



Zolgensma (onasemnogene abeparvovec-xioi) Clinical Coverage Criteria

Description

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

Policy

This Policy applies to the following Fallon Health products:

- Medicare Advantage (Fallon Medicare Plus, Fallon Medicare Plus Central)
- MassHealth ACO
- NaviCare HMO SNP, NaviCare SCO
- PACE (Summit Eldercare PACE, Fallon Health Weinberg PACE)
- Community Care

Zolgensma (onasemnogene abeparvovec-xioi) requires prior authorization by a Fallon Health Medical Director. Prior authorization for Zolgensma (onasemnogene abeparvovec-xioi) is separate from any prior authorization that may be required for the member's inpatient or outpatient encounter. The treating physician must submit the prior authorization request and medical record documentation supporting medical necessity to Fallon Health.

Medicare Advantage (Fallon Medicare Plus, Fallon Medicare Plus Central)

Fallon Health complies with CMS's national coverage determinations (NCDs), local coverage determinations (LCDs) of Medicare Contractors with jurisdiction for claims in the Plan's service area, and applicable Medicare statutes and regulations when making medical necessity determinations for Medicare Advantage members. When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, Fallon Health may create internal coverage criteria under specific circumstances described at § 422.101(b)(6)(i) and (ii).

Medicare statutes and regulations do not have coverage criteria for Zolgensma (onasemnogene abeparvovec-xioi). Medicare does not have an NCD for Zolgensma (onasemnogene abeparvovec-xioi). National Government Services does not have an LCD or LCA for Zolgensma (MCD search 04/16/2024).

Coverage criteria for Zolgensma (onasemnogene abeparvovec-xioi) are not fully established by Medicare, therefore, the Plan's clinical coverage criteria are applicable.

MassHealth ACO

Fallon Health follows Medical Necessity Guidelines/coverage criteria published by MassHealth when making medical necessity determinations for MassHealth members.

The MassHealth Drug List has coverage criteria for Zolgensma (onasemnogene abeparvovec-xioi) Original Effective Date: 05/2018. Last Revised Date: 03/2024 (MassHealth Drug List search 04/16/2024), therefore the Plan's criteria are not applicable.

MassHealth Drug List: <https://mhdل.pharmacy.services.conduent.com/MHDL/>.

NaviCare HMO SNP, NaviCare SCO

For plan members enrolled in NaviCare, Fallon Health first follows guidance from CMS when making medical necessity determinations. CMS's national coverage determinations (NCDs), local coverage determinations (LCDs) and applicable Medicare statutes and regulations are the basis for medical necessity determinations.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, or if the member does not meet coverage criteria in applicable Medicare statutes, regulations, NCDs or LCDs, Fallon Health will then follow Medical Necessity Guidelines/coverage criteria published by MassHealth when making necessity determinations for NaviCare members.

PACE (Summit Eldercare PACE, Fallon Health Weinberg PACE)

Each PACE plan member is assigned to an Interdisciplinary Team. PACE provides participants with all the care and services covered by Medicare and Medicaid, as authorized by the interdisciplinary team, as well as additional medically necessary care and services not covered by Medicare and Medicaid. With the exception of emergency care and out-of-area urgently needed care, all care and services provided to PACE plan members must be authorized by the interdisciplinary team.

Fallon Health Clinical Coverage Criteria

Single-dose intravenous infusion of Zolgensma is considered medically necessary for the treatment of spinal muscle atrophy (SMA) when medical record documentation confirms all of the following criteria:

1. The member is less than 2 years of age on the date of Zolgensma infusion.
2. The treating provider is a neuromuscular specialist with expertise in diagnosing and treating SMA.
3. Genetic testing confirms the presence of biallelic survival motor neuron 1 (*SMN1*) mutation (e.g. homozygous deletion or compound heterozygous mutation) and 2, 3 or 4 copies of the *SMN2* gene.
4. Anti-adenovirus serotype 9 (AAV9) antibody titer is $\leq 1:50$ as determined by Enzyme-linked Immunosorbent Assay (ELISA) binding immunoassay.
5. The member does not have evidence of advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence). Permanent ventilator dependence is defined as invasive ventilatory support (endotracheal tube or tracheostomy) or non-invasive respiratory assistance for 16 hours or more per day for 14 continuous days in the absence of an acute reversible illness).

The plan member may not receive concomitant survival motor neuron protein (SMN) modifying therapy, e.g., Spinraza, (nusinersen) or Evrysdi (risdiplam). The plan member's medical record will be reviewed and any current authorizations for SMN modifying therapy will be terminated upon Zolgensma approval.

The recommended dose of Zolgensma is 1.1×10^{14} vector genomes per kilogram (vg/kg) of body weight. Administer Zolgensma as a single-dose intravenous infusion over 60 minutes. Starting one day prior to Zolgensma infusion, administer systemic corticosteroids equivalent to oral prednisolone at 1 mg/kg of body weight per day for a total of 30 days.

Exclusions

- Zolgensma is FDA-approved for single-dose intravenous infusion only. The safety and effectiveness of repeat administration of Zolgensma has not been evaluated in clinical trials and therefore is considered investigational.

