Policy Number	**RX501.086**
Policy Effective Date	**12/15/2024**

Nusinersen

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Related Policies (if applicable)
None

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

Initial Treatment

Initial treatment with Nusinersen (Spinraza™) **may be considered medically necessary** for 6 months duration in individuals with spinal muscular atrophy (SMA) who meet ALL of the following criteria:

1. Diagnosis of SMA Type I, II, or III; **AND**
2. The individual is not dependent on invasive ventilation/tracheostomy or noninvasive ventilation beyond use for naps and nighttime sleep; **AND**
3. Documentation of 5q SMA homozygous gene deletion, homozygous gene mutation, or compound heterozygote; **AND**
4. Submission of medical records (e.g., chart notes, laboratory values) of the baseline exam of at least **ONE** of the following exams (based on the individual's age and motor ability) to establish baseline motor ability:
    a. Hammersmith Infant Neurological Exam Part 2 (**HINE-2**) (infant to early childhood);
    b. Hammersmith Functional Motor Scale Expanded (**HFMSE**);
    c. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (**CHOP INTEND**);
    d. Revised Upper Limb Module (**RULM**) Test (Non-ambulatory);
    e. 6-Minute Walk Test (6MWT).

Continuation Treatment

Continuation of treatment with nusinersen (Spinraza™) beyond 6 months after initiation of therapy, and every 4 months thereafter, **may be considered medically necessary** when:

1. Criteria for initial treatment was met; **AND**
2. Submission of medical records (e.g., chart notes, laboratory values) with the most recent results (< 6 months prior to request) documenting a positive clinical response from pretreatment baseline status to Spinraza therapy as demonstrated by at least one of the following exams:
    a. **HINE-2** milestones:
    One of the following:

i. Improvement or maintenance of previous improvement of at least 2 point (or maximal score) increase in ability to kick.
ii. Improvement or maintenance of previous improvement of at least 1 point increase in any other HINE-2 milestone (e.g., head control, rolling, sitting, crawling, etc.), excluding voluntary grasp.

and

One of the following:

i. The individual exhibited improvement, or maintenance of previous improvement in more HINE motor milestones from pretreatment baseline (net positive improvement).
ii. Achieved and maintained any new motor milestones when they would otherwise be unexpected to do so (e.g., sit unassisted, stand, walk).

OR

b. **HFMSE:**

One of the following:

i. Improvement or maintenance of previous improvement of at least a 3 point increase in score from pretreatment baseline.
ii. The individual has achieved and maintained any new motor milestone from pretreatment baseline when they would otherwise be unexpected to do so.

OR

c. **CHOP INTEND:**

One of the following:

i. Improvement or maintenance of previous improvement of at least a 4 point increase in score from pretreatment baseline.
ii. The individual has achieved and maintained any new motor milestone from pretreatment baseline when they would otherwise be unexpected to do so.

OR

d. **RULM:**

One of the following:

i. Improvement or maintenance of previous improvement of at least a 2 point increase in score from pretreatment baseline.
ii. The individual has achieved and maintained any new motor milestone from pretreatment baseline when they would otherwise be unexpected to do so.

OR

e. **6-Minute Walk Test:**

One of the following:

i. >30-meter change in 6MWT walking distance.
ii. The individual has achieved and maintained any new motor milestone from pretreatment baseline when they would otherwise be unexpected to do so.

Nusinersen (Spinraza™) **is considered not medically necessary** for individuals who have a diagnosis of SMA when the criteria above are not met, as a clinical benefit has not been established.

Nusinersen (Spinraza™) **is considered experimental, investigational and/or unproven** for all other indications.

Concurrent use of Nusinersen (Spinraza™) with Zolgensma® (onasemnogene abeparvovec-xioi) or Evrysdi™ (risdiplam) **is considered experimental, investigational and/or unproven**.

Use of Nusinersen (Spinraza™) after Zolgensma® (onasemnogene abeparvovec-xioi) **is considered experimental, investigational and/or unproven.**

Policy Guidelines

None.

Description

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is a rare autosomal recessive genetic disorder caused by homozygous deletions or variants in the SMN1 gene located on chromosome 5. This gene produces the "survival of motor neuron" protein (SMN1), which is essential for motor neuron functioning. In 95% of cases of SMA, there is a homozygous deletion of exon 7 in the SMN1 gene. The remaining 5% of cases are compound heterozygotes for SMN1 exon 7 deletions and small intragenic variants. (1) Due to absent or low levels of the SMN1 protein, motor neurons in the spinal cord degenerate, resulting in atrophy of the voluntary muscles of the limbs and trunk affecting the ability to crawl, walk, sit up, and control head. In more severe cases, feeding, swallowing, and breathing are affected as well. The exact role of the survival motor neuron (SMN) protein in motor neurons has not been completely elucidated and levels of the SMN protein required for optimal functioning are unknown. (2)

