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Onasemnogene Abeparvovec-xioi

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Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For Illinois only: Illinois Public Act 103-0458 [Insurance Code 215 ILCS 5/356z.61] (HB3809 Impaired Children) states all group or individual fully insured PPO, HMO, POS plans amended, delivered, issued, or renewed on or after January 1, 2025 shall provide coverage for therapy, diagnostic testing, and equipment necessary to increase quality of life for children who have been clinically or genetically diagnosed with any disease, syndrome, or disorder that includes low tone neuromuscular impairment, neurological impairment, or cognitive impairment.

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug

approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

Onasemnogene abeparvovec-xioi (Zolgensma) **may be considered medically necessary** if ALL of the following conditions are met:

1. Diagnosis of spinal muscular atrophy confirmed by genetic testing demonstrating bi-allelic mutations in the survival motor neuron 1 (*SMN1*) gene as stated 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 1 copy and deletion of the second copy of the *SMN1* gene.
2. Documentation of a genetic test confirms no more than 4 copies of the *SMN2* gene.
3. The individual is less than 2 years of age at the time of infusion of onasemnogene abeparvovec-xioi.
4. Documentation of baseline laboratory assessments such as AST, ALT, total bilirubin, and prothrombin time.
5. The individual does not have advanced spinal muscular atrophy (e.g., complete paralysis of limbs, permanent ventilator dependence).
6. Negative baseline titers for anti-adeno-associated virus serotype 9 (AAV9) antibody (see **NOTE 1** in Policy Guidelines).
7. Prescribed by a neurologist with expertise in treating spinal muscular atrophy.

Repeat treatment or ante-partum use of onasemnogene abeparvovec-xioi (Zolgensma) **is considered experimental, investigational, and/or unproven**.

Onasemnogene abeparvovec-xioi (Zolgensma) **is considered experimental, investigational, and/or unproven** for all other indications.

Concurrent use of onasemnogene abeparvovec-xioi (Zolgensma) with nusinersen and/or risdiplam **is considered experimental, investigational, and/or unproven.**

Use of nusinersen and/or risdiplam after administration of onasemnogene abeparvovec-xioi (Zolgensma) **is considered experimental, investigational, and/or unproven.**

Policy Guidelines

NOTE 1: Currently, there are two facilities that run Enzyme Linked Immunosorbent Assay (ELISA) titers necessary for Zolgensma in the United States. They have two different, but acceptable, definitions of a negative result (Athena Diagnostics [<1:25]; Cellular Technology Ltd. [CTL] [<1:50]).

Description

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 months	Little ability to move and may be unable to breathe and swallow independently.	1
Type I (infantile SMA or Werdnig-Hoffman disease)	0-6 months	<2 years without respiratory support	Never rolls or sits unsupported.	2
Type II (intermediate SMA or Dubowitz disease)	<18 months	>2 years; ≈70% alive at 25 years of age	Sits independently once properly positioned; sometimes stands but never able to walk.	3 or 4
Type III (Kugelberg-Welander disease)				
Subtype IIIa	>18 months to 3 years	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 years	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 years	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 (2024), (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	
3 *SMN2* copies	7.2	82.8	10.0	
4 *SMN2* copies	1.6	14.8	83.6	

Adapted from Feldkötter 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.

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.

The FDA labeling for use of Zolgensma in specific populations (i.e., pediatric use) states: "Use of Zolgensma in premature neonates before reaching full-term gestational age is not recommended because concomitant treatment with corticosteroids may adversely affect neurological development. Delay Zolgensma infusion until full-term gestational age is reached." (14)

Rationale

Medical policies 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 individuals who have a genetic diagnosis of spinal muscular atrophy is to provide a treatment option that is an improvement on existing therapies. Potential benefits of this gene therapy (15) 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 following PICO was used to select literature to inform this policy.

Populations
The relevant population of interest is individuals who are symptomatic infants diagnosed with type 1 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. For details, see Table 4. 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. For details, see Tables 3 and 4.

