. This review is relevant to Onasemnogene abeparvovec-xioi and 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 spinal muscular atrophy. 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 survival motor neuron protein expression.

ONASEMNOGENE ABEPARVOVEC-XIOI

Infantile-Onset or Spinal Muscular Atrophy Type I

For individuals who have spinal muscular atrophy type I (infantile-onset) who receive onasemnogene abeparvovec-xioi, the evidence includes 2 single-arm studies. Relevant outcomes are overall survival, change in disease status, functional outcomes, quality of life, and treatment-related mortality and morbidity. The FDA approval was based on a pooled analysis of 21 patients from the 2 single-arm studies. 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 spinal muscular atrophy type I with 2 copies of *SMN2.* Results of the phase 3 confirmatory study (STRIVE-US) published after the FDA approval were largely consistent with previously available findings at the time of approval. Results of an ongoing study to assess long-term safety and durability of response in infants with SMA type 1 with a median time since dosing of 5.2 years showed that the developmental milestones achieved in the phase 1 clinical trial were

maintained and new milestones gained. Thirteen of 15 original patients were included in the analysis. All 10 patients in the therapeutic-dose cohort remained alive and without the need for permanent ventilation. All 10 patients treated with the therapeutic dose maintained previously acquired motor milestones. Two patients attained the new milestone of "standing with assistance" without the use of nusinersen. However, 7 of the 13 subsequently received concomitant nusinersen. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Presymptomatic Patients with a Diagnosis of Spinal Muscular Atrophy and Less Than 4 Copies of *SMN2*

For individuals who are presymptomatic with a genetic diagnosis of spinal muscular atrophy and less than 4 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. 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. The trial is ongoing and the results of 29 patients (14 infants with 2 copies and 12 infants with 3 copies of *SMN2* gene with an average age of 11.2 and 9.7 months respectively are available). Among the cohort of infants with 2 copies of *SMN2* gene, 57% (8/14) sat for 30 seconds or more without assistance as measured by the Bayley-III, 21% (3/14) stood for 10 seconds or more without assistance and 29% (4/14) walked 5 steps or more without assistance as measured by WHO-MGRS and 100% (14/14) reached a CHOP INTEND score of 50 points or higher by 6 months of age. Among the cohort of infants with 3 copies of *SMN2* gene, 27% (4/15) stood for 3 seconds or more without assistance, 60% (9/15) stood for 10 seconds or more with assistance and 13% (2/15) walked 5 steps or more without assistance as measured by WHO-MGRS. Because only limited data are available, and the study has not been completed yet, summarizing study strengths and limitations would be premature. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Spinal Muscular Atrophy Type II

For individuals with spinal muscular atrophy 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 the 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 that the technology results in an improvement in the net health outcome.

OBJECTIVE

The objective of this evidence review is to assess whether treatment of spinal muscular atrophy improves the net health outcome.

BACKGROUND

Spinal Muscular Atrophy

Spinal muscular atrophy 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 spinal muscular atrophy, 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.[1,] Due to absent or low levels of the survival motor neuron 1 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 survival motor neuron protein in motor neurons has not been completely elucidated, and levels of the survival motor neuron protein required for optimal functioning are unknown.[2,]

There is wide phenotypic heterogeneity in spinal muscular atrophy, 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.[3,] The number of copies of the *SMN2* gene varies widely (range, 0-6), resulting in a less severe form of spinal muscular atrophy among those with more copies of the *SMN2* gene and vice-versa.[4,] The relation between the *SMN2* copy number and spinal muscular atrophy phenotype is summarized in Table 2. These data were generated from DNA samples of 375 patients with spinal muscular atrophy who previously had been classified as follows: 188 with spinal muscular atrophy type I, 110 with spinal muscular atrophy type II, and 77 with spinal muscular atrophy type III.[5,]

Table 1. Characteristics and Subtypes of Spinal Muscular Atrophy

Type of SMA	Age at Symptoms Onset	Life Span	Highest Motor Milestone Achieved	*SMN2* Copy Number[a]
Type 0 (antenatal-onset SMA)	Prenatal	<6 mo	Little ability to move and may be unable to breathe and swallow independently.	1
Type I (infantile SMA or Werdnig-Hoffman disease)	0-6 mo	<2 y without respiratory support	Never rolls or sits unsupported	2
Type II (intermediate SMA or	<18 mo	>2 y; »70% alive at 25 y of age	Sits independently once properly positioned;	3 or 4