There is wide phenotypic heterogeneity in SMA, as summarized in Table 1. This is due to the presence of survival motor neuron 2 (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 SMA among those with more copies of the SMN2 gene and vice-versa. (4) The relation between the SMN2 copy number and SMA phenotype is summarized in Table 2. These data were generated from deoxyribonucleic acid (DNA) samples of 375 patients with SMA who previously had been classified as follows: 188 with SMA type I, 110 with SMA type II, and 77 with SMA type III. (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 (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	
3 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

SMA can be diagnosed using multiple molecular genetic testing techniques such as multiplex ligation-dependent probe amplification or quantitative polymerase chain reaction or a comprehensive next-generation sequencing-based approach. Individuals are classified as having SMA if they have a homozygous deletion of the SMN1 gene or a homozygous absence of the SMN1 gene due to gene conversion (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 SMA symptom onset may occur shortly after birth to months to years later, estimating the incidence and prevalence of SMA subtypes is difficult. The incidence, as reported in the literature, is more precisely a birth prevalence rate, which is estimated between 9.1 and 10 per 100,000 live births, (12-13) which translates to 500 new SMA cases annually.

Treatment

Medical management of SMA patients includes respiratory, nutritional, and musculoskeletal supportive care. Respiratory management includes airway clearance, antibiotic treatment of infections, noninvasive and invasive ventilation. Nutritional management includes changing food consistency, gastrostomy tube feeding, and dietician assessment. Musculoskeletal supportive care includes a variety of 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).

Nusinersen (Spinraza™) is a modified antisense oligonucleotide (a synthetic genetic material) that binds to a specific sequence in the intron downstream of exon 7 of the SMN2 transcript; nusinersen causes the inclusion of exon 7 in the SMN2 transcript, leading to the production of full length functional SMN2 protein. (14)

Regulatory Status

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

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.

NUSINERSEN

Clinical Context and Therapy Purpose

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

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

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

Populations

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

Interventions

The therapy being considered is nusinersen.

Comparators

Prior to the availability of nusinersen, there was no U.S. Food and Drug Administration (FDA) approved treatment for spinal muscular atrophy. Medical management includes respiratory, nutritional, and musculoskeletal supportive care.

Outcomes

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

Table 3. Health Outcome Measures Relevant to Spinal Muscular Atrophy

Outcome	Age	Description	Relevance
BSID-III	• Appropriate for ages 1 to 42 months (15)	• 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 (15)	• 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 (16, 17)	• Score >40 rare in SMA type I with 2 SMN2 gene copies (18) • 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 (19)	• 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	• Multiple studies have shown that HFMSE scores decline progressively in patients with SMA type II or III. However,

		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	there is conflicting data on whether such declines are linear (20, 21)
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 (22)
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) (23) • 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 (24, 25) • 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 (26)
RULM Test		• An objective evaluation of functional exercise capability in ambulatory patients which includes 19 items, with total scores ranging from 0 to 64 points. Higher scores indicate better function	• Clinician-administered tool designed to evaluate the upper limb function of ambulatory and non-ambulatory patients with SMA (27)
6MWT		• An objective evaluation of functional exercise capability in ambulatory individuals. Patients walk as far as possible in six minutes	• Appropriate for individuals with later-onset (Type II or Type III) SMA (28)
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): • 50% by 8-10.5 months • 25% by 13.6 months • 8% by 20 months	• With the availability of nusinersen, conducting placebo-controlled trials in patients with SMA type I who face near-term mortality would be unethical. Therefore, good quality natural history data from SMA and non-SMA populations using validated cohorts are essential to assess relative health benefit over short- and long-term

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; 6MWT: 6-Minute Walk Test; SMA: spinal muscular atrophy.

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

nusinersen 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. Given the significant uncertainty about the durability of the long-term benefits and safety of therapies, long-term data in an observational setting are also a requirement. The timing of outcomes measures relevant to spinal muscular atrophy subtypes is summarized in Table 4.

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

Presymptomatic Patients with a Genetic Diagnosis of Spinal Muscular Atrophy and a Minimum of 2 But Less Than 4 Copies of Survival Motor Neuron 2 (SMN2)

Review of Evidence

Non-Randomized Studies

In the pivotal single-arm NURTURE trial, 25 infants received nusinersen. Of the 25 infants, 15 had 2 copies of SMN2 (most likely to develop type 1 SMA) and 10 had 3 copies of SMN2 (most likely to develop type II SMA). Infants' age at first dose ranged from 8 to 41 days (≤14 days, n=9; >14 to ≤28 days, n=12; >28 days, n=4). See Table 5 for study key characteristics summary.