Table 3. Health Outcome Measures Relevant to Spinal Muscular Atrophy

Outcome	Age	Description	Relevance
BSID-III	• Appropriate for ages 1 to 42 months (16)	• Designed to measure movements of the limbs and torso in infants and toddlers • A range of motor functions including rolling, sitting upright, crawling, stepping motions, standing, walking, climbing stairs, running, maintaining balance, and other activities requiring full-body control or coordination (16)	• In the natural history of the disease, infants with Type I SMA are not expected to achieve independent sitting or any of the other subsequent milestones evaluated
CHOP INTEND	• Appropriate for 3. 8 months to >4 years	• Motor skills includes 16 items scored on a scale of 0 (no response) to 4 (complete response) and total score ranges from 0 to 64 (17, 18)	• Score >40 rare in SMA type I with 2 *SMN2* gene copies (19) • Mean CHOP INTEND score in healthy

			infants (n=14; age, 3.3 months) was 501.1 vs 20.2 in SMA type I (n=16; age, 3.7 months)
HFMSE	• Appropriate for individuals with SMA types II and III (20)	• 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 minutes	• 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 (21, 22)
HINE Section 2	• Appropriate for infants 2-24 months	• Motor milestones include 8 items scored on a 5-point scale with 0 as the absence of activity, and a maximum score of 4 points	• Infants with the most severe symptoms of SMA (early onset) may show a score of 0 on all 8 items of the HINE Section 2 (23)
MFM-32	• Appropriate for ages: 2 to 62 years	• Evaluates gross and fine motor function in a broad patient population (weak nonambulant to stronger ambulant, and all levels of severity) • 3 domains including standing and transfers, axial limb and proximal limb motor function, and distal motor function • Scored using 4-point Likert scale based on subject's maximal abilities without assistance (0 to 3)	• Results of an observational retrospective analysis of 12 type 2 and 19 type 3 SMA patients showed a slow deterioration (-0.9 points/y and -0.6 points/y respectively) (24) • Studies assessing the validity and reliability of MFM-32 support its use in longitudinal research in individuals with type 2 and non-ambulant type 3 SMA. (25, 26) • Results of a retrospective analysis

			of 81 patients with type 2 and non-ambulatory type 3 SMA aged 2–25 years suggest that a within-patient change of 3 to 4 points was meaningful. Further, the authors conclude that given the progressive nature of SMA, a 3 to 4-point improvement should not be viewed as minimal as arguably stabilization is also meaningful (27)
RULM	• Appropriate for children and adults with SMA age ≥ 30 months	• Evaluates upper limb function • Scale consists of 20 items that test proximal and distal motor functions of the arm. The total score ranges from 0, if all the items cannot be performed, to 37, if all the activities are achieved fully without any compensatory maneuvers • Higher scores indicate higher function (28)	• The purpose of an upper limb scale for use in SMA is to assess change that occurs in motor performance of the upper limb overtime. Literature search did not identify threshold for clinically meaningful difference
Natural history with and without SMA		Infants without SMA at 1 year (29): • 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 months: • 90% stand/walk unaided Event-free survival rates in infants with SMA type I (9, 30):	• 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

		• 50% by 8-10.5 months • 25% by 13.6 months • 8% by 20 months	health benefit over short- and long-term

BSID: Bayley Scales of Infant and Toddler Development (Third Edition); CHOP INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFMSE: Hammersmith Functional Motor Scale-Expanded; HINE: Hammersmith Infant Neurological Examination; MFM-32: Motor Function Measure (32 items); RULM: Revised Upper Limb Module; SMA: spinal muscular atrophy.

Table 4. Timing of Outcome Measures Relevant to Spinal Muscular Atrophy

SMA Subtype	Purpose	Timing
Presymptomatic with a genetic diagnosis of SMA and less than 4 copies of *SMN2*	• To assess short-term benefit (efficacy & safety)	• 6 months to 1 year may be sufficient
Types I to III	• To assess short-term benefit (efficacy and safety)	• 1-2 years may be sufficient
Types I to III	• To assess durability of benefit and delayed/rare adverse events	• 10-15 years (survival, comparative development milestones versus natural history of SMA and non-SMA patients, safety)

SMA: spinal muscular atrophy.

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 5.

Table 5. Summary of the Clinical Development Program for Onasemnogene Abeparvovec-Xioi

Study	Phase	N	Status
Infants under 6 weeks (presymptomatic with a genetic diagnosis of SMA and less than 4 copies of *SMN2*)			
SPR1NT (NCT03505099) (31, 32)	3	44	Completed

Children <6 months of age (SMA type I)			
Pivotal (NCT02122952) (33)	1	15	Completed
STR1VE-US trial (NCT03306277) (34)	3	21	Completed
STR1VE-EU trial (NCT03461289) (35)	3	30	Completed
START (NCT03421977)[a] (36)	4	15	Ongoing; estimated completion: December 2033
Children up to 60 months of age (SMA type II)			
STRONG (NCT03381729) (37)	1	32	Completed

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 and is summarized in Table 5. These trials enrolled a total of 65 patients with symptomatic spinal muscular atrophy type I. The study characteristics and results are summarized in Tables 6 and 7.