- The use of Zolgensma in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been evaluated in clinical trials and therefore is considered investigational.
- 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.
- The use of Zolgensma in patients with one copy of *SMN2* has not been evaluated in clinical trials and therefore is considered investigational. All subjects in the Phase 1 and Phase 3 pivot trial clinical trials had two or three copies of *SMN2*.
- Antepartum use of Zolgensma has not been evaluated in clinical trials and therefore is considered investigational.
- The use of Zolgensma in patients with more than 4 copies of *SMN2* is not medically necessary.

Summary of Evidence

Background

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease caused by a deficiency of survival motor neuron (SMN) protein resulting from biallelic deletions or pathogenic variants of the *SMN1* (survival motor neuron 1) gene on chromosome 5q13.2. Before the genetic basis of SMA was understood, SMA was classified into clinical subtypes 0-4 based on onset and severity of symptoms. This classification is still useful for both management and prognosis, however it is now apparent that the phenotype of SMA spans a broad continuum without clear delineation of subtypes:

- SMA 0: Prenatal onset of symptoms, usually fatal in the first six months of life.
- SMA 1 (Werdnig-Hoffman disease): Onset before six months of age. Infants may present with muscle weakness and hypotonia. Facial weakness is minimal or absent. Life expectancy is normally less than 2 years.
- SMA 2: Onset between 6 and 18 months. Sits independently, never stands or ambulates. More than 70% of affected individuals have a life expectancy over 25 years.
- SMA 3 (Kugelberg-Welander syndrome): Onset in childhood after 18 months of age. Affected individuals achieve independent mobility, but over time, may lose their ability to stand and walk. Normal life expectancy.
- SMA 4: Adult onset > 30 years. Ambulates independently. Normal life expectancy.

In 1995, the gene responsible for SMA, *SMN1*, was identified. Genetic testing of *SMN1* has enabled precise epidemiological studies, revealing that SMA occurs in 1 of 10,000 to 20,000 live births and that more than 95% of affected patients are homozygous for *SMN1* deletion. *SMN2* is a copy of the *SMN1* gene present in a duplicated region of chromosome 5q. Absence of *SMN2* does not cause SMA, however *SMN2* copy number has been correlated with modification of the SMA phenotype, where increased copy number of *SMN2* is associated with a more mild presentation of the disease. Numerous studies have demonstrated an inverse relationship between *SMN2* copy number and disease severity in SMA.

An early study published by Mailman et al., 2002, analyzed the outcome of genetic testing for *SMN1* deletions in 610 patients. To determine whether mild SMA patients have more *SMN2* copies than severe patients, the authors performed a comparison of *SMN2* copy number in SMA type 1 patients (n = 52) compared to SMA type 3 patients (N = 90). The results clearly demonstrated that there were more copies of *SMN2* in mild SMA cases compared with severe cases (p < 0.0001), 100% of type III patients had at least three copies of *SMN2* and 20 of 90 had four copies.

Relationship between *SMN2* copy number and SMA phenotype

	Type 1	Type 3
1 Copy <i>SMN2</i>	7 (13.5%)	0 (0%)

2 Copy SMN2	43 (82.7%)	0 (0%)
3 Copy SMN2	2 (3.9%)	70 (77.8%)
4 Copy SMN2	0 (0%)	20 (22.2%)
Total	52	90

Adapted from Mailman et al., 2002

A quantitative analysis of *SMN2* copies in 375 patients with type I, type II, or type III SMA, conducted by Feldkötter et al., 2002 showed a significant inverse correlation between *SMN2* copy number and type of SMA. Thus, 80% of patients with type I SMA carry one or two *SMN2* copies, and 82% of patients with type II SMA carry three *SMN2* copies, whereas 96% of patients with type III SMA carry three or four *SMN2* copies. A strong correlation between *SMN2* copy number and SMA phenotype was observed; however, this correlation is not absolute.

Relationship between *SMN2* copy number and SMA phenotype

Type of SMA	Percent with 1 <i>SMN2</i> copy	Percent with 2 <i>SMN2</i> copies	Percent with 3 <i>SMN2</i> copies	Percent with 4 <i>SMN2</i> copies
Type 1	6.9	73.4	19.7	0
Type 2	0	10.9	81.8	7.3
Type 3	0	3.9	50.6	45.5

Adapted from Feldkötter et al., 2002.

Probability that an unaffected child who has been tested after birth and has been found to carry a homozygous absence of *SMN1* will develop Type I, II, or III SMA, on the basis of number of *SMN2* copies

<i>SMN2</i> Copy Number	Type 1	Type 2	Type 3
1 Copy	99.9%	< 0.1%	< 0.1%
2 Copies	97.26%	2.7%	0.04%
3 Copies	7.2%	82.8%	10.0%
4 Copies	1.6%	14.8%	83.6%

Adapted from Feldkötter et al., 2002.

A recent meta-analysis assessed the correlation of *SMN2* copy number to SMA phenotype in 3,459 patients worldwide from reports published after 1999. Analysis of the North American cohort showed similar findings. Seventy-three percent of patients of patients with 2 copies were diagnosed with Type I SMA, accounting for 79% of all Type I SMA cases. Patients with 3 copies of *SMN2* were the most numerous in the entire cohort, accounting for approximately half of the cases. Fifteen percent of patients with 3 copies of *SMN2* were diagnosed with Type I SMA. Approximately 15% of patients in the worldwide cohort had 4 copies of *SMN2*. Patients with 4 copies of *SMN2* were highly unlikely to be diagnosed with Type I SMA, as 99% were diagnosed with type 2 or type 3 SMA, with 88% of patients with 4 copies of *SMN2* developing SMA type 3 or 4. Patients with four copies or more of *SMN2* accounted for 1% of all cases diagnosed with type I SMA (Calucho et al., 2018).