Results are summarized in Table 6. The primary endpoint was time to death or respiratory intervention (invasive or noninvasive for ≥6 hours per day continuously for ≥7 days or

tracheostomy). The median (range) age at the first dose of nusinersen among enrolled infants was 22.0 (3–42) days. At the last visit, the median age was 34.8 months (range 25.7 to 45.4) which is generally considered past the expected age of symptom onset for spinal muscular atrophy Types I or II based on known natural history. All 25 children were alive, and none required tracheostomy or permanent ventilation. Four (16%) participants with 2 SMN2 copies utilized respiratory support for ≥6 hours/day for ≥7 consecutive days that was initiated during acute, reversible illnesses. All 25 participants achieved the ability to sit without support, 23/25 (92%) achieved walking with assistance, and 22/25 (88%) achieved walking independently. Eight infants had adverse events considered possibly related to nusinersen by the study investigators. (31)

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

Table 5. Key Characteristics Summary of NURTURE Study

Study	Study Type	Country	Sites	Dates	Participants
Nusinersen					
DeVivo et al. (2019); NURTURE (NCT02386553) (31)	Single-arm cohort	U.S., EU, Asia	15	2015-ongoing	Presymptomatic infants (N=25) documented to have 5q SMA homozygous gene deletion, homozygous variant or compound heterozygote variant, and deemed likely to develop SMA type I (n=15) or II (n=10)

EU: European Union; U.S.: United States; SMA: spinal muscular atrophy. NURTURE: A Study of Multiple Doses of Nusinersen (ISIS 396443) Delivered to Infants With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy.

Table 5. Key Characteristics Summary of NURTURE Study Continued

Study	Interventions		Follow-Up
	Active		
Nusinersen			
De Vivo et al. (2019); NURTURE (NCT02386553) (31)	Nusinersen at FDA-approved dose		Analysis March 2019: median age 34.8 (25.7 to 45.4), and median time on treatment 2.9 years.

NURTURE: A Study of Multiple Doses of Nusinersen (ISIS 396443) Delivered to Infants with Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy; FDA: U.S. Food and Drug Administration; SMA: spinal muscular atrophy.

Table 6. Summary of Results of NURTURE Study

Study	All	2 SMN2 copy number	3 SMN2 copy number
De Vivo et al. (2019); NURTURE (31)			
N	25	15	10
Primary Endpoint: Survival and respiratory intervention (invasive or non-invasive for ≥6 hours per day continuously for ≥7 days or tracheostomy)	Not estimable[a] as there were too few events	-	-
Secondary endpoints			
Sitting without support (%)	100%	100%	100%
Walking with assistance (%)	92%	87%	100%
HINE-2 motor milestone, mean (range) Baseline Post treatment	 Not reported Not reported	 2.7 (0–5) 23.9 (16–26)	 3.2 (0–7) 26.0 (26–26)
CHOP-INTEND scores at last visit, mean (range) % with maximum CHOP INTEND score of 64 Clinically manifested SMA, % (95% CI) At age of 13 months At age of 24 months	Not reported Not reported Not reported Not reported Not reported	 62.1 (48–64) 67% 67 (39 to 87%) 47 (22 to 73%)	 63.4 (58–64) 100% 20 (4 to 56%) 0

CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE: Hammersmith Infant Neurologic Examination; NURTURE: A Study of Multiple Doses of Nusinersen (ISIS 396443) Delivered to Infants With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy.

[a] All are alive and none required permanent ventilation. Four (16%) infants (all with 2 SMN2 copies) utilized respiratory intervention for ≥6 hours per day continuously for ≥7 days during an acute, reversible illness.

At the last study day prior to data cutoff, 2 of these infants no longer utilized respiratory intervention; these infants had previously received respiratory intervention for ≥6 hours per day for totals of 20 and 266 days during the course of the study.

The other 2 infants continued to receive respiratory intervention for 2 and 10 hours per day, respectively, at the last study day prior to data cutoff; these infants received respiratory intervention for ≥6 hours per day for totals of 236 and 644 days, respectively, over the course of the study.

Table 7. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
De Vivo et al. (2019); NURTURE (31)					1. Not sufficient duration for benefit 2. Not sufficient

					duration for harms

NURTURE: A Study of Multiple Doses of Nusinersen (ISIS 396443) Delivered to Infants With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy.
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 8. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
De Vivo et al. (2019); NURTURE (31)	1. Participants not randomly allocated 2. Allocation not concealed 3. Allocation concealment unclear	3. Outcome assessed by treating physician				

NURTURE: A Study of Multiple Doses of Nusinersen (ISIS 396443) Delivered to Infants with Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy.
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.

