Molina Clinical Policy
Zolgensma (onasemnogene abeparvovec): Policy No. 348

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DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Spinal Muscular Atrophy (SMA) is an inherited disorder characterized by progressive degeneration of the spinal cord and brainstem motor neurons. Degeneration of motor neurons leads to muscle atrophy, hypotonia and in severe cases, early death (Zhang et al. 2020). SMA has an autosomal recessive inheritance pattern. It is estimated that SMA affects 1 in 8,000 to 10,000 people worldwide (Genetics Home Reference, 2019; Keinath et al. 2021). The severe forms of SMA are the number one genetic cause of infant mortality.

SMA is caused by a defect in the survival motor neuron 1 (*SMN1*) gene, with nearly all cases resulting from deletion, rearrangement, or mutation in the SMN1 gene. Pathogenic changes in SMN1 result in significantly lower levels of functional SMN protein, leading to loss of motor neurons. The majority SMA patients have a homozygous deletion of exon 7 of the SMN1 gene on chromosome 5q13. Although approximately 95% of patients have the same homozygous deletion of the SMN1 gene, there is significant variation in clinical presentation/phenotypes (Cure SMA, 2018). Part of this variability is due to another gene that can modify the effect of pathogenic mutations in the SMN1 gene. The modifier gene is called the SMN2 gene. The SMN2 gene sequence is very similar to the SMN1 gene but a small section of its sequence differs in such a way that when it is translated to a protein, a portion of the protein is missing. Despite SMN2's sequence difference, a normal SMN protein is occasionally made from the SMN2 gene. That small percentage of normal SMN protein made from the SMN2 gene is what modifies the effect of the loss of the SMN1 gene function. The total number and function of SMN2 copies present are inversely correlated with phenotypic severity; a greater number of SMN2 copies provides protection and reduces the severity of the disease. Historically, SMA has been divided into sub-types (SMA types 0, 1, 2, 3, and 4) based on disease onset and severity. The severity correlates with the level of SMN protein. The most severe form of SMA, Type I (Werdnig-Hoffman disease), typically results in death or the need for permanent breathing support by 2 years of age without treatment (MDA.org). An overview of the different subtypes is available in the "Supplemental Information" section of the policy (Table 1). The life expectancy of SMA patients is inversely related to the age of onset, with higher mortality rates associated with early disease onset. SMA is associated with multiple progressive clinical problems affecting respiration, nutrition, and neuromuscular function. The leading cause of morbidity and mortality in SMA types 1 and 2 is respiratory failure. Prior to approval of disease-modifying therapies, the focus of treatment has been on supportive care for symptomatic and related clinical problems.

Zolgensma (onasemnogene abeparvovec; formerly AVXS-101) was approved by the FDA in 2019 for the treatment of children under the age of two who have SMA and bi-allelic mutations in SMN1. The indication includes all SMA patients; however, there is limited published data and evidence of efficacy in older children and adults.

Studies defining the appropriate patient population for Zolgensma are currently ongoing and patient selection criteria will be evaluated and revised as clinical trial results and evidence become available. At this time, there are no direct clinical trials or comparative data available between the FDA-approved treatments Spinraza (nusinersen), Evrysdi (risdiplam), and Zolgensma.

Zolgensma is a single dose treatment that targets the root cause of SMA by delivering a fully functional SMN gene into target motor neuron cells. This gene therapy uses a viral vector, that is a non-replicating, recombinant, adeno-associated virus, serotype 9 (AAV9). The AAV9 vector crosses the blood-brain barrier to deliver a functional copy

of the SMN1 gene and restore production of a working, full-length SMN1 protein in motor nerve cells. AAV9 is a naturally occurring virus and because of its presence in nature some pediatric patients may have already been exposed to AAV viruses and developed antibodies against this virus. If AAV9 antibodies are present at high levels, patients may be ineligible for Zolgensma treatment due to the risk of severe immunologic reactions on repeat exposure to the AAV9 capsid (part of the zolgensma viral vector). It is reported that in 150+ patients intended to be treated with Zolgensma, only 5% were excluded due to AAV9 antibody titers greater than 1:50 (Novartis 2019).

The labeling includes a black box warning, updated in February of 2023, noting reports of acute serious liver injury, acute liver failure, and elevated aminotransferases. In addition, there have been cases of acute liver failure that led to fatalities. Patients with preexisting liver impairment may be at high risk. Other adverse events (AEs) also include thrombocytopenia, elevated blood creatine phosphokinase, elevated troponin, croup, lethargy, and hypercalcemia.