Relationship between *SMN2* copy number and SMA phenotype

<i>SMN2</i> Copy Number	SMA Clinical Phenotype		
	SMA Type 1	SMA Type 2	SMA Type 3/4
1	96%	4%	0%
2	79%	16%	5%
3	15%	54%	31%
≥ 4	1%	11%	88%

Adapted from Calucho et al., 2018

Determination of *SMN2* copy number is a useful prognostic tool in order to establish accurate genotype-phenotype correlations, predict disease course and determine appropriate SMA patients for treatment. Calucho et al. established quantitative *SMN2* correlations to predict

disease evolution. The higher the number of *SMN2* copies, the milder the SMA phenotype, as most patients comply with the following rule: SMA type I patients had 2 *SMN2* genes, type II had 3 *SMN2*, type III had 3 or 4 *SMN2* copies and type IV patients had 4 *SMN2* copies. Nevertheless, this correlation is not absolute, and some discordant cases based on this rule are found, which can be further subdivided in better-than-expected or worse-than-expected patients (Calucho et al., 2018). In some of these individuals, apart from the *SMN2* copy number, different variants have been reported to modify the SMA phenotype, which can help inform prognostic outcomes. Two positive modifiers in *SMN2* gene have been described, both associated with a milder phenotype (c.859G>C and c.835-44A>G). Multiple other variants have been proposed to modify the SMA phenotype, although studies to demonstrate an effect in the SMN protein have not been performed or more cases have not yet been reported. When *SMN2* copy number is discordant with phenotype, testing should be repeated with another sample, method and/or laboratory (Costa-Roger et al., 2021).

Assessment of *SMN2* copy number in patients with SMA is essential to establish careful genotype-phenotype correlations and predict disease evolution. This issue is becoming crucial in the present scenario of therapeutic advances with the perspective of SMA neonatal screening and early diagnosis to initiate treatment, as this value is critical to stratify patients for clinical trials and to define those eligible to receive medication. It is important to highlight that copy number studies in positive patients detected by newborn screening should be performed in expertise centers and with a validated methodology.

Cuscó and colleagues (2020) published guidelines for managing discordant SMA cases according to *SMN2* copy number and phenotype. The recommendations are based on their previously published analysis of SMA genotype-phenotype correlations (i.e., Calucho et al., 2018).

The treatment recommendations for presymptomatic cases with 4 *SMN2* copies are still an evolving issue. Based on available evidence, and in the absence of a reliable biomarker of disease evolution, in the United States, it has been recently recommended to initiate treatment of all infants with 4 copies of *SMN2* (Glascock et al., 2020). In the meta-analysis conducted by Calucho et al., 2018, patients with 4 copies accounted for less than 14% of all reported SMA cases. If copy number is confirmed, the patient has >90% probability of being a walker later in their life (SMA types III or IV). In the shared decision to immediately start treatment of neonates with 4 *SMN2* copies or delay the initiation of treatment, several alternatives—each with advantages and disadvantages—have to be considered. Whatever decision is taken, it is important to recall that disease onset in these patients before the first year of life is rather unlikely, giving the health care team and the parents more time to weigh advantages and disadvantages of each therapeutic alternative. (Costa-Roger et al., 2021).

In 2018, the Cure SMA Newborn Screening (NBS) Multidisciplinary Working Group (consisting of 15 clinicians and geneticists with SMA experience) formulated a treatment algorithm for infants with a positive SMA NBS test. The recommendation at that time was that all infants with two or three copies of *SMN2* should receive immediate treatment. For those infants in which immediate treatment is not recommended, guidelines were developed that outline the timing and appropriate screens and tests to be used to determine the timing of treatment initiation.

Infants identified as having ≥ 4 copies of *SMN2* should be referred to someone who can identify their exact copy number. The Cure SMA NBS working group acknowledged that current laboratory assays designed to detect *SMN2* copy number often have difficulty distinguishing high copy numbers, and that many labs report results as \geq four copies, being unable to give an exact number. Recognizing this fact, the group encouraged follow-up with a laboratory able to distinguish exact *SMN2* copy number (Glascock et al., 2018). Müller-Felber et al., 2020, published a report on outcomes of newborn screening for 278,970 newborns between January 15, 2018 and November 2019 in Germany; 15 newborns had 4 copies of *SMN2* and none had > 4 copies. Of the 15 SMA newborns with 4 *SMN2* copies, one child developed physical signs of

SMA by the age of 8 months. Reanalysis of the *SMN2* copy number by a different test method revealed 3 copies.