Section Summary: Presymptomatic Patients with a Genetic Diagnosis of Spinal Muscular Atrophy and a Minimum of 2 but Less Than 4 Copies of SMN2

The evidence for use of nusinersen for presymptomatic type I (infantile-onset) SMA consists of a single-arm study. After a median follow-up of 2.9 years of 25 infants who received the first dose of nusinersen at median age of 22 days and are now median age of 34.8 months, 100% were alive, 100% achieved the ability to sit without support, 92% achieved the ability to walk with assistance, and 88% achieved the ability to walk independently. While none required permanent ventilation or tracheostomy, 4 (16%) participants with 2 SMN2 copies utilized respiratory support for ≥6 hours/day for ≥7 consecutive days that was initiated during acute, reversible illnesses. These results demonstrate that early treatment resulted in the achievement of motor milestones among patients who are not likely to attain them without treatment. However, the data is limited for the durability of response and long-term data documenting safety and efficacy are needed.

Type I (Infantile-Onset) Spinal Muscular Atrophy

The evidence base for infantile-onset or type I SMA is summarized in Table 9. The supporting EMBRACE and CS3A studies are not reviewed in detail. EMBRACE was terminated early to roll over participants to an open label extension study after the demonstration of motor function benefit with nusinersen in ENDEAR.

Table 9. Summary of Key Clinical Trials in Infantile-Onset or Type I Spinal Muscular Atrophy Patients

Study (Trial)	Trial Name	Design	Dates	Patients (N)	Outcome
Finkel et al. (2017) (32) (NCT02193074)	ENDEAR	RCT	Aug 2014	Symptomatic (82)	Efficacy, safety
Ascadi et al. (2021) (33) (NCT02462759)	EMBRACE	RCT	Aug 2015	Symptomatic (21)	Safety, tolerability
Finkel et al. (2016) (18) (NCT01839656)	CS3A	Single arm	May 2013	Symptomatic (20)	Safety, PK

EMBRACE: A Study to Assess the Safety and Tolerability of Nusinersen in Participants with Spinal Muscular Atrophy; ENDEAR: A Study to Assess the Efficacy and Safety of Nusinersen (ISIS 396443) in Infants with Spinal Muscular Atrophy; PK: pharmacokinetics; RCT: randomized controlled trial.

Randomized Studies

The pivotal ENDEAR trial was a multicenter randomized, double-blind trial in which 121 infants with a documented genetic diagnosis of SMA with symptom onset before 6 months of age were randomized 2:1 to nusinersen (n=80) or to sham injection (n=41). (32) Nusinersen was approved on the basis of a planned interim analysis of 82 patients who completed at least 183 days of treatment or died or withdrew. Patients' demographics at baseline were 44% male and 87% white, with a median length of treatment 261 days (range, 6-442 days). The primary endpoint was the proportion of motor milestone responders. See Table 10 for the study summary.

Results summarized in Table 11. (32) The trial met its coprimary endpoints, with nusinersen showing clinically meaningful improvement in motor milestones and probability of surviving or receiving permanent-assisted ventilation compared with sham control. The median time to death or the use of permanent-assisted ventilation was 22.6 weeks in the control group and was not reached in the nusinersen group. Multiple secondary endpoints showed a consistency in treatment effect favoring nusinersen over sham control. While no irreversible harms were observed in the preliminary clinical data analyzed by the FDA before drug approval, the FDA noted that such harms could not be ruled out based on animal toxicity data (potential of neurotoxicity) and class effects of antisense oligonucleotides (coagulation abnormalities, thrombocytopenia, renal toxicity). Given the limited data on the durability of response, long-term data documenting safety and efficacy is needed.

The purpose of the study limitations table (see Table 12) is to display notable limitations identified in a study. This information is synthesized as a summary of the body of evidence following each table. No study design and conduct gaps were identified. Notable study limitations include a relatively short follow-up, which is inadequate to assess the durability of the treatment effect or safety, especially those that are potentially rare or have delayed onset. In addition to the gaps identified in the tables, the 2 treatment groups were not balanced with respect to age at symptom onset, use of ventilatory support, and the presence of symptoms specific to spinal muscular atrophy. These were higher in the nusinersen group than the control group. None of these differences were tested for statistical significance.

Table 10. Summary of Key ENDEAR Trial

Study	Study Type	Country	Sites	Dates	Participants	Interventions		Follow-Up
						Active	Comp-arator	
Nusinersen								
Finkel et al. (2017); ENDEAR (32)	DB-RCT	U.S., EU, Asia	31	2014-2016	SMA type I with symptom onset before 6 months (N=121)	Nusinersen at FDA-approved dose (n=80)	Placebo (n=41)	Median length of treatment of 261 days (range, 6-442 days); trial terminated early

ENDEAR: A Study to Assess the Efficacy and Safety of Nusinersen (ISIS 396443) in Infants With Spinal Muscular Atrophy; DB-RCT; double-blind randomized controlled trial; U. S.: United States; EU: European Union; FDA: U.S. Food and Drug Administration; SMA: spinal muscular atrophy.