Type of SMA	Age at Symptoms Onset	Life Span	Highest Motor Milestone Achieved	*SMN2* Copy Number[a]
Dubowitz disease)			sometimes stands but never able to walk	
Type III (Kugelberg-Welander disease)				
Subtype IIIa	>18 mo to 3 y	Similar to that of the general population	Sits, stands, and walks independently until puberty; many no longer walk after puberty. Never runs or jumps well	3 or 4
Subtype IIIb	>3 y	Similar to that of the general population	Sits, stands, and walks independently until puberty; many no longer walk after puberty. Walks, runs, jumps, and can participate in sports.	4
Type IV (adult-onset SMA)	>21 y	Similar to that of the general population	Similar to that of the general population	4-8

Adapted from the Muscular Dystrophy Association (n.d.),[6,] National Organization for Rare Disorders (2012),[7,] Zerres et al (1995),[8,] Finkel et al (2014),[9,] and Rudnik-Schoneborn et al (2001).[10,]
SMA: spinal muscular atrophy.
[a] 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.[5,]
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.[11,]

Table 2. Relation Between *SMN2* Copy Numbers and Spinal Muscular Atrophy Phenotype

Type of SMA	Percent With 1 *SMN2* Copy	Percent With 2 *SMN2* Copies	Percent With 3 *SMN2* Copies	Percent With 4 *SMN2* Copies
Type I	6.9	73.4	19.7	0
Type II	0	10.9	81.8	7.3
Type III	0	3.9	50.6	45.5
	Probability[a] of SMA Type I	**Probability[a] of SMA Type II**	**Probability[a] of SMA Type III**	
1 *SMN2* copy	99.9	0	0	
2 *SMN2* copies	97.3	2.7	0	
2 *SMN2* copies	7.2	82.8	10.0	
4 *SMN2* copies	1.6	14.8	83.6	

Adapted from Feldkotter et al (2002)[5,]
SMA: spinal muscular atrophy.
[a] 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

Spinal muscular atrophy 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 spinal muscular atrophy if they have a homozygous deletion of the *SMN1* gene or a homozygous absence of the *SMN1* gene due to gene conversion (i.e., *SMN1* gene conversion to *SMN2* gene) or a compound heterozygote variant in the *SMN1* gene. Individuals are defined as carriers if they have 1 copy of the *SMN1* gene on 1 chromosome and no copies on the other or 2 copies of the *SMN1* gene on 1 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 spinal muscular atrophy symptom onset may occur shortly after birth to months to years later, estimating the incidence and prevalence of spinal muscular atrophy 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 100,000 live births,[12,13,] which translates to 500 new spinal muscular atrophy cases annually.

Treatment

Medical management of spinal muscular atrophy 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 interventions 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 (e.g., gastrostomy feeding and noninvasive/invasive ventilation).

Onasemnogene abeparvovec-xioi, a 1-time gene replacement therapy is intended as an intravenous infusion for patients with spinal muscular atrophy type I and an intrathecal infusion for spinal muscular atrophy type II. There are 4 major components of this technology—the vector, the *SMN* transgene, the self-complementary DNA technology, and the promoter.[12,] 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 *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 survival motor neuron protein.

Because motor neurons are nondividing cells, it is has been suggested that once the *SMN* gene is incorporated in the cells, it would be retained over time and potentially allow for long-term, sustained survival motor neuron protein expression with a 1-time dose, and provide a durable therapeutic effect based on studies in animal models.[16,17,18,19,]

REGULATORY STATUS

On May 24, 2019, onasemnogene abeparvovec-xioi (Zolgensma®; Avexis) was approved by the FDA for the 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.

POLICY

A. **Onasemnogene Abeparvovec-Xioi (Low-Control)**

1. Onasemnogene abeparvovec-xioi may be considered **medically necessary** if **ALL** of the following conditions are met:
   a. Diagnosis of spinal muscular atrophy based on the results of SMA newborn screening
      AND
   b. Diagnosis of spinal muscular atrophy confirmed by genetic testing demonstrating bi-allelic mutations in the survival motor neuron 1 (*SMN1*) gene as stated below
      I. deletion of both copies of the *SMN1* gene **OR**
      II. compound heterozygous mutations of the *SMN1* gene (defined below):
         i. pathogenic variant(s) in both copies of the *SMN1* gene
         ii. pathogenic variant in 1 copy and deletion of the second copy of the *SMN1* gene.

      AND
   c. Documentation of a genetic test confirms no more than 3 copies of the *SMN2* gene.
      AND
   d. The patient is less than 2 years of age at the time of infusion of onasemnogene abeparvovec-xioi.
      AND
   e. Documentation of baseline laboratory assessments such as AST, ALT, total bilirubin, and prothrombin time.
      AND
   f. The patient does not have advanced spinal muscular atrophy (e.g., complete paralysis of limbs, permanent ventilator dependence).
      AND
   g. Baseline anti-adeno-associated virus serotype 9 (AAV9) antibody titers < 1:50.
      AND
   h. Prescribed by a neurologist with expertise in treating spinal muscular atrophy.