In September 2019, the Cure SMA NBS working group reconvened to reassess the treatment algorithm for newborns with SMA identified through newborn screening based upon new experience and therapeutic options. The working group updated their position to a recommendation for immediate treatment for infants diagnosed with SMA via NBS with four copies of *SMN2*. The working group noted that disease has been largely prevented in the patients with three copies of *SMN2*, as these patients have met motor milestones on schedule and currently do not manifest clinical signs of SMA. The working group argues the same predicted outcomes would apply for patients with four copies of *SMN2* as to those with three copies. With early treatment, disease would be mostly eradicated in presymptomatic patients with four copies of *SMN2*. The *SMN1* replacement gene therapy onasemnogene abeparvovec is now approved for all genotypes of patients under two years of age, also pushing toward treatment instead of waiting. The working group also noted that the presence of anti-AAV antibodies may preclude treatment with onasemnogene abeparvovec and children are more likely to develop antibodies as they age. 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. Once again, 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 \geq four *SMN2* copies, being unable to give an exact number. Recognizing this fact, the working group encourages follow-up with a laboratory able to distinguish exact *SMN2* copy number (Glascock et al., 2020).

FDA-Approval

On May 24, 2019, the U.S. Food and Drug Administration (FDA) approved Zolgensma (AveXis, Inc., Bannockburn, IL, a subsidiary of Novartis), an adeno-associated virus vector-based gene therapy indicated for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (*SMN1*) gene.

FDA approval of Zolgensma was based on safety and effectiveness data from a Phase 1 safety trial involving 15 patients (NCT02122952) and a Phase 3 clinical trial involving 22 patients (NCT 03306277).

The Zolgensma label has a boxed warning for serious liver injury and acute liver failure. Last update 02/2023.

- Cases of acute liver failure with fatal outcomes have been reported. Acute serious liver injury and elevated aminotransferases can also occur with Zolgensma.
- Patients with pre-existing liver impairment may be at higher risk.
- Prior to infusion, assess liver function of all patients by clinical examination and laboratory testing. Administer systemic corticosteroid to all patients before and after Zolgensma infusion. Continue to monitor liver function for at least 3 months after infusion, and at other times as clinically indicated.

The vector delivers a fully functional copy of human *SMN* gene into the target motor neuron cells. The administration of Zolgensma results in expression of the *SMN* protein in a child's motor neurons, which improves muscle movement and function, and survival of a child with SMA.

The safety and effectiveness of repeat administration of Zolgensma have not been evaluated.

The use of Zolgensma in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been evaluated.

Clinical Evidence

The safety and effectiveness studies described in this section include one open label phase 1 study involving 15 patients (NCT02122952), and its long-term follow-up study (NCT03421977), and two open label phase 3 studies (NCT 03306277 and NCT03461289). A total of 66 patients received Zolgensma in these studies. Studies included patients with genetically confirmed bi-allelic *SMN1* mutations and 2 or 3 copies of *SMN2*.

START was an open-label phase 1 study with 15 patients. Eligible patients were six or nine months of age and younger (depending on cohort) on the day of infusion with SMA type 1 defined as genetically confirmed bi-allelic *SMN1* mutations (deletion or point mutations) and 2 copies of *SMN2*, onset of disease at birth up to 6 months of age, and hypotonia by clinical evaluation with delay in motor skills, poor head control, round shoulder posture and hypermobility of joints (NCT02122952). Patients with the c.859G→C disease modifier in exon 7 of *SMN2* were excluded, because this genetic modifier predicts a milder phenotype of the disease. Patients with anti-AAV9 antibody titers >1:50 as determined by ELISA binding immunoassay were excluded. START was completed on December 15, 2017, and results are published by Mendell et al., 2017. Patients were enrolled in two cohorts, according to the dose of gene therapy that was administered. Patients in cohort 1 received a low dose and were enrolled from May 2014 through September 2014; those in cohort 2 received a high dose and were enrolled from December 2014 through December 2015. Of the 15 patients who were included in the study, 3 were enrolled in the low-dose cohort 1 and 12 were enrolled in the high-dose cohort 2. The mean age of patients at the time of treatment was 6.3 months (range 5.9 to 7.2 months) in the low-dose cohort and 3.4 months (range 0.9 to 7.9 months) in the high-dose cohort. The primary outcome was the determination of safety on the basis of any treatment-related adverse events of grade 3 or higher. The secondary outcome was the time until death or the need for permanent ventilatory assistance. Three of the patients received a low dose (6.7×10^{13} vg per kilogram of body weight), and 12 received a high dose (2.0×10^{14} vg per kilogram). There was a clear dose-response relationship with respect to effectiveness in favor of the higher dose. As of the data cutoff on August 7, 2017, all 15 patients all the patients had reached an age of at least 20 months and did not require permanent mechanical ventilation. The median age at their last pulmonary assessment was 30.8 months in cohort 1 and 25.7 months in cohort 2. In contrast, only 8% of the patients in a historical cohort did not require permanent mechanical ventilation. All the patients in cohorts 1 and 2 had increased scores from baseline on the CHOP INTEND scale and maintained these changes during the study. Patients in cohort 2 had mean increases of 9.8 points at 1 month and 15.4 points at 3 months ($P < 0.001$ for both comparisons). A total of 11 of 12 patients in cohort 2 were able to sit unassisted for at least 5 seconds, 10 for at least 10 seconds, and 9 for at least 30 seconds. A total of 11 achieved head control, 9 could roll over, and 2 were able to crawl, pull to stand, stand independently, and walk independently. Eleven patients attained the ability to speak. No patients in the historical cohorts had achieved any of these motor milestones and rarely had achieved the ability to speak. Among the 12 patients in cohort 2, 10 did not require noninvasive ventilation at baseline as compared with 7 who were independent of ventilatory assistance at the last follow-up visit. At baseline, 7 patients did not require enteral feeding, including 1 who later required placement of a gastrostomy tube after gene-replacement therapy, possibly in association with scoliosis surgery. Of the 5 patients who had received enteral feeding before gene-replacement therapy, at the last follow-up, 11 of the 12 patients had achieved or retained the ability to swallow independently and 4 were able to feed orally. No patient in this study died. One patient in the low-dose cohort required tracheostomy (i.e., permanent ventilation), and thus did not reach the survival efficacy endpoint. Of the 15 total subjects, 13 were reported to experience at least one serious adverse event: all 3 subjects in the low-dose cohort, and 10 of the 12 subjects in the high-dose cohort. The majority were pulmonary infections. Pulmonary infections are a common occurrence in the natural history of infantile-onset SMA. Two serious adverse events (elevated aminotransferases) were considered definitely related to treatment with Zolgensma (Mendell et al., 2017).