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 7. The inclusion and exclusion criteria of the phase 3 confirmatory study (STRIVE-US) were the same as the phase 1 dose-finding study. (34) 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 Table 7.

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 (range 4.6 to 6.2 years) have been published (36) and summarized in Tables 6 and 7. 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.

Table 6. Summary of Key Characteristics of Nonrandomized Trials

Study	Study Type	Country	Dates	Participants	Treatment	Follow-Up
Mendell et al. (2017) (33)	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) (34)	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) (36)	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	No treatment; intent was long-term follow-up for safety	Median time since dosing 5.2

				c.859G>C variant in *SMN2* exon 7 were excluded from the study.[b]		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. (38)
[c] At 6.7×10^{13} vg/kg.
[d] At 2.0×10^{14} vg/kg.
[e] The oldest patient is 46.2 months of age, with 40.6 months of follow-up.

Table 7. 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) (39)					
N	21				44
Onasemnogene abeparvovec-xioi	90.5%	NR	NR	• 1 patient died at age 7.8 months due to 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	Elevated ALT/AST[a] (> ULN): 12 (27.3%) Vomiting: 3 (6.8%)

				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) (34)					
N	22				
Onasemnogene abeparvovec-xioi	95%	NR	21 (95%)	• 59% (13 of 22 patients achieved functional independent sitting for 30 s or longer at the 18 months of age study visit) • 41% (9 of 22 patients maintained the ability to thrive[b] at the 18 months of age study visit)	• All patients had at least 1 adverse event (most common was pyrexia). 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	• NA

				independent sitting for 30 seconds or longer at the 18 months of age in the PNCR cohort • Ability to thrive data was not reported for the PNCR cohort	
Mendell et al. (2021) (36)					
N	13				
Onasemnogene abeparvovec-xioi	100% (10 of 10 in therapeutic dose) 100% (3 of 3 in low dose)	NA	NA	• 7 of 13 receiving 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	Serious adverse events (n=8; 62%) • Acute respiratory failure (4 [31%]) • Pneumonia (4 [31%]) • Dehydration (3 [23%]) • Respiratory distress (2 [15%]) • Bronchiolitis (2 [15%])

				milestones. Two attained the new milestone of "standing with assistance" without the use of nusinersen	

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.

[a] 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.

[b] 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)

The purpose of the study limitations tables (see Tables 8 and 9) 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. (40) 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.

Table 8. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Mendell et al. (2017) (33)					1. Not sufficient duration for benefit (long-term) 2. Not sufficient duration for harms (long-term)

Day et al. (2021) (34)					1. Not sufficient duration for benefit (long-term) 2. Not sufficient duration for harms (long-term)
Mendell et al. (2021) (36)		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 literature 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 9. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Mendell et al. (2017) (33)	1. Participants not randomly allocated	3. Outcome assessed by treating physician				
Day et al. (2021) (34)	1. Participants not randomly allocated	3. Outcome assessed by treating physician				

Mendell et al. (2021) (36)	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 literature 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.

Findings from the industry-sponsored RESTORE registry were published in 2024. (41) RESTORE is a prospective, multicenter, multinational, observational registry, whose objective was to describe patients with SMA treated with onasemnogene abeparvovec monotherapy in the real-world setting. Recruitment started in September 2018. As of May 23, 2022, data were available for 168 patients treated with onasemnogene abeparvovec monotherapy. Median (IQR) age at initial SMA diagnosis was 1 (0-6) month and at onasemnogene abeparvovec infusion was 3 (1-10) months. Eighty patients (47.6%) had two and 70 (41.7%) had three copies of SMN2, and 98 (58.3%) were identified by newborn screening. Infants identified by newborn screening had a lower age at final assessment (mean age 11.5 months) and greater mean final (SD) CHOP INTEND score (57.0 [10.0] points) compared with clinically diagnosed patients (23.1 months; 52.1 [8.0] points). All patients maintained/achieved motor milestones. 48.5% (n = 81/167) experienced at least one treatment-emergent adverse event (AE), and 31/167 patients (18.6%) experienced at least one serious AE, of which 8/31 were considered treatment-related. Authors concluded that these real-world outcomes support findings from the interventional trial program and demonstrate effectiveness of onasemnogene abeparvovec over a large patient population, which was consistent with initial clinical data and published 5-year follow-up data. Observed AEs were consistent with the established safety profile of onasemnogene abeparvovec.