2. Repeat treatment or ante-partum use of onasemnogene abeparvovec-xioi is considered **experimental / investigational**.

3. Onasemnogene abeparvovec-xioi is considered **experimental /investigational** for all other indications.

4. Concurrent use of onasemnogene abeparvovec-xioi with nusinersen and/or risdiplam is considered **experimental / investigational.**

5. Use of nusinersen and/or risdiplam after administration of onasemnogene abeparvovec-xioi is considered **experimental / investigational.**

POLICY GUIDELINES

Onasemnogene Abeparvovec-Xioi

A. The recommended dosage of onasemnogene abeparvovec-xioi is 1.1×10^{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 U.S. Food and Drug Administration (FDA) approved prescribing label.
B. 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.
C. 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.
D. Liver function (clinical exam, AST, ALT, total bilirubin, prothrombin time), platelet counts, and troponin-I levels should be monitored as per the prescribing label.
E. Where feasible, the patient's vaccination schedule should be adjusted to accommodate concomitant corticosteroid administration prior to and following onasemnogene abeparvovec-xioi infusion.
F. 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.
G. Efficacy of onasemnogene abeparvovec-xioi in patients with c.859G>C variant in *SMN2* gene has not been evaluated.

Dosing Limits

A. 1 injection per lifetime

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through August 12, 2021.

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, 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, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 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.

ONASEMNOGENE ABEPARVOVEC-XIOI

Clinical Context and Therapy Purpose

The purpose of onasemnogene abeparvovec-xioi in patients who have spinal muscular atrophy type I is to provide a treatment option that is an improvement on existing therapies. Potential benefits of this gene therapy[42,] 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.

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 spinal muscular atrophy?

The following PICO was used to select literature to inform this review.

Populations

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

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. Given the heterogeneity and varying life expectancies among patients with different spinal muscular atrophy subtypes, the timing of follow-up of studies to reasonably assess whether onasemnogene abeparvovec-xioi offers a net health benefit will differ

by spinal muscular atrophy subtypes as well as by the timing of treatment initiation relative to symptom onset.

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 RCTs;
- 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 3.

Table 3. Summary of the Clinical Development Program for Onasemnogene Abeparvovec-Xioi

Study	Phase	N	Status
Infants under 6 wk (presymptomatic with a genetic diagnosis of SMA and less than 4 copies of *SMN2*)			
SPR1NT (NCT03505099)	3	44	Completed
Children <6 mo of age (SMA type I)			
Pivotal (NCT02122952)[43,]	1	15	Completed
STR1VE-US trial (NCT03306277)[44,]	3	21	Completed
STR1VE-EU trial (NCT03461289)	3	30	Completed
START (NCT03421977)[a45,]	4	15	Ongoing; estimated completion: Dec 2033
Children up to 60 mo of age (SMA type II)			
STRONG (NCT03381729)	1	27	Suspended Apr 2024
Patients between 6 mo and 18 y who are ineligible for the other studies			
REACH (yet to register)			

PIVOTAL: Gene Transfer Clinical Trial for Spinal Muscular Atrophy Type 1; SPR1NT: Pre-Symptomatic Study of Intravenous Onasemnogene Abeparvovec-xioi in Spinal Muscular Atrophy (SMA) for Patients With Multiple Copies of SMN2; START: Long-Term Follow-up Study for Patients From AVXS-101-CL-101; STRIVE EU: Single-Dose Gene Replacement Therapy Clinical Trial for Patients With Spinal Muscular Atrophy Type 1; STRIVE US: Gene Replacement Therapy Clinical Trial for Patients With Spinal Muscular Atrophy Type 1; STRONG: Study of Intrathecal Administration of Onasemnogene Abeparvovec-xioi for 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 spinal muscular atrophy type I includes 4 prospective cohort studies; 2 dose-finding

studies, 2 phase 3 confirmatory studies (STRIVE-US: Gene Replacement Therapy Clinical Trial for Patients With Spinal Muscular Atrophy Type 1; STRIVE EU: Single-Dose Gene Replacement Therapy Clinical Trial for Patients With Spinal Muscular Atrophy Type 1), and 1 long-term follow-up study (START: Long-Term Follow-up Study for Patients From AVXS-101-CL-101). These trials will enroll a total of 65 patients with symptomatic spinal muscular atrophy type I. The study characteristics and results are summarized in Tables 4 and 5.