START participants were eligible to enroll into a long-term follow-up study for continuous safety monitoring for up to 15 years (NCT03421977). The primary objective is to collect long term safety data of patients with SMA Type 1 who were treated with onasemnogene abeparvovec-xioi in the

AVXS-101-CL-101 gene replacement therapy clinical trial by assessing incidence of SAEs and Adverse Events of Special Interest (AESIs). These AESIs included gene therapy–related delayed adverse events; liver function enzyme elevations; new malignancies; new incidence or exacerbation of a pre-existing neurologic disorder, or prior rheumatologic or other autoimmune disorder; or new incidence of hematologic disorder. Efficacy outcomes included motor-milestone achievement and assessment of ventilation. Patients will return annually for follow up study visits for five (5) years, and then will be contacted via phone annually for ten (10) years. Five year results are published by Mendell et al., 2021. At data cutoff on June 11, 2020, 13 of 15 patients treated in START were enrolled in this study, 3 patients from the low-dose cohort and 10 from the therapeutic-dose cohort of the START study. Median age, 38.9 (range, 25.4-48.0) months. As of this data cutoff, the maximum follow-up was 6.2 years after dosing. Serious adverse events were reported for 8 patients (62%): 1 patient in the low-dose cohort and 7 patients in the therapeutic-dose cohort. The most frequently reported SAEs were related to the underlying SMA disease process: acute respiratory failure (n = 4), pneumonia (n = 4), dehydration (n = 3), respiratory distress (n = 2), and bronchiolitis (n = 2). No SAE led to study discontinuation, and all were considered by the investigators to be unrelated to onasemnogene abeparvovec-xioi therapy. All SAEs were considered severe, all were grade 3, except for three grade 4 events in 1 patient in the low-dose cohort precipitated by an episode of hypoxemic respiratory failure due to a mucous plug that led to cardiac arrest, requiring resuscitation and intubation. The patient was subsequently extubated and returned to baseline status. No AESIs have been reported in the study to date. As of June 11, 2020, the median time since dosing was 5.2 (range, 4.6-6.2) years in the overall population, 5.9 (range, 5.8-6.2) years in the low-dose cohort, and 5.0 (range, 4.6-5.6) years in the therapeutic-dose cohort. All 10 patients in the therapeutic-dose cohort were alive and did not require permanent ventilation; all 3 of the patients in the low-dose cohort remain alive, and 2 of these 3 remain free of permanent ventilation. At baseline, 6 of the 10 patients in the therapeutic-dose cohort did not require regular ventilatory support. No patient in this cohort has initiated new mechanical respiratory support to date during the follow-up study. The remaining 4 patients in this cohort had required noninvasive ventilatory support in the START study and maintained this requirement in the START LTFU, with no decline in their respiratory status or increased need for baseline respiratory support. Two of the 10 patients in the therapeutic-dose cohort attained the new video-confirmed motor milestone of standing with assistance since completing the START study, 15 both of which were confirmed by a central reviewer. In the remaining 8 patients of the cohort, all motor milestones attained in the START study were maintained, with no regression or loss of function. As of June 11, 2020, 7 of the 13 patients were receiving concomitant nusinersen (all 3 patients in the low-dose cohort and 4 of the 10 patients in the therapeutic-dose cohort) in an attempt to maximize benefit and not because of a loss in motor function or perceived regression. Six patients in the therapeutic-dose cohort were recorded as receiving no further treatment for SMA apart from onasemnogene abeparvovec-xioi more than 4 years after onasemnogene abeparvovec-xioi dosing. The 2 patients in the therapeutic-dose cohort, who achieved the new milestones in the START long term follow-up study, did not receive nusinersen at any point.

The STR1VE-US study is an open-label, single-arm phase 3 clinical trial (NCT03306277). STR1VE-US was completed on November 12, 2019 and results of are published by Day et al., 2021. Eligible patients had SMA type 1, may be either symptomatic or pre-symptomatic and are genetically defined bi-allelic mutation of the *SMN1* gene with 1 or 2 copies of *SMN2* and who are < 6 months of age at the time of gene replacement therapy. Patients with anti-adenovirus serotype 9 (AAV9) antibody titer > 1:50 as determined by Enzyme-linked Immunosorbent Assay (ELISA) binding immunoassay were excluded. Should a potential participant demonstrate Anti-AAV9 antibody titer > 1:50, he or she could receive retesting within 30 days of the screening period and would be eligible to participate if the Anti-AAV9 antibody titer upon retesting is ≤ 1:50. Coprimary efficacy outcomes were independent sitting for 30 seconds or longer at the 18 month of age study visit and survival (absence of death or permanent ventilation) at age 14 months. Before treatment with Zolgensma, none of the 22 patients required non-invasive ventilatory support and all patients were able to exclusively feed orally (i.e., no need for non-oral nutrition). The mean age of patients at the time of treatment was 3.9 months (range 0.5 to 5.9 months).