Subsection 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 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.

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 SPR1NT. The study characteristics are summarized in Table 10 and results are summarized in Table 11. The study included 2 cohorts: 14 children with 2 copies of *SMN2* and 14 children with 3 copies of *SMN2* expected to develop SMA type 1. Results of the cohorts were reported in 2 separate publications. (31, 32) All patients with 2 copies of *SMN2* reached 18-months-of-age (study end) and achieved the primary endpoint of sitting without support for at least 30 seconds. (31) Seventy-nine percent (11/14) achieved this milestone within an age-appropriate time period based on the World Health Organization Multicentre Growth Reference Study (WHO MGRS) of healthy children living under conditions highly unlikely to constrain growth. (42) All patients with 3 copies of *SMN2* reached 24-months-of-age (study end) and achieved the primary endpoint of standing without support up to the 24-months-of-age visit. Ninety-three percent (14/15) achieved this milestone within an age-appropriate time period. (32) 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).

The purpose of the study limitations tables (see Tables 12 and 13) 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 10. Summary of Key Nonrandomized Trials

Study	Study Type	Country	Dates	Participants	Treatment	Follow-Up
Strauss et al. (2022) (31) and Strauss et al. (2022; SPR1NT) (32)	Single arm	U.S., Europe, Asia	2018-2021	• Presymptomatic infants with biallelic deletions of *SMN1* and 2 (n=14) or 3 copies (n=15) of *SMN2* (N=29) • 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	Single dose intravenous infusion of onasemnogene abeparvovec-xioi at 1.1 X 10^{14} vector genomes/kg	18 or 24 of age, dependent upon respective *SMN2* copy number

SPRINT: Pre-Symptomatic Study of Intravenous Onasemnogene Abeparvovec-xioi in Spinal Muscular Atrophy (SMA) for Patients With Multiple Copies of *SMN2*.

Table 11. Summary of Key Results of Nonrandomized Trial

Study	Survival	Change in Mean (±SD) CHOP INTEND Score	Patients With CHOP INTEND >40, n (%)	Others	Safety
Strauss et al. (2022) (31)					
N	14				
Onasemnogene abeparvovec-xioi	100%	1 month: 3.9 (±8.3)	14 (100%)	• All 14 (100%) children achieved independent sitting for at least	• No serious adverse events were considered

		3 months: 11.2 (±8.8) 6 months: 14.8 (±8.1)		30 seconds at any visit up to 18 months of age • All 14 (100%) children achieved motor milestones as defined by BSID and WHO-MGRS • 11 of 14 (79%) children stood alone without assistance based on BSID definition and 9 children (64%) walked independently • No child required mechanical respiratory support during the trial	treatment-related by the investigator • 1 patient had serum amino-transferase enzyme concentration >3x ULN. Resolved with prednisolone dose modification
Strauss et al. (2022) (32)					
N	15				
Onasemnogene abeparvovec-xioi	100%	NA	NA	• All 15 (100%) children stood independently based on BSID definition by 24 months of age and all maintained this motor milestone at the 24-month study visit • 14 (93%) of 15 children sat independently based on BSID definition by 24 months of age • 14 (93%) of 15 children walked independently for at least 5 steps	No serious adverse events were considered treatment-related by the investigator

				based on BSID definition by 24 months of age ○ The walk of one child was observed during the 24-month study visit but was not recorded. Per study protocol, the child was judged not to have achieved the motor milestone due to absence of recording. • No child required mechanical respiratory support during the trial	

BSID: Bayley-III Scales of Infant and Toddler Development; CHOP INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; ITT: Intention-to-treat; NA: not applicable; NR: not reported; SAE: serious adverse event; SD: standard deviation; TULN: upper limit of normal; WHO-MGRS: World Health Organization Multicentre Growth Reference Study.

Table 12. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Strauss et al. (2022) (31) and Strauss et al. (2022; SPR1NT) (32)					1. Not sufficient duration for benefit (long-term) 2. Not sufficient duration for harms (long-term)

The study limitations stated in this table are those notable in the current literature 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 13. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Strauss et al. (2022) (31) and Strauss et al. (2022; SPR1NT) (32)	1. Participants not randomly allocated	3. Outcome assessed by treating physician				

The study limitations stated in this table are those notable in the current literature 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.