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 spinal muscular atrophy type I with 2 copies of the *SMN2* gene, 8% of patients are expected to survive beyond 2 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 rare[23,] 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 2 patients. The early data in a small number of patients diagnosed with spinal muscular atrophy type I is indicative of a positive impact on survival and motor functions that are durable up to 2 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 spinal muscular atrophy was the primary evidence for the effectiveness of onasemnogene abeparvovec-xioi. The FDA analysis is summarized in Table 5.

The inclusion and exclusion criteria of the phase 3 confirmatory study (STRIVE-US) were the same as the phase 1 dose-finding study.[44,] 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 the 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 are summarized in Tables 4 and 5. The results are largely consistent with previously available findings.

Results of an ongoing study to assess long-term safety and durability of response in infants with SMA type 1 with a median time since dosing of 5.2 (range 4.6 to 6.2 years) have been published[45,] and summarized in Tables 4 and 5. Seven of 13 were receiving concomitant nusinersen (all 3 patients in the low-dose cohort and 4 of the 10 patients in the therapeutic-dose cohort). The primary objective is to assess safety, and the secondary objective is to determine whether developmental milestones achieved in the phase 1 clinical trial were maintained and new milestones gained. Thirteen of 15 original patients were included in the analysis; 2 patients'

families declined follow-up participation. At the data cutoff on June 11, 2020, the median age of 13 patients followed was 38.9 months. Serious adverse events occurred in 8 patients (62%), none of which resulted in study discontinuation or death. All 10 patients in the therapeutic-dose cohort remained alive and without the need for permanent ventilation. All 10 patients treated with the therapeutic dose maintained previously acquired motor milestones. Two patients attained the new milestone of "standing with assistance" without the use of nusinersen.

While the current evidence for symptomatic type I spinal muscular atrophy patients is limited to patients with 2 copies of *SMN2*, approximately 20% of type I spinal muscular atrophy patients may have 3 copies of *SMN2*.[5,] 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 spinal muscular atrophy patients who are administered onasemnogene abeparvovec-xioi after 6 months of age.

The purpose of the study limitations tables (see Tables 6 and 7) 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 (e.g., *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 spinal muscular atrophy type I patients was 2.5 (0.6) and 6.3 (2.2) months, respectively, based on a systematic literature review of studies published between 2000 and 2014.[46,] The weighted diagnostic delay in this systematic review was 3.6 months. In the onasemnogene abeparvovec-xioi phase 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 spinal muscular atrophy, it is possible that the delay in diagnosis of spinal muscular atrophy may be shortened.

AveXis, is planning to create a prospective, long-term registry of at least 500 spinal muscular atrophy 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 , 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 4. Summary of Key Characteristics of Nonrandomized Trials

Study	Study Type	Country	Dates	Participants	Treatment	Follow-Up
Mendell et al (2017)[43,]	Single Cohort	U.S.	2014-2017	Infants <9 months[a] with biallelic *SMN1* deletions or variants with 2 copies of *SMN2* (n=15). Patients with c.859G>C variant in *SMN2* exon 7 were excluded from the study.[b]	Onasemnogene abeparvovec-xioi (3 minimally effective dose[c]; 12 proposed therapeutic dose[d])	Median, 30.7[c] and 27.8[d] months[e]
Day et al (2021)[44,]	Single Cohort	U.S.	2017-2019	Infants <6 months with biallelic *SMN1* deletions or variants with 1 or 2 copies of *SMN2* (n=22). Patients with c.859G>C variant in *SMN2* exon 7 were included in the study.[b]	Onasemnogene abeparvovec (single IV dose of 1.1 X 10^{14} vector genomes per kg)	18 months
Mendell et al (2021)[45,]	Single Cohort	U.S.	2017-2021	Infants <9 months[a] with biallelic *SMN1* deletions or variants with 2 copies of *SMN2* (n=13). Patients with c.859G>C variant in *SMN2* exon 7 were excluded from the study.[b]	No treatment; intent was long-term follow-up for safety	Median time since dosing 5.2 years (range, 4.6 to 6.2)

[a] Protocol was amended to lower the age to 6 months of age or younger.
[b] c.859G>C substitution is a positive modifier and has been shown to results in a mild SMA phenotype.[47,]
[c] At 6.7×10^{13} vg/kg.
[d] At 2.0×10^{14} vg/kg.
[e] The oldest patients is 46.2 months of age, with 40.6 months of follow-up.