COVERAGE POLICY

Zolgensma (onasemnogene abeparvovec) gene therapy for the treatment of SMA **may be considered medically necessary** when **ALL** of the following clinical criteria are met:

1. Prescribed by, or in consultation with, a board-certified pediatric neurologist, neuromuscular specialist or neurologist with experience in the diagnosis and management of SMA; **AND**

2. Definitive diagnosis of spinal muscular atrophy (SMA) defined by genetic testing.

AND

3. Genetic testing confirms bi-allelic mutations (chromosome 5q related deletion or point mutations) in the survival motor neuron 1 (SMN1) gene documented by the presence of **ONE** of the following:
    a. Homozygous deletions of SMN1 gene (e.g., homozygous deletion of exon 7 at locus 5q13); **OR**
    b. Homozygous mutation in the SMN1 gene (e.g., biallelic mutations of exon 7); **OR**
    c. Compound heterozygous mutation in the SMN1 gene [e.g., deletion of SMN1 exon 7 (allele 1) and mutation of SMN1 (allele 2)]

AND

4. Four or fewer copies of SMN2 gene identified by a laboratory assay capable of distinguishing the difference between four copies and five copies of SMN2.

AND

5. Less than 2 years of age at time of *administration* of Zolgensma
   AND
   For premature neonates: Full-term gestational age must be reached. Documentation required.
   Informational Note: It is not recommended to administer Zolgensma to premature neonates prior to attaining the full-term gestational age because concurrent corticosteroid treatment may impair neurodevelopment. Delay infusion until full-term gestational age has been attained.

AND

6. Member is less than 13.5 kg. Submit current weight (in kilograms) for determination of dosage.
   Informational Note: In the consideration of the currently available data and existing treatment alternatives, it is recommended that gene replacement therapy with Zolgensma for patients with a body weight >13.5 kg only be performed under a more rigorous protocol with continuous monitoring of safety and efficacy which might be best achieved in a clinical trial setting (Consensus statement 10: European ad-hoc consensus statement on gene replacement therapy for SMA).

AND

7. Confirmation/attestation of member's current and previous SMA treatments:
    a. Member is not currently enrolled in SMA clinical trials and is ineligible for clinical trial enrollment.
    NOTE: Members eligible for, or currently enrolled in, SMA clinical trial enrollment will not be authorized. Individual should receive treatment and monitoring per clinical trial protocols in place by the applicable Institutional Review Board.
    AND
    b. Member has not previously received gene therapy, or Zolgensma;
    AND
    c. Zolgensma will not be used in combination with an investigational treatment or alternative SMA therapy (e.g., Spinraza, Evrysdi). Treatment must be discontinued prior to infusion of Zolgensma.

Molina Clinical Reviewer: Review clinical history and profile; terminate current authorizations for SMN modifying therapy upon approval of Zolgensma.

AND

8. Baseline motor function assessment using at least **ONE** of the following assessment tools appropriate for participant age and motor function does not indicate advanced SMA at baseline (e.g., complete paralysis of limbs; permanent ventilation support):
    a. CHOP INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
    b. HFMS: Hammersmith Functional Motor Scale
    c. HFMSE: Hammersmith Functional Motor Scale Expanded
    d. Hammersmith Infant Neurologic Exam Part 2 (HINE-2)
    e. 6-minute walk test (6MWT)
    f. Upper Limb Module (ULM) score *(non-ambulatory patients)*

    Refer to 'Supplemental Information' section (Table 2) for additional information on neurological function assessments for motor development. Measures that have been developed and validated specifically for SMA populations include CHOP INTEND, HFMS, HFMSE.

AND

9. Baseline (pre-treatment) laboratory tests within normal limits. Required within 30 days of request.
    a. Liver function: normal clinical exam, total bilirubin, and prothrombin time; AST and ALT levels <2 x Upper Limit of Normal; **AND**
    b. Complete blood count (including hemoglobin and platelet count); **AND**
    c. Troponin-I.

AND

10. Baseline anti-AAV9 antibody titers **less than or equal to** 1:50 prior to infusion, measured using an enzyme-linked immunosorbent assay (ELISA). Documentation required.
    **The safety and efficacy of Zolgensma patients with anti-AAV9 antibody titers above 1:50 have not been evaluated.*

AND

11. Member does **not** have advanced SMA, including but not limited to ANY of the following:
    a. Complete paralysis of limbs; or
    b. Invasive ventilatory support (tracheostomy); or
    c. Non-invasive ventilator support (e.g., CPAP, BPAP) for greater than 16 hours/day

AND

12. Member will receive systemic corticosteroids (equivalent to oral prednisolone at 1 mg/kg) prior to and following administration of Zolgensma in accordance with the FDA approved Zolgensma labeling

CONTINUATION OF THERAPY

Zolgensma is indicated to be dosed and infused one time only. Repeat treatment or re-administration of a dose is not supported by labeling or compendia and is not considered medically necessary.

The safety and effectiveness of repeat administration 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 (Prescribing Information 2022).