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

The evidence for use of onasemnogene abeparvovec-xioi for presymptomatic infants with a genetic diagnosis of SMA and less than 4 copies of *SMN2* consists of a single-arm study (SPR1NT). This trial included infants less than 6 weeks of age who did not display any symptoms of SMA at the time of infusion. The trial was divided into 2 cohorts based on *SMN2* copy number. All patients irrespective of *SMN2 copy* numbers achieved their respective primary endpoint, able to sit without support for ≥30 seconds at 18 months of age for 2 copies

of *SMN2* or ability to stand for 3 seconds or more without assistance at 24 months for those with 3 copies of *SMN2.* Multiple secondary endpoints were also supportive of clinical benefit including achievement of age-appropriate gross motor milestones and functions and independence from nutritional and respiratory support. In the natural history of SMA type 1, untreated children with 2 or 3 copies of the *SMN2* backup gene would not achieve such skills. These results demonstrate that early treatment resulted in the achievement of motor milestones among patients who are not likely to attain them without treatment.

Summary of Evidence

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 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 one single-arm study - SPR1NT. Relevant outcomes are overall survival, change in disease status, functional outcomes, quality of life, and treatment-related mortality and morbidity. The SPR1NT trial included infants less than 6 weeks of age who did not display any symptoms of SMA at the time of infusion. The trial was divided into 2 cohorts based on SMN2 copy number. All patients irrespective of *SMN2 copy* numbers achieved their respective primary endpoint, able to sit without support for at least 30 seconds at 18 months of age for 2 copies of *SMN2* or ability to stand for 3 seconds or more without assistance at 24 months for those with 3 copies of *SMN2.* Multiple secondary endpoints were also supportive of clinical benefit including achievement of age-appropriate gross motor milestones and functions and independence from nutritional and respiratory support. In the natural history of SMA Type 1, untreated children with 2 or 3 copies of the *SMN2* backup gene would not achieve such skills.

These results demonstrate that early treatment resulted in the achievement of motor milestones among patients who are not likely to attain them without treatment. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

National Institute for Health and Care Excellence (NICE)

On July 7, 2021, the NICE issued specialized technology appraisal guidance on onasemnogene abeparvovec for treating spinal muscular atrophy. (43) Recommendations are summarized below.

Onasemnogene abeparvovec is recommended as an option for treating 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of type 1 SMA in babies, only if:

- They are 6 months or younger, or they are aged 7 to 12 months, and their treatment is agreed by the national multidisciplinary team. It is only recommended for these groups if permanent ventilation for more than 16 hours per day or a tracheostomy is not needed and the company provides it according to the commercial arrangement.
- For babies aged 7 to 12 months, the national multidisciplinary team should develop auditable criteria to enable onasemnogene abeparvovec to be allocated to babies in whom treatment will give them at least a 70% chance of being able to sit independently.
- Onasemnogene abeparvovec is recommended as an option for treating presymptomatic 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene in babies. It is recommended only if the conditions in the managed access agreement are followed.

On April 19, 2023, the NICE issued a specialized technology appraisal guidance on onasemnogene abeparvovec for treating presymptomatic spinal muscular atrophy. (44) Recommendations are summarized below.

- Onasemnogene abeparvovec is recommended as an option for treating presymptomatic 5q SMA with a biallelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene in babies aged 12 months and under. It is only recommended if the company provides it according to the commercial arrangement.

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 spinal muscular atrophy on April 3, 2019, and subsequently on May 24, 2019, published an update following the U.S. Food and Drug Administration (FDA) approval of onasemnogene abeparvovec-xioi. (15)

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.

Cure Spinal Muscular Atrophy (SMA) Working Group

In September 2019, Cure SMA reconvened the multidisciplinary working group to reassess the treatment algorithm for newborns with SMA identified through newborn screening based upon new experience and therapeutic options. (45) The working group has updated their position to a recommendation for immediate treatment for infants diagnosed with SMA via newborn screening with four copies of *SMN2.* The working group also revisited the published recommendation to wait to treat for infants with five copies of *SMN2* and unanimously voted to uphold the recommendation of watchful waiting. The working group acknowledged that current laboratory assays designed to detect *SMN2* copy number often have difficulty distinguishing high copy numbers of *SMN2* and that many laboratories report results as four or more *SMN2* copies, being unable to give an exact number. Recognizing this fact, the working group encouraged follow-up with a laboratory able to distinguish exact *SMN2* copy number.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 14.