Table 5. Summary of Key Results of Nonrandomized Trials

Study	Survival	Change in Mean CHOP INTEND Score	Patients With CHOP INTEND Score >40, n (%)	Others	Safety
FDA Label (as of the March 2019 data cutoff)[48,]					
N	21				44
Onasemnogene abeparvovec-xioi	90.5%	NR	NR	• 1 patient died at age 7.8 months due to	Elevated ALT/AST[d] (> ULN): 12 (27.3%) Vomiting: 3 (6.8%)

Study	Survival	Change in Mean CHOP INTEND Score	Patients With CHOP INTEND Score >40, n (%)	Others	Safety
				disease progression • 1 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.	
Day et al (2021)[44,]					
N	22				
Onasemnogene abeparvovec-xioi	95%	NR	21 (95%)	• 59% (13 of 22 patients achieved functional independent	• All patients had at least 1 adverse event (most common was pyrexia).

Study	Survival	Change in Mean CHOP INTEND Score	Patients With CHOP INTEND Score >40, n (%)	Others	Safety
				sitting for 30 s or longer at the 18 months of age study visit) • 41% (9 of 22 patients maintained the ability to thrive[e] at the 18 months of age study visit)	Frequently reported serious adverse events were bronchiolitis, pneumonia, • respiratory distress, and respiratory syncytial virus bronchiolitis. • 3 serious adverse events were related or possibly related to the treatment (2 cases of elevated hepatic aminotransferases and 1 of hydrocephalus).
Historical cohort (PNCR)[9,]	20%	NR	Rare	• None of the 23 untreated patients achieved functional independent sitting for 30 s or longer at the 18 months of age in the PNCR cohort • Ability to thrive data was not reported for the PNCR cohort	• NA
Mendell et al (2021)45,					
N	13				
Onasemnogene abeparvovec-xioi	100% (10 of 10 in	NA	NA	• 7 of 13 receiving	Serious adverse events (n=8; 62%)

Study	Survival	Change in Mean CHOP INTEND Score	Patients With CHOP INTEND Score >40, n (%)	Others	Safety
	therapeutic dose) 100% (3 of 3 in low dose)			concomitant nusinersen (all 3 in the low-dose cohort and 4 of the 10 patients in the therapeutic-dose cohort) • None of the 10 in the therapeutic-dose cohort require permanent ventilation • 2 of 3 in the low dose remain free of permanent ventilation • All 10 patients in therapeutic dose cohort maintained previously acquired motor milestones. Two attained the new milestone of "standing with assistance" without the use of nusinersen.	• Acute respiratory failure (4 [31%]) • Pneumonia (4 [31%]) • Dehydration (3 [23%]) • Respiratory distress (2 [15%]) • Bronchiolitis (2 [15%])

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

[d] In the completed clinical trial, 1 patient (the first patient infused in that study) was enrolled prior to the protocol amendment instituting administration of prednisolone before and after infusion.
[e] Ability to thrive was a composite endpoint defined by swallowing function (the ability to tolerate thin liquids shown by a formal clinical swallowing assessment [e.g., bedside swallow exam]) AND nutritional support (feeding exclusively by mouth, defined as not receiving nutrition through a feeding tube or other non-oral methods) AND weight maintenance (maintaining weight greater than the third percentile for the appropriate age and sex)

Table 6. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Mendell et al (2017)[43]					1. Not sufficient duration for benefit (long-term) 2. Not sufficient duration for harms (long-term)
Day et al (2021)[44]					1. Not sufficient duration for benefit (long-term) 2. Not sufficient duration for harms (long-term)
Mendell et al (2021)[45]		4. Not the intervention of interest (7 out of 13 patients received continue to receive nusinersen after receiving one-time gene therapy).			

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

Table 7. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[d]	Data Completeness[e]	Power[d]	Statistical[f]
Mendell et al (2017)[43,]	1. Participants not randomly allocated	3. Outcome assessed by treating physician				
Day et al (2021)[44,]	1. Participants not randomly allocated	3. Outcome assessed by treating physician				
Mendell et al (2021)[45,]	1. Participants not randomly allocated	3. Outcome assessed by treating physician		5. Two of the 13 in the high dose cohort did not participate		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[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: Symptomatic Spinal Muscular Atrophy Type I (Infantile-Onset)
The evidence for use of onasemnogene abeparvovec-xioi for symptomatic spinal muscular atrophy type I (infantile-onset) consists of 2 single-arm studies. The FDA approval was based on a pooled analysis of 21 patients from the 2 single-arm studies. The observed treatment effect on survival, event-free survival and achievement of motor functions is beyond what is typically based on the known natural history of patients with spinal muscular atrophy type I with 2 copies of *SMN2.* Results of the phase 3 confirmatory study (STRIVE-US) published after the FDA approval were largely consistent with previously available findings at the time of approval. Results of an ongoing study to assess long-term safety and durability of response in infants with SMA type 1 with a median time since dosing of 5.2 years showed that the developmental milestones achieved in the phase 1 clinical trial were maintained and new milestones gained. Thirteen of 15 original patients were included in the analysis. All 10 patients in the therapeutic-dose cohort remained alive and without the need for permanent ventilation. All 10 patients treated with the therapeutic dose maintained previously acquired motor milestones. Two patients attained the new milestone of "standing with assistance" without the use of nusinersen. However, 7 of the 13 subsequently received concomitant nusinersen.