Table 11. Summary of Results of ENDEAR Trial

Study	Percent motor	No death or use of	≥ 4-point improvement	No death	No use of permanent-	CMAP response[d]

	milestone response (HINE section 2)[a]	permanent-assisted ventilation[b]	in CHOP INTEND score[c]		assisted ventilation[b]	
Finkel et al. (2017); ENDEAR (32)						
N	121	121	121	121	121	121
Nusinersen	37/73(51)	49/80(61)	52/73(71)	67/80(84)	62/80(78)	26/73(36)
Sham	0/37(0)	13/41(32)	1/37 (3)	25/41 (61)	28/41 (68)	2/37 (5)
HR (95% CI)	-	0.53 (0.32 to 0.89)	-	0.37 (0.18 to 0.77)	0.66 (0.32 to 1.37)	-
P value	<.001	.005	<.001	.004	.13	-

CI: confidence interval; CMAP: compound muscle action potential; HINE: Hammersmith Infant Neurologic Examination; HR: hazard ratio; CHOP INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; ENDEAR: A Study to Assess the Efficacy and Safety of Nusinersen (ISIS 396443) in Infants with Spinal Muscular Atrophy; Adapted from Finkel et al. (2017). (32) Values are percent or n (%) or as otherwise indicated.

Final analysis conducted on November 21, 2016 included 121 data from infants who had undergone randomization and the assigned procedure at least once.

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

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

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

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

Table 12. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Finkel et al. (2017); ENDEAR (32)					1. Not sufficient duration for benefit 2. Not sufficient

					duration for harms

ENDEAR: A Study to Assess the Efficacy and Safety of Nusinersen (ISIS 396443) in Infants With Spinal Muscular Atrophy

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.

Section Summary: Type I (Infantile-Onset) Spinal Muscular Atrophy

The evidence for use of nusinersen for symptomatic type I (infantile-onset) spinal muscular atrophy consists of a double-blind RCT. The phase 3 confirmatory ENDEAR trial (N=121) showed clinically meaningful and statistically significant improvement in motor milestones and event-free survival that exceeded those seen in the control group. However, most patients had a modest response or no response, and only a small proportion of patients (6%) gained the ability to sit without assistance. On average, the mean motor milestone score in nusinersen-treated patients improved by three points over 6 months. Given the limited data on the durability of response, long-term data documenting safety and efficacy are needed.

Type II or III Spinal Muscular Atrophy

The evidence base for patients with type II or III SMA is summarized in Table 13. The evidence base for patients with type II and III spinal muscular atrophy consists of 4 early-phase, open-label studies and a double-blind phase 3 RCT. Of these, data from phase 1 single-arm studies are not reviewed in detail because they were early dose-finding and proof-of-concept studies.

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

Study (Trial)	Trial Name	Design	Dates	N	Outcomes
Chiriboga et al. (2016) (34) (NCT01494701)	CS1	1 arm	Nov 2011	28	Safety and tolerability
Chiriboga et al. (2016) (34) (NCT01780246)	CS10	1 arm	Jan 2013	18	Safety and tolerability
Darras et al. (2019) (35) (NCT01703988)	CS2	1 arm	Oct 2012	34	Safety and tolerability

Darras et al. (2019) (35) (NCT02052791)	CS12	1 arm	Jan 2014	47	Safety and tolerability
Mercuri et al. (2018) (36) (NCT02292537)	CHERISH	RCT	July 2014	126	Efficacy and safety

CHERISH: A Study to Assess the Efficacy and Safety of Nusinersen in Participants With Later-onset Spinal Muscular Atrophy (SMA); RCT: randomized controlled trial; SMA: spinal muscular atrophy.

Randomized Studies

The pivotal CHERISH trial randomized 126 nonambulatory individuals. See Table 14 for the study summary.

The primary end point was change in Hammersmith Functional Motor Scale Expanded (HFMSE) score compared with baseline. Results are summarized in Table 15. The trial met its primary endpoints with nusinersen showing clinically meaningful improvement in mean HFMSE scores compared with sham control. In terms of responder analysis, a higher percentage of children in the nusinersen group (57%) than in the control group (26%; p<.001) had an increase from baseline to month 15 in the HFMSE score of at least 3 points, which was considered meaningful. Multiple secondary endpoints summarized in Table 15 showed a consistency in treatment effect favoring nusinersen compared with sham control. The overall incidences of adverse events and moderate and serious adverse events were similar for the nusinersen group and the control group (93% and 100% vs 46% and 55%, respectively). Adverse events with an incidence of 5 or more percentage points higher in the nusinersen group than in the control group were pyrexia, headache, vomiting, back pain, and epistaxis. Given the limited data on the durability of response, long-term data documenting safety and efficacy are needed.