Primary efficacy endpoints for the intention-to-treat population were compared with untreated infants aged 6 months or younger (n=23) with spinal muscular atrophy type 1 (biallelic deletion of *SMN1* and two copies of *SMN2*) from the Pediatric Neuromuscular Clinical Research (PNCR) dataset. Patients received a one-time intravenous infusion of onasemnogene abeparvovec (1.1×10^{14} vector genomes per kg). Thirteen of 22 patients achieved functional independent sitting for 30 seconds or longer at the 18 month of age study visit vs 0 of 23 patients in the untreated PNCR cohort; $p < 0.0001$. Twenty patients (91%) survived free from permanent ventilation at age 14 months vs 6 (26%), $p < 0.0001$ in the untreated PNCR cohort. All patients who received Zolgensma had at least one adverse event. The most frequently reported serious adverse events were bronchiolitis, pneumonia, respiratory distress, and respiratory syncytial virus bronchiolitis. Three serious adverse events were related or possibly related to the treatment (two patients had elevated hepatic aminotransferases, and one had hydrocephalus) (Day et al., 2021).

SPR1NT is a phase 3, multicenter, open-label trial (NCT03505099) evaluating the safety and efficacy of Zolgensma in patients less than 6 weeks of age with SMA based on a genetic confirmation of a bi-allelic mutation of the *SMN1* gene with 2 or 3 copies of the *SMN2* who have yet to develop symptoms (presymptomatic) who have a baseline compound muscle action potential (CMAP) > 2 mV at baseline. A total of 29 SPR1NT participants comprised 14 children with two copies of *SMN2* (cohort 1) and 15 with three copies of *SMN2* (cohort 2). Patients with AntiAAV9 antibody titer $> 1:50$ as determined by Enzyme-linked Immunosorbent Assay (ELISA) binding immunoassay were excluded. Should a potential patient demonstrate AntiAAV9 antibody titer $> 1:50$, he or she could receive retesting inside the 30-Day screening period and will be eligible to participate if the AntiAAV9 antibody titer upon retesting is $\leq 1:50$, provided the < 6 Week age requirement at the time of dosing is still met. Patients received a one-time intravenous administration of Zolgensma at a dose on 1.1×10^{14} vg per kg. Results for the two cohorts are published separately by Strauss et al., 2022a (cohort 1) and Strauss et al., 2022b (cohort 2). The primary outcome for SPR1NT cohort 1 was the number of patients who achieved sitting alone for at least 30 seconds from day 1 up to 18 months of age visit. The primary outcome measure for SPR1NT cohort 2 was the number of patients who achieved standing alone for at least 3 seconds from day 1 up to 24 months of age visit. All children were admitted into the hospital for pretreatment baseline procedures 1 day before infusion. Outpatient follow-up assessments were conducted on Days 7, 14, 21, 30, 44, 60, and 72 post-dose, and then at 3 months of age and every 3 months thereafter through 24 months of age (that is, the end-of-study visit).

Results for the 14 children with two *SMN2* copies (cohort 1) were reported by Strauss et al., 2022a. Most children with two copies of *SMN2* are expected to develop SMA type 1. Efficacy was compared with a matched Pediatric Neuromuscular Clinical Research natural-history cohort (n = 23). All 14 infants enrolled in the two-copy cohort received the entire onasemnogene abeparvovec-xioi infusion without interruption at median age 21 days of life (range, 8–34 days). All completed the study and were included in the intention-to-treat (ITT) population. All 14 enrolled infants sat independently for ≥ 30 seconds at any visit up to 18 months of age compared with none of 23 untreated patients with SMA type 1 in the Pediatric Neuromuscular Clinical Research (PNCR) natural history population ($P < 0.0001$). Eleven of 14 patients achieved this milestone within the normal developmental window of 12 children assessed for independent sitting at the end of study, all 12 (100%) retained this motor milestone at 18 months of age. The remaining two patients could not be assessed. All 14 (100%) children in the two-copy cohort were alive and free of permanent ventilation at 14 months of age (first secondary endpoint), compared with 6 of 23 (26%) patients in the PNCR cohort ($P < 0.0001$). Thirteen children (93%) maintained weight at or above the 3rd percentile without the need for non-oral/mechanical feeding support at all visits up to 18 months of age (second secondary endpoint, $P < 0.0001$). One hundred and fifty-nine treatment-emergent AEs (TEAEs) were observed for the two-copy cohort during the study. Each child experienced at least one TEAE, and five (36%) had at least one TEAE deemed to be serious. Ten of 14 (71%) had at least one TEAE considered by the investigator to be related to study treatment, but none were serious. Zolgensma was effective and well-tolerated for children with genetically confirmed SMA and two *SMN2* copies, expected to develop SMA type 1.