Presymptomatic Infants with a Genetic Diagnosis of Spinal Muscular Atrophy and Less Than 4 Copies of *SMN2*

The clinical development program of onasemnogene abeparvovec-xioi for presymptomatic infants with a genetic diagnosis of spinal muscular atrophy and less than 4 copies of *SMN2* includes a single prospective cohort study called SPRINT. 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. The trial is ongoing and the results of 29 patients (14 infants with 2 copies and 12 infants with 3 copies of *SMN2* gene with an average age of 11.2 and 9.7 months, respectively, are available). Among the cohort of infants with 2 copies of the *SMN2* gene, 57% (8/14) sat for 30 seconds or more without assistance as measured by the Bayley-III, 21% (3/14) stood for 10 seconds or more without assistance and 29% (4/14) walked 5 steps or more without assistance as measured by WHO-MGRS and 100% (14/14) reached a CHOP INTEND score of 50 points or higher by 6 months of age. Overall, 50% (7/14) achieved motor scores within the age-appropriate range for unaffected patients. These scores include the ability to achieve skills such as sitting, standing, or walking with assistance. In the natural history of SMA Type 1, untreated children with 2 copies of the *SMN2* backup gene would not achieve such skills. Among the cohort of infants with 3 copies of *SMN2* gene, 27% (4/15) stood for 3 seconds or more without assistance, 60% (9/15) stood for 10 seconds or more with assistance and 13% (2/15) walked 5 steps or more without assistance as measured by WHO-MGRS. All patients (29/29) did not need temporary breathing support and remained free of feeding support and 97% (28/29) remained within a normal weight range (3rd-97th percentile for age). Because only limited data are available, and the study has not yet been completed, 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 8. Summary of Key Nonrandomized Trials

Study	Study Type	Country	Dates	Participants	Treatment	Follow-Up
Schultz et al (2018);SPRINT[49],	Cohort	U.S., Europe, Asia	2018-ongoing	Presymptomatic infants with biallelic deletions of *SMN1* and 2 or 3 copies of *SMN2* (n=44)[a]	Onasemnogene abeparvovec-xioi (therapeutic dose[b])	Planned for 2 y

SPRINT: Pre-Symptomatic Study of Intravenous Onasemnogene Abeparvovec-xioi in Spinal Muscular Atrophy (SMA) for Patients With Multiple Copies of *SMN2*.
[a] As of August 22, 2018, 3 infants have been treated with onasemnogene abeparvovec-xioi.
[b] 1.1×10^{14} vg/kg.

Symptomatic Spinal Muscular Atrophy Type II

The clinical development program of intrathecal administration of onasemnogene abeparvovec-xioi for patients with spinal muscular atrophy type II includes a single prospective cohort study (STRONG: Study of Intrathecal Administration of Onasemnogene Abeparvovec-xioi for Spinal Muscular Atrophy) 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 spinal muscular atrophy

(biallelic *SMN1* gene variants or deletions) with exactly 3 copies of *SMN2*. Children will be enrolled in the study if they demonstrate the ability to sit unassisted for 10 or more seconds but cannot stand or walk. The study will evaluate the efficacy and safety of 2 doses given intrathecally ($6.0´10^{13}$ mg/kg and $1.2´10^{14}$ mg/kg) in multiple cohorts.

As of August 20,2021, the trial is suspended as FDA has placed intrathecal studies on clinical hold pending further discussions regarding pre-clinical findings.