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

Table 14. Summary of Key Characteristics of CHERISH Trial

Study	**Study Type**	**Country**	**Sites**	**Dates**	**Participants**	**Interventions**		**Follow-Up**
						Active	**Comp-arator**	
Nusinersen								
Mercuri et al. (2018); CHERISH (36)	DB-RCT	U.S., EU, Asia	24	2014-2017	SMA type II (N=126) with genetic documentation	Nusinersen at FDA-approved	Placebo (n=42)	Prespecified interim analysis when all children

					of 5q SMA (a homozygous deletion, variant, or compound heterozygote in SMN1) with the onset of signs and symptoms at more than 6 months and between ages 2 and 12 years at screening as well as the presence of the following features at screening: the ability to sit independently, no history of the ability to walk independently (defined as the ability to walk ≥15 feet unaided), and a HFMSE score between 10 and 54. Children were excluded if they had a severe contracture, evidence of severe scoliosis on radiography, respiratory	dose (n=84)		followed for a minimum of 6 months and 39 or more children had completed 15-month evaluations

					insufficiency, or a gastric tube placed to provide adequate nutrition.			

CHERISH: A Study to Assess the Efficacy and Safety of Nusinersen (ISIS 396443) in Participants with Later-onset Spinal Muscular Atrophy (SMA); DB-RCT; double-blind randomized controlled trial; U.S.: United States; EU: European Union; FDA: U.S. Food and Drug Administration; SMA: spinal muscular atrophy; HFMSE: Hammersmith Functional Motor Scale–Expanded.

Table 15. Summary of Results of CHERISH Trial

Study	Change in HFMSE score from baseline, LSM (95% CI)[a]	Patients with change In HFMSE score ≥3 points Percent (95% CI)	Patients who achieved ≥ 1 new WHO motor milestone Percent (95% CI)	Change from baseline in number of WHO motor milestones achieved, LSM (95% CI)[a]	Change from baseline in RULM score, LSM (95% CI)[a]	Patients who achieved ability to stand alone Percent (95% CI)	Patients who achieved ability to walk with assistance Percent (95% CI)
Mercuri et al. (2018); CHERISH (36)							
N	126	126	126	126	126	126	126
Nusinersen	3.9 (3.0 to 4.9)	57 (46 to 68)	20 (11 to 31)	0.2 (0.1 to 0.3)	4.2 (3.4 to 5.0)	2 (0 to 8)	2 (0 to 8)
Sham	-1.0 (-2.5 to 0.5)	26 (12 to 40)	6 (1 to 20)	-0.2 (-0.4 to 0)	0.5 (-0.6 to 1.6)	3 (0 to 15)	0 (0 to 10)
Difference (95% CI)	4.9 (3.1 to 6.7)	30.5 (12.7 to 48.3)	14 (-7 to 34)	0.4 (0.2 to 0.7)	3.7 (2.3 to 5.0)	-1 (-22 to 19)	2 (-19 to 22)
Odds ratio (95% CI)[b]	-	6 (2 to 15)	-	-	-	-	-
P value	<.001[c]	<.001	-	-	-	-	-

CHERISH: A Study to Assess the Efficacy and Safety of Nusinersen (ISIS 396443) in Participants With Later-onset Spinal Muscular Atrophy (SMA); CI: confidence interval; HFMSE: Hammersmith Functional Motor Scale–Expanded; LSM: least-squares mean; RULM: Revised Upper Limb Module; WHO: World Health Organization.

Adapted from Mercuri et al. (2018). (36)

Outcomes assessed at 15 Months. In the final analysis, the multiple imputation method was used for missing data to assess changes from baseline in the HFMSE score, percentage of children with a change in HFMSE score of at least 3 points and change from baseline in the RULM score.

The proportion of missing data for 15-month time-point for HFMSE score were 21% (18/84) and 19% (8/42) in the nusinersen and control group, respectively, and imputed using a multiple imputation method to conduct an intention-to-treat analysis.
[a] LSM change and LSM difference in change between groups were based on analysis of covariance with group assignment as a fixed effect and with adjustment for each child's age at screening and the value at baseline.
[b] This value is an odds ratio rather than a difference. The odds ratio for nusinersen vs control was based on logistic regression, with group assignment as a fixed effect and with adjustment for each child's age at screening and the HFMSE score at baseline.
[c] Because the p-value for the primary endpoint was significant in the interim analysis, this endpoint was not formally tested for significance in the final analysis.

