Zolgensma (onasemnogene abeparvovec-xioi) Clinical Coverage Criteria

Overview

Spinal muscular atrophy (SMA) with bi-allelic mutations in the SMN1 gene is a serious autosomal recessive neurodegenerative disorder. In approximately 96% of patients, SMA is caused by homozygous deletions of exons 7 and 8 of the SMN1 gene, or, in some cases, only of exon 7of the SMN1 gene on chromosome 5q13.2, whereas the remaining patients harbor compound heterozygous mutations, such as an SMN1 deletion in one allele and an intragenic mutation (insertions, deletions, or point mutations) in the other SMN1 allele (Mercuri et al., 2018).

Infantile SMA is the most severe and common form of SMA, with an estimated incidence of 1 in 10,000 live births and prevalence of about 1–2 per 100,000. Infants with SMA have problems with motor function, such as holding their head up, sucking and breathing that may be present at birth or by the age of 6 months. Most patients with infantile-onset SMA do not survive past early childhood due to respiratory failure. It is the most common monogenic cause of infant mortality.

On May 24, 2019, the U.S. Food and Drug Administration (FDA) approved Zolgensma (AveXis, Inc., Bannockburn, IL), 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. 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. Dosing is determined based on the weight of the patient. Zolgensma is for single-dose intravenous infusion only

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).

START was an open-label study with 15 patients All patients had a genetically confirmed diagnosis of SMA1, homozygous SMN1 exon 7 deletions, and two copies of SMN2. 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. 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)

The e STR1VE-US study was an open-label, single-arm phase 3 clinical trial (NCT 03306277). . Eligible patients had SMA Type 1 with biallelic SMN1 mutations (deletion or point mutations) and one or two copies of SMN2 were younger than 6 months and were symptomatic. 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. 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).

All patients enrolled in these two trials experienced onset of clinical symptoms consistent with SMA before 6 months of age. All patients had genetically confirmed bi-allelic SMN1 deletions and 2 copies of SMN2, and absence of the c.859G>C modification in exon 7 of SMN2 (which predicts a milder phenotype). All patients had baseline anti-AAV9 antibody titers of ≤ 1:50, measured by enzyme-linked immunosorbent assay (ELISA). Patients treated in both trials received a course of oral corticosteroid to suppress potential immune reactions to Zolgensma.

Patients enrolled in the Phase 1 study (NCT02122952) were invited to participate in a 15-year long-term follow-up study (NCT 03421977). Thirteen of the original 15 patients enrolled, including 3 patients from the low-dose cohort and 10 from the therapeutic-dose cohort. Two families declined participation. The estimated completion date for this study is December 2033. At 5-years post treatment, 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. Serious adverse events were reported for 8 patients (62%).

The most frequently reported SAEs were related to the underlying SMA disease process (Mendell et al., 2021).

The Zolgensma label has a black boxed warning for acute serious liver injury and acute liver failure.

- Acute serious liver injury, acute liver failure, and elevated aminotransferases can occur.
- 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 (e.g., hepatic aminotransferases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], total bilirubin, and prothrombin time). Administer systemic corticosteroid to all patients before and after Zolgensma infusion. Continue to monitor liver function for at least 3 months after infusion.

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 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). Results for the two cohorts are published separately by Strauss et al., 2022a and Strauss et al., 2022b. 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). Patients received a one-time intravenous administration of Zolgensma at a dose on 1.1 x 1014 vg per kg.

Results for the 14 children with two SMN2 copies were reported by Strauss et al., 2022a. Most children with two copies of SMN2 are expected to develop SMA type 1. 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 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 estimated study completion date is December 2033.

Policy

This Policy applies to the following Fallon Health products:

☒ Commercial

☒ Medicare Advantage

☒ MassHealth ACO

☒ NaviCare

☒ PACE

Fallon Health follows guidance from the Centers for Medicare and Medicaid Services (CMS) for organization (coverage) determinations for Medicare Advantage plan members. National Coverage Determinations (NCDs), Local Coverage Determinations (LCDs), Local Coverage Articles (LCAs) and guidance in the Medicare manuals are the basis for coverage determinations. When there is no NCD, LCD, LCA or manual guidance, Fallon Health Clinical Coverage Criteria will be used for coverage determinations.

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 12/04/2022), therefore, the health plan's Clinical Coverage Criteria are applicable.

For plan members enrolled in NaviCare, Fallon Health follows Medicare guidance for coverage determinations. Unless otherwise noted, when there is no Medicare guidance or if the plan member does not meet medical necessity criteria in Medicare guidance, Fallon Health Clinical Coverage Criteria are used for coverage determinations. Fallon Health's Clinical Coverage Criteria are developed in accordance with the definition of Medical Necessity in 130 CMR 450.204 and are therefore no more restrictive than MassHealth Medical Necessity Guidelines.

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 approved 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 approved by the interdisciplinary team.

Unless otherwise noted, Fallon Health Clinical Coverage Criteria are used for coverage determinations for MassHealth ACO members. Fallon Health's Clinical Coverage Criteria are developed in accordance with the definition of Medical Necessity in 130 CMR 450.204 and are therefore no more restrictive than MassHealth Medical Necessity Guidelines.

Fallon Health Clinical Coverage Criteria

Zolgensma requires prior authorization. This prior authorization is separate from any prior authorization that may be required for the member's inpatient or outpatient encounter.

The physician treating the member must submit the prior authorization request and medical record documentation supporting medical necessity to Fallon Health.

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 prescriber is a neurologist 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 at least 2 copies but not more than 3 copies of the SMN2 gene.
4. Anti-adeno-associated virus serotype 9 (AAV9) antibody titer is </= 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 day 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). The plan member's medical record will be reviewed and any current authorizations for SMN modifying therapy will be terminated upon Zolgensma approval.

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 copies of SMN2.
- Antepartum use of Zolgensma has not been evaluated in clinical trials and therefore is considered investigational.

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 5x1015 vector genomes

MassHealth Acute Hospital Carve-Out Drugs List

Zolgensma is on the MassHealth Acute Hospital Carve-out Drugs List. 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

References

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Policy history

Origination date:	09/01/2021
Approval(s):	Technology Assessment Committee (TAC): 06/22/2021 (policy origination). TAC 12/06/2022: Under Policy section, updated boxed warning and added results of SPR1NT NCT03505099.

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.