SUMMARY OF EVIDENCE

ONASEMNOGENE ABEPARVOVEC-XIOI

Infantile-Onset or Spinal Muscular Atrophy Type I

For individuals who have spinal muscular atrophy type I (infantile-onset) who receive onasemnogene abeparvovec-xioi, the evidence includes 2 single-arm studies. Relevant outcomes are overall survival, change in disease status, functional outcomes, quality of life, and treatment-related mortality and morbidity. The FDA approval was based on a pooled analysis of 21 patients from the 2 single-arm studies. 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 spinal muscular atrophy type I with 2 copies of *SMN2.* Results of the phase 3 confirmatory study (STRIVE-US) published after the FDA approval were largely consistent with previously available findings at the time of approval. Results of an ongoing study to assess long-term safety and durability of response in infants with SMA type 1 with a median time since dosing of 5.2 years showed that the developmental milestones achieved in the phase 1 clinical trial were maintained and new milestones gained. Thirteen of 15 original patients were included in the analysis. All 10 patients in the therapeutic-dose cohort remained alive and without the need for permanent ventilation. All 10 patients treated with the therapeutic dose maintained previously acquired motor milestones. Two patients attained the new milestone of "standing with assistance" without the use of nusinersen. However, 7 of the 13 subsequently received concomitant nusinersen. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Presymptomatic Patients with a Diagnosis of Spinal Muscular Atrophy and Less Than 4 Copies of *SMN2*

For individuals who are presymptomatic with a genetic diagnosis of spinal muscular atrophy and less than 4 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. 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. The trial is ongoing and the results of 29 patients (14 infants with 2 copies and 12 infants with 3 copies of *SMN2* gene with an average age of 11.2 and 9.7 months, respectively, are available). Among the cohort of infants with 2 copies of *SMN2* gene, 57% (8/14) sat for 30 seconds or more without assistance as measured by the Bayley-III, 21% (3/14) stood for 10 seconds or more without assistance and 29% (4/14)

walked 5 steps or more without assistance as measured by WHO-MGRS and 100% (14/14) reached a CHOP INTEND score of 50 points or higher by 6 months of age. Among the cohort of infants with 3 copies of *SMN2* gene, 27% (4/15) stood for 3 seconds or more without assistance, 60% (9/15) stood for 10 seconds or more with assistance and 13% (2/15) walked 5 steps or more without assistance as measured by WHO-MGRS. Because only limited data are available, 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.[52,53,] The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Spinal Muscular Atrophy Type II
For individuals with spinal muscular atrophy 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 that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Institute for Clinical and Economic Review
The Institute for Clinical and Economic Review published a final report on comparative effectiveness and value of onasemnogene abeparvovec-xioi for spinal muscular atrophy on April 3, 2019, and subsequently on May 24, 2019, published an update following U.S. Food and Drug Administration (FDA) approval of onasemnogene abeparvovec-xioi.[42,]

Onasemnogene Abeparvovec-Xioi
The report only included and appraised the published evidence from the Phase I 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 spinal muscular atrophy, 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 spinal muscular atrophy due to lack of evidence.
- For infantile-onset spinal muscular atrophy, 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 Institute for Clinical and Economic Review 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, the Institute for Clinical and Economic Review 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, the Institute for Clinical and Economic Review 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

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 9

Table 9. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing (Onasemnogene abeparvovec)			
NCT03381729 (STRONG)[a,b]	Study of Intrathecal Administration of AVXS-101 for SMA	27	Apr 2024 (Clinical Hold)
NCT03421977 (START)[a,b]	Long-Term Follow-up Study for Patients From AVXS-101-CL-101	15	Dec 2033
NCT04042025[a]	Long-term Follow-up Study of Patients Receiving Onasemnogene Abeparvovec-xioi	308	Dec 2035
REACH (yet to register)[a]	Information not available	Information not available	Information not available
Unpublished			

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT03461289 (STRIVE-EU)[a]	Single-Dose Gene Replacement Therapy Clinical Trial for Patients With SMA Type 1	30	Sep 2020
NCT03505099 (SPRINT)[a]	Pre-Symptomatic Study of Intravenous Onasemnogene Abeparvovec-xioi in SMA for Patients With Multiple Copies of *SMN2*	44	Jul 2021

NCT: national clinical trial; SMA: spinal muscular atrophy.
[a] Denotes industry-sponsored or cosponsored trial. [b] As of October 13, 2020, the trial is suspended as FDA has placed intrathecal studies on clinical hold pending further discussions regarding pre-clinical findings.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
96450	Chemotherapy administration, into CNS (e.g., intrathecal), requiring and including spinal puncture
J3399	Injection, onasemnogene abeparvovec-xioi, per treatment, up to 5x10^15 vector genomes

ICD-10 DIAGNOSES	
G12.0	Injection, onasemnogene abeparvovec-xioi, per treatment, up to 5x10^15 vector genomes
G12.1	Other inherited spinal muscular atrophy
Z92.86	Personal history of gene therapy