Table 16. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Mercuri et al. (2018); CHERISH (36)				1. Key health outcomes not addressed;	1. Not sufficient duration for benefit 2. Not sufficient duration for harms

CHERISH: A Study to Assess the Efficacy and Safety of Nusinersen (ISIS 396443) in Participants with Later-onset Spinal Muscular Atrophy (SMA); 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.

Section Summary: Type II or III Spinal Muscular Atrophy

The evidence for the use of nusinersen for patients with type II or III SMA consists of a double-blind RCT. The phase 3 confirmatory CHERISH trial (126 patients) showed clinically meaningful and statistically significant improvement in motor milestones that exceeded those seen in the control group. Multiple secondary endpoints showed a consistency in treatment effect favoring nusinersen over sham control. The treatment effect was greater in younger children and in those who received treatment earlier in their disease course. Given the limited data on the durability of response, long-term data documenting safety and efficacy are needed.

Safety: Nusinersen

As per the prescribing label, thrombocytopenia (including acute, severe thrombocytopenia) and renal toxicity (including potentially fatal glomerulonephritis) have been observed with antisense oligonucleotides. (14) In the controlled ENDEAR trial, the most common adverse events that occurred in at least 20% of nusinersen-treated patients and occurred at least 5% more

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

Development of anti-nusinersen antibodies was assessed in 126 patients of whom 5 (4%) developed treatment-emergent antidrug antibodies, of which 3 were transient and 2 were persistent. There are insufficient data to evaluate the effect of antidrug antibodies on clinical response, adverse events, or the pharmacokinetic profile of nusinersen. (14)

Summary of Evidence

Presymptomatic Patients with a Genetic Diagnosis of Spinal Muscular Atrophy (SMA) and a Minimum of 2 but Less Than 4 Copies of survival motor neuron 2 (SMN2)

For individuals who are presymptomatic with a genetic diagnosis of SMA and a minimum of 2 but less than 4 copies of SMN2 who receive nusinersen, the evidence includes an open-label single-arm trial. Relevant outcomes are overall survival, change in disease status, morbid events, functional outcomes, quality of life, and treatment-related mortality and morbidity. After a median follow-up of 2.9 years of follow-up of 25 infants who received the first dose of nusinersen at a median age of 22 days and are now median age of 34.8 months, 100% were alive, 100% achieved the ability to sit without support, 92% achieved the ability to walk with assistance, and 88% achieved the ability to walk independently. While none required permanent ventilation or tracheostomy, 4 (16%) participants with 2 SMN2 copies utilized respiratory support for ≥6 hours/day for ≥7 consecutive days that was initiated during acute, reversible illnesses. These results demonstrate that early treatment resulted in the achievement of motor milestones among patients who are not likely to attain them without treatment. However, the data is limited for the durability of response and long-term data documenting safety and efficacy are needed. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Infantile-Onset or Type I SMA

For individuals who have type I (infantile-onset) SMA who receive nusinersen, the evidence includes a randomized, double-blind, controlled trial. Relevant outcomes are overall survival, change in disease status, morbid events, functional outcomes, quality of life, and treatment-related mortality and morbidity. The largest phase 3 confirmatory ENDEAR trial (N=121) showed clinically meaningful and statistically significant improvement in motor milestones, event-free survival, and overall survival that exceeded those seen in the control group with an acceptable safety profile. The proportion of patients, who met the primary endpoint responder definition of achieving motor milestones, was 51% in the nusinersen arm compared with 0% in

the sham-controlled arm. Further, the hazard ratio for event-free survival was 0.53 favoring nusinersen over sham-controlled. It is notable, however, that 50% of nusinersen-treated subjects did not achieve the primary endpoint motor milestone response. Only a small proportion of patients (6%) gained the ability to sit without assistance. On average, the mean motor milestone score in nusinersen-treated patients improved by 3 points over 6 months. Given the limited data on the durability of response, long-term safety, and lack of efficacy in a substantial number of patients continued risk-benefit assessment of long-term treatment with nusinersen is necessary. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Type II and III SMA

For individuals who have type II or III SMA who receive nusinersen, the evidence includes a double-blind, randomized controlled trial (RCT). Relevant outcomes are overall survival, change in disease status, morbid events, functional outcomes, quality of life, and treatment-related mortality and morbidity. Efficacy findings from single-arm studies of type II and III SMA are difficult to interpret because these trials used a wide range of nusinersen doses and lacked control arms. The phase 3 confirmatory, CHERISH trial (N=126) showed clinically meaningful and statistically significant improvement in motor milestones (measured using Hammersmith Functional Motor Scale–Expanded [HFMSE] scores) that exceeded those seen in the control group (difference of 5.9 points favoring nusinersen over sham control, p<.001). The respective proportion of patients with clinically meaningful improvements in HFMSE scores greater than 3 points was 57% vs 26% (p<.001). Multiple secondary endpoints also showed a consistency in treatment effect favoring nusinersen over sham control. Given the limited data on the durability of response, long-term safety, and lack of efficacy in a substantial number of patients continued risk-benefit assessment of long-term treatment with nusinersen is necessary. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