Table 14. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03421977 (START)[a]	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	85	Dec 2035
NCT05386680 (STRENGTH)	Phase IIIb, Open-label, Single-arm, Multi-center Study to Evaluate the Safety, Tolerability and Efficacy of OAV101 Administered Intrathecally to Participants With SMA Who Discontinued Treatment With Nusinersen or Risdiplam	28	Dec 2024
NCT05089656 (STEER)	A Randomized, Sham-controlled, Double-blind Study to Evaluate the Efficacy and Safety of Intrathecal OAV101 in Type 2 Spinal Muscular Atrophy (SMA) Patients Who Are ≥ 2 to < 18 Years of Age, Treatment Naive, Sitting, and Never Ambulatory	125	Feb 2025
NCT05335876	Long-term Follow-up of Patients With Spinal Muscular Atrophy Treated With OAV101 IT or OAV101 IV in Clinical Trials	260	Oct 2039
Unpublished			
NCT03381729 (STRONG)[a]	Study of Intrathecal Administration of Onasemnogene Abeparvovec-xioi for Spinal Muscular Atrophy	32	Nov 2021

NCT: national clinical trial; SMA: spinal muscular atrophy.
[a] Denotes industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	96365
HCPCS Codes	J3399

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
02/01/2025	Document updated with literature review. The following change was made to Coverage: Modified criterion on baseline titers for anti-adeno-associated virus serotype 9 (AAV9) antibody. Added/updated references 6, 7, 14, 31, 32, 35, 37, and 41-44.
05/01/2023	Document updated with literature review. The following change was made to Coverage: Changed criteria on number of survival motor neuron 2 gene (SMN2) copies to 4. Added references 38, 39 and 43; others updated.
11/01/2022	Document updated. The following change was made to Coverage: Removed "Documentation of onset of symptoms consistent with a clinical diagnosis of spinal muscular atrophy" from Coverage criteria.
10/01/2022	Document updated with literature review. The following change was made to Coverage: Coverage was modified in its entirety with minimal change in intent. References 5, 11, 14-33, and 35-40 were added; some updated and others removed.
01/01/2022	Reviewed. No changes.
02/01/2021	Document updated with literature review. The following changes were made to Coverage: 1) Changed criteria on number of survival motor neuron 2 gene (SMN2) copies from ≤ 2 to ≤ 3; and 2) Added Evrysdi™ (risdiplam) to the experimental, investigational and/or unproven statement on concurrent use. Reference 15 was added, and others updated. Title changed from: Zolgensma (onasemnogene abeparvovec-xioi).
01/01/2020	New medical document. A single-dose intravenous infusion of Zolgensma® (onasemnogene abeparvovec-xioi) administered in accordance with the U.S. Food and Drug Administration (FDA) labeling may be considered medically necessary for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) and meet ALL of the following criteria prior to infusion: Confirmed diagnosis of SMA based on gene mutation analysis with bi-allelic survival motor neuron 1 (SMN1) mutations (deletion

	or point mutations) and < 2 copies of survival motor neuron 2 gene (SMN2), inclusive of the known SMN2 gene modifier mutation (c.859G>C); Baseline anti-AAV9 antibody titers of < 1:50. Zolgensma® (onasemnogene abeparvovec-xioi) is considered experimental, investigational, and/or unproven for all other indications and clinical situations, including but not limited to: Repeat administration of Zolgensma (onasemnogene abeparvovec-xioi); Signs of a possible viral respiratory infection (e.g., coughing, wheezing, sneezing, runny nose, sore throat, fever); Patients with anti-AAV9 antibody titers > 1:50; In patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator-dependence); Patients > 2 years of age. Concurrent or sequential use of Zolgensma® (onasemnogene abeparvovec-xioi) and Nusinersen (Spinraza™) is considered experimental, investigational, and/or unproven. NOTE 1: Per the FDA labeling in use of Zolgensma in specific populations, pediatric use notes the following: administration of Zolgensma to premature neonates before reaching full-term gestational age is not recommended, because concomitant treatment with corticosteroids may adversely affect neurological development. Delay Zolgensma infusion until the corresponding full-term gestational age is reached. NOTE 2: Per the FDA label, prior to infusion of Zolgensma complete liver function assessment by clinical examination and laboratory testing (e.g., hepatic aminotransferases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], total bilirubin, and prothrombin time); measure platelet counts and troponin-I ;administer systemic corticosteroids one day prior to infusion and continue for a total of 30 days.