Results for the 15 children with three copies of *SMN2* (cohort 2) at risk for SMA2 were reported separately by Strauss et al., 2022b. Most children with biallelic *SMN1* deletions and three *SMN2* copies develop SMA type 2. All 15 (100%) children achieved the primary endpoint of independent standing, confirmed by independent video review, for at least 3 seconds at any visit up to 24 months of age, compared to 24% of patients in the PNCR natural history population ($P < 0.0001$). Fourteen (93%) children in the three-copy cohort walked independently for at least five steps at any visit up to 24 months of age, compared to 17 of 81 patients (21%) in the PNCR population ($P < 0.0001$). The median age of independent walking was 422 days (range, 362–563), and 11 (73%) children achieved this motor milestone within the WHO normal developmental window of ≤ 534 days of age. All 15 (100%) children in the three-copy cohort were alive and free from permanent ventilation at 14 months of age, and ventilator-free survival remained 100% at the end of the study. Ten of 15 (67%) children were at or above the 3rd reference percentile for weight at all study visits, and all children were at or above this percentile at the end of the study. In addition, no child required a feeding tube at any point during the study. A total of 166 treatment-emergent adverse events (TEAEs) were reported. Each child experienced at least one TEAE, and three (20%) had a TEAE reported as serious. Eight of 15 (53%) children had a TEAE considered by the investigator to be related to the study treatment, but none was serious.

All SPR1NT participants were invited to enroll in an ongoing 15-year long-term follow-up study (NCT04042025). The study start date was February 10, 2020. The estimated study completion date is December 2035. Safety as well as monitoring of continued efficacy and durability of response to onasemnogene abeparvovec-xioi treatment will be monitored. To date, no results have been published.

RESTORE is a multicenter prospective observational registry to assess long-term outcomes for patients with genetically confirmed SMA treated with Zolgensma. All patients will be managed according to the clinical site's normal practice. Recruitment started in September 2018. The primary objective of the Registry is to gather long-term follow-up information on patients' outcomes that cannot be collected in the time frame of a typical clinical trial. In addition, long-term data collection from a large patient sample may provide important insights regarding prognostic factors, characteristics of best responders to therapies, and estimation of the duration of unsuccessful treatment after which a patient can be considered a non-responder. Another very important question that can only be assessed by long-term follow-up is the need for and the cost-effectiveness of treating pre-symptomatic patients. Even if there are few or no questions about this approach in patients with 2 or 3 *SMN2* copies, this question will undoubtedly arise for patients with 4 copies, reflecting the creation of numerous newborn screening programs (Finkel et al., 2020).

Servais et al., 2024 published interim results from RESTORE (NCT04174157) for patients with 2 or 3 copies of *SMN2*. As of the May 23, 2022, data cutoff, there were 168 patients with SMA treated with onasemnogene abeparvovec monotherapy. Eighty patients (47.6%) had two and 70 (41.7%) had three copies of *SMN2*, and 98 (58.3%) were identified by newborn screening. All patients maintained/achieved motor milestones, 48.5% ($n=81/167$) experienced at least one treatment related adverse event, and 31/167 patients (18.6%) experienced at least one serious adverse event, of which 8/31 were considered treatment-related. Included in the 168 patients were 3 patients (1.8%) with one copy of *SMN2* and 14 patients (8.3%) with four or more copies of *SMN2*, and one patient with unknown copy number.

Finkel and colleagues presented Outcomes in Patients with Spinal Muscular Atrophy and Four or More *SMN2* Copies Treated with Onasemnogene Abeparvovec: Findings from RESTORE (NCT04174157) at the Muscular Dystrophy Association's MDA Clinical & Scientific Conference, held March 19-22, 2023. While clinical trials of onasemnogene abeparvovec have only included patients with two or three *SMN2* gene copies, patients with 4 or more copies may be treated in clinical practice. Natural history and outcomes following SMA treatment have not been well-characterized for these patients. As of the May 23, 2022, data cut, nine children with four *SMN2* copies and five with ≥ 4 copies were available for evaluation of post-treatment motor function,

motor milestone achievement, use of ventilatory/nutritional support, and adverse events. All 14 cases were identified by newborn screening in the United States and treated presymptomatically. Median age at onasemnogene abeparvovec administration was 3.5 (range, 1–11) months. All six children with evaluable motor milestone assessments achieved new milestones. All four children evaluable for Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) maintained/achieved the maximum score of 64 points. One child was evaluable for Hammersmith Infant Neurological Examination Section 2 (HINE-2) and achieved a ≥ 2 -point increase. One child was evaluable for Hammersmith Functional Motor Scale–Expanded (HFMSE) and achieved a ≥ 3 -point increase. Six children with recorded AE data had ≥ 1 treatment-emergent AE. Two children reported AEs \geq Grade 3 (one had otitis media and one with history of fetal stroke had seizure ~ 3.5 months post-OA). No deaths or use of ventilatory/nutritional support were reported. Presentation with 4 or more *SMN2* copies is heterogeneous, and laboratory determination of *SMN2* copy number may be unreliable, highlighting the importance of early identification and intervention to optimize outcomes for all SMA patients.

Analysis of Evidence (Rationale for Determination)

A strong correlation between *SMN2* copy number and SMA phenotype has been observed; however, this correlation is not absolute. It is important to highlight that copy number studies in positive patients detected by newborn screening should be performed in expertise centers and with a validated methodology.