National Institute for Health and Care Excellence

On July 24, 2019, the National Institute for Health and Care Excellence (NICE) issued technology appraisal guidance on nusinersen for treating spinal muscular atrophy. Nusinersen is recommended as an option for treating SMA only if people have pre-symptomatic SMA, or SMA types 1, 2 or 3 and the conditions laid out in the managed access agreement were followed. (37)

Institute for Clinical and Economic Review

The Institute for Clinical and Economic Review published a final report on comparative effectiveness and value of nusinersen 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. (38)

Based on the lack of relevant data, the report concluded that the evidence for nusinersen was insufficient for type 0 and IV spinal muscular atrophy.

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

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

- For presymptomatic spinal muscular atrophy, the report concluded with moderate certainty of a small or substantial net health benefit with a high certainty of at least a small net health benefit and rate the evidence as "incremental or better" (B+).

Ongoing and Unpublished Clinical Trials
Some currently ongoing trials that might influence this policy are listed in Table 17.

Table 17. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02594124 (SHINE)[a]	A Study for Participants with Spinal Muscular Atrophy Who Previously Participated in Nusinersen (ISIS 396443) Investigational Studies	292	Aug 2023
NCT04488133 (RESPOND)[a]	A Study of Nusinersen Among Participants with Spinal Muscular Atrophy Who Received Onasemnogene Abeparvovec	60	Sep 2024
NCT04089566 (DEVOTE)[a]	Study of Nusinersen in Participants with Spinal Muscular Atrophy	145	Jul 2023
NCT05067790 (ASCEND)	A Phase 3b Study to Evaluate Higher Dose Nusinersen (BIIB058) in Patients with Spinal Muscular Atrophy Previously Treated with Risdiplam	135	Jun 2027
NCT03709784 (SAS)	Spinraza in Adult Spinal Muscular Atrophy (SAS)	48	Jan 2024
NCT04729907 (ONWARD)	Extension Study of Nusinersen (BIIB058) in Participants with Spinal Muscular Atrophy Who Previously Participated in a Study With Nusinersen	172	May 2026

Registries			
NCT05042921	Pediatric SMA China Registry	300	Jun 2024
NCT05618379	Adult Spinal Muscular Atrophy (SMA) China Registry	200	Jun 2028
NCT04177134	French Register of Patients With Spinal Muscular Atrophy	1000	Jan 2029
NCT05475691	Longitudinal Data Collection in Pediatric and Adult Patients With Spinal Muscular Atrophy in Latin America	300	Jan 2025

NCT: national clinical trial.

[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	96450
HCPCS Codes	J2326, J3490

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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
12/15/2024	Reviewed. No changes.
09/15/2023	Document updated with literature review. Coverage unchanged. No new references added; some updated and one removed.
10/15/2022	Document updated with literature review. The following editorial change was made to Coverage: Initial therapy with 6 months was added to the initial therapy medically necessary for patients with spinal muscular atrophy (SMA). References 15, 23-26, 33, and 38-39 were added; some updated and others removed.
04/15/2022	The following change was made in Coverage under Continuation Therapy: changed the timeline for submission of medical records with the most recent results from <1 month prior to request to <6 months prior to request.
03/15/2021	Reviewed. No changes.
01/01/2021	Document updated with literature review. The following changes were made to Coverage: For Initiation Therapy 1) Removed requirement of < 15 year of age. 2) Added
01/01/2020	Document updated with literature review. The following statement was added to Coverage: Concurrent use of Zolgensma® (onasemnogene abeparvovec-xioi) and Nusinersen (Spinraza™) AND use of Nusinersen (Spinraza™) after Zolgensma® (onasemnogene abeparvovec-xioi) is considered experimental, investigational and/or unproven. References 5, 15-17, and 19 were added.
06/15/2018	Reviewed. No changes.
06/15/2017	New medical document. The use of nusinersen (Spinraza™) may be considered medically necessary for patients with Type I, II, or III spinal muscular atrophy (SMA) with a documented genetic diagnosis of SMA when

	meeting specific criteria. Nusinersen (Spinraza™) is considered not medically necessary for SMA patients not meeting criteria. Nusinersen (Spinraza™) is considered experimental, investigational, and/or unproven for all other indications.