REVISIONS	
08-25-2022	Policy added to the bcbsks.com web site.
10-13-2022	Updated Policy Section ▪ Added to Section A and A1 Onasemnogene Abeparvovec-Xioi: "(High-Control)" ▪ Added Section Ae: "Documentation of baseline laboratory assessments such as AST, ALT, total bilirubin, and prothrombin time." ▪ Added Section B: "Onasemnogene Abeparvovec-Xioi (Low-Control)" 1. Onasemnogene abeparvovec-xioi (Low-Control) may be considered medically necessary if ALL of the following conditions are met: a. Diagnosis of spinal muscular atrophy confirmed by genetic testing demonstrating bi-allelic mutations in the survival motor neuron 1 (SMN1) gene as stated below I. deletion of both copies of the SMN1 gene OR II. compound heterozygous mutations of the SMN1 gene (defined below): i. pathogenic variant(s) in both copies of the SMN1 gene ii. pathogenic variant in 1 copy and deletion of the second copy of the SMN1 gene. AND b. Documentation of signs and symptoms consistent with a clinical diagnosis of spinal muscular atrophy. AND c. Documentation of a genetic test confirms no more than 3 copies of the SMN2 gene. AND

REVISIONS	
	d. The patient is less than 2 years of age at the time of infusion of onasemnogene abeparvovec-xioi. AND e. Documentation of baseline laboratory assessments such as AST, ALT, total bilirubin, and prothrombin time. AND f. The patient does not have advanced spinal muscular atrophy (e.g., complete paralysis of limbs, permanent ventilator dependence). AND g. Baseline anti-adeno-associated virus serotype 9 (AAV9) antibody titers < 1:50. AND h. Prescribed by a neurologist with expertise in treating spinal muscular atrophy. 2. Repeat treatment or ante-partum use of onasemnogene abeparvovec-xioi is considered experimental / investigational. 3. Onasemnogene abeparvovec-xioi is considered experimental /investigational for all other indications. 4. Concurrent use of onasemnogene abeparvovec-xioi with nusinersen and/or risdiplam is considered experimental / investigational. 5. Use of nusinersen and/or risdiplam after administration of onasemnogene abeparvovec-xioi is considered experimental / investigational.
	Updated Policy Guideline Section ▪ Added: Dosing Limits A. 1 injection per lifetime
02-09-2023	Updated Policy Section ▪ Removed Section A **Onasemnogene Abeparvovec-Xioi (High-Control)** A. **Onasemnogene Abeparvovec-Xioi (High-Control)** 1. Onasemnogene abeparvovec-xioi (High-Control) may be considered **medically necessary** if **ALL** of the following conditions are met: a. Diagnosis of spinal muscular atrophy confirmed by genetic testing demonstrating bi-allelic mutations in the survival motor neuron 1 (*SMN1*) gene as stated below I. deletion of both copies of the *SMN1* gene **OR** II. compound heterozygous mutations of the *SMN1* gene (defined below): i. pathogenic variant(s) in both copies of the *SMN1* gene ii. pathogenic variant in 1 copy and deletion of the second copy of the *SMN1* gene. **AND** b. Documentation of onset of symptoms consistent with a clinical diagnosis of type I spinal muscular atrophy less than 6 months of age. **AND** c. Documentation of a genetic test confirms no more than 2 copies of the SMN2 gene. **AND** d. The individual is less than 6 months of age at the time of infusion of onasemnogene abeparvovec-xioi. **AND** e. Documentation of baseline laboratory assessments such as AST, ALT, total bilirubin, and prothrombin time. **AND** f. The individual does not have advanced spinal muscular atrophy (e.g., complete paralysis of limbs, permanent ventilator dependence). **AND** g. Baseline anti-adeno-associated virus serotype 9 (AAV9) antibody titers < 1:50. **AND** h. Prescribed by a neurologist with expertise in treating spinal muscular atrophy. 2. Repeat treatment or ante-partum use of onasemnogene abeparvovec-xioi is considered **experimental/investigational**. 3. Onasemnogene abeparvovec-xioi is considered **experimental/investigational** for all other indications.

REVISIONS	
	4. Concurrent use of onasemnogene abeparvovec-xioi with nusinersen and/or risdiplam is considered **experimental/investigational**. 5. Use of nusinersen and/or risdiplam after administration of onasemnogene abeparvovec-xioi is considered **experimental / investigational**. ▪ Section B (new A) **Onasemnogene Abeparvovec-Xioi (Low-Control)** • Added A1a "Diagnosis of spinal muscular atrophy based on the results of SMA newborn screening" • Removed A1c "Documentation of signs and symptoms consistent with a clinical diagnosis of spinal muscular atrophy."

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