The safety and effectiveness of Zolgensma has been evaluated in patients with genetically confirmed bi-allelic *SMN1* mutations and 2 or 3 copies of *SMN2*. Findings demonstrate substantial improvement and outcome gains versus the natural history of SMA. The long-term durability of Zolgensma remains unknown, with the longest follow-up reported in published studies currently being 5 years. At this time, there is no published data available to assess the potential benefits and harms of such treatment patients with four copies of *SMN2*. The Cure SMA NBS working group noted that disease has been largely prevented in the patients with three copies of *SMN2*, as these patients have met motor milestones on schedule and currently do not manifest clinical signs of SMA. The working group argues the same predicted outcomes would apply for patients with four copies of *SMN2* as to those with three copies. With early treatment, disease would be mostly eradicated in presymptomatic patients with four copies (but not five) of *SMN2*.

Coding

The following codes are included below for informational purposes only; inclusion of a code does not constitute or imply coverage or reimbursement.

ICD-10 Diagnosis Codes

Code	Description
G12.0	Infantile spinal muscular atrophy, type I [Werdnig-Hoffman]
G12.1	Other inherited spinal muscular atrophy
G12.8	Other SMAs and related syndromes
G12.9	Spinal muscular atrophy, unspecified

HCPCS Codes

Code	Description
J3399	Injection, onasemnogene abeparvovec-xioi, per treatment, up to 5x10 ¹⁵ vector genomes

MassHealth Acute Hospital Carve-Out Drugs List

Zolgensma is listed on the MassHealth Acute Hospital Carve-out Drugs List. Hospitals should review the **Acute Hospitals - Billing instructions for Carve-Out Drugs** posted on the “Billing Tips” section of the MassHealth website.

In accordance with **MassHealth All Provider Bulletin 390** (April 2024) and MassHealth Managed Care Entity Bulletin 114 (April 2024), effective July 1, 2024, payment will only be made for Zolgensma for MassHealth members when non-340B stock is used.

In accordance with **MassHealth Managed Care Entity Bulletin 42**, Fallon Health requires hospitals to take the following actions with respect to drugs and biologics on the MassHealth Acute Hospital Carve-Out List for MassHealth ACO plan members:

1. Drugs and biologics on the MassHealth Acute Hospital Carve-Out Drugs List require prior authorization. The hospital must obtain prior authorization for the drug or biologic from Fallon Health. This prior authorization is separate from any prior authorization that may be required for the member's inpatient or outpatient encounter.
2. A drug or biologic designated by MassHealth as a carve-out drug must not be included on the facility/institutional claim that the hospital submits for the plan member's inpatient or outpatient encounter.
3. The hospital must instead submit a separate claim for the carve-out drug on a facility/institutional claim form (i.e., UB-04). (In other words, the drug is the only item on the UB-04 claim.) The charge reported on the claim must be the "hospital's actual acquisition cost" for the drug.*
4. The claim for the carve-out drug must be reported with revenue code 0636 (Drugs requiring detailed coding), the HCPCS code for the drug, the National Drug Code (NDC) for the drug, and number of units of the carve-out drug administered to the member.
5. The hospital must also include the following as separate attachments to the claim:
 - a. A statement of the hospital's actual acquisition cost of the carve-out drug (as defined below) used to treat the member; and
 - b. A copy of the invoice(s) for the carve-out drug from the drug manufacturer, supplier, distributor, or other similar party or agent; and
 - c. Other additional documentation that the Plan deems necessary to evidence the hospital's actual acquisition cost of the carve-out drug.

* For purposes of this requirement, the "hospital's actual acquisition cost" of the carve-out drug is defined as follows:

"...the hospital's invoice price for the drug, net of all on-or-off invoice reductions, discounts, rebates, charge backs and similar adjustments that the hospital has or will receive from the drug manufacturer or other party for the drug that was administered to the member including any efficacy, outcome, or performance-based guarantees (or similar arrangements), whether received pre-or post-payment."

The MassHealth Acute Hospital Carve-out Drugs List is available at:
<https://masshealthdruglist.ehs.state.ma.us/MHDL/>. This list may be updated from time to time.

Claims for Zolgensma (J3399) for MassHealth ACO and NaviCare plan members must be submitted with the 11-digit NDC Code. When reporting an NDC, all of the following NDC information is required:

- NDC Qualifier (F4)
- NDC Unit of Measure Qualifier (F2, GR, ME, UN, ML)
- NDC quantity

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Policy history

Origination date:	09/01/2021
Review/Approval(s):	Technology Assessment Committee (TAC): 06/22/2021 (policy origination), 12/06/2022 (under Policy section, updated boxed warning and added results of SPR1NT NCT03505099), 04/23/2024 (annual review; added coverage for 4 copies of SMN2 effective for dates of

service on or after 05/01/2024; updated references; added Summary of Evidence and Analysis of Evidence (Rationale for Determination).

Not all services mentioned in this policy are covered for all products or employer groups. Coverage is based upon the terms of a member's particular benefit plan which may contain its own specific provisions for coverage and exclusions regardless of medical necessity. Please consult the product's Evidence of Coverage for exclusions or other benefit limitations applicable to this service or supply. If there is any discrepancy between this policy and a member's benefit plan, the provisions of the benefit plan will govern. However, applicable state mandates take precedence with respect to fully insured plans and self-funded non-ERISA (e.g., government, school boards, church) plans. Unless otherwise specifically excluded, federal mandates will apply to all plans.