LIMITATIONS AND EXCLUSIONS

There are no contraindications listed in the manufacturer's labeling. The following are considered **exclusions** based on insufficient evidence:

1. Known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients
2. Concomitant use of any of the following: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, or ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, or immunosuppressive therapy within 3 months of planned Zolgensma therapy (SPR1NT)
3. Concurrent therapy with an investigational or FDA approved therapies, including but not limited to: Spinraza

(nusinersen), Evrysdi (risdiplam)
NOTE: There are insufficient data to render definitive clinical decisions regarding the risks and benefits of adding Zolgensma to ongoing Spinraza or Evrysdi therapy; therefore, treatment must be discontinued prior to Zolgensma therapy. Members who have not experienced sustained or substantial clinical benefit, or who are experiencing AEs, may be required to submit additional clinical information. Molina Clinical Reviewer may also consult with prescribing/treating physicians to determine if switching to Zolgensma therapy offers a greater probability of clinical benefit.

4. Clinically significant abnormalities in hematology or clinical chemistry parameters [i.e., GGT > 3X ULN, bilirubin ≥ 3.0 mg/dL, creatinine ≥ 1.8 mg/dL, Hgb < 8 or > 18 g/Dl; WBC > 20,000 per cm]
5. Active viral infection (includes human immunodeficiency virus [HIV] or positive serology for hepatitis B or C, or Zika virus)
6. Zolgensma is not intended for use in pregnant women (FDA approved labeling, 2023)

The following are considered **experimental, investigational, and unproven** based on insufficient evidence:

1. Any indication other than those listed above
   Based on the peer-reviewed medical literature the safety and effectiveness for indications other than the medically necessary indication listed above has not been established.
2. Prior treatment, or being considered for treatment, with other gene therapy
3. SMA Type 0 or 4: There is insufficient evidence to support safety and efficacy in SMA Type 0 or 4.
4. 2 years of age and older (FDA approved labeling, 2023)
5. Permanent ventilator dependence (FDA approved labeling, 2023)
   NOTE: Permanently ventilated is defined by the need for continuous ventilator support (invasive or non-invasive ventilation) for more than 16 hours during a 24-hour period for at least 14 days without an acute, reversible illness, including: Invasive ventilation or tracheostomy; Pulse oximetry < 96% saturation; Use of non-invasive ventilation (BiPAP) beyond use for naps and nighttime sleep.)
6. Complete paralysis of limbs (FDA approved labeling, 2023)
7. Advanced Spinal Muscular Atrophy (FDA approved labeling, 2023)

DURATION OF APPROVAL: Infusion may be performed up to ONE MONTH from time of authorization OR until 2 years of age, whichever occurs first.

QUANTITY LIMITATIONS: FDA approved dosing with one-time dose per lifetime. Additional infusions of will not be authorized.

DOSING CONSIDERATIONS: The intravenous dosage is determined by patient body weight (in kilograms), with a recommended dose of 1.1×10^{14} vector genomes (vg) per kg of body weight for pediatric patients and administered as an IV infusion over 60 minutes. Refer to the Zolgensma Treatment Guide for further dosing information.

Concomitant therapy: Beginning the day prior to Zolgensma infusion, oral prednisolone (1 mg/kg/day or equivalent) should be administered and continued for at least 30 days to help prevent hepatic toxicity. At the end of 30 days, clinically assess liver and test hepatic function (ALT, AST, total bilirubin, and prothrombin time [PT]); if unremarkable findings (normal clinical exam, total bilirubin, and PT, and ALT and AST concentrations <2 x ULN), taper prednisolone over 28 days. If evidence of hepatic impairment exists, continue oral prednisolone (1 mg/kg/day or equivalent) until AST/ALT <2 x ULN and all other assessments return to normal, then taper over 28 days. If unresponsive to corticosteroid therapy, consult expert.

ADMINISTRATION:

1. Administered as a single, one-time (slow IV infusion only; over 60 minutes) by healthcare professionals experienced in the diagnosis and management of SMA.
2. Administer Zolgensma to patients who are clinically stable in their overall baseline health status prior to infusion (Labeling, 2023)
3. Refer to MHI Policy & Procedure: Specialty Medication Administration Site of Care Policy: MHI Pharm 11

MONITORING PARAMETERS:

- Anti-AAV9 antibody testing at baseline (may re-test if anti-AAV9 antibody titers are reported >1:50)
- Liver function: Clinical exam, AST, ALT, total bilirubin, prothrombin time at baseline, weekly for the first month, then every other week for the second and third months; continue testing until results are unremarkable (normal clinical exam, total bilirubin and prothrombin time; AST and ALT levels <2 x ULN).

- Platelet count: Baseline, weekly for the first month, then every other week for the second and third months; continue testing until platelet count returns to baseline.
- Signs and symptoms of thrombotic microangiopathy (e.g., hypertension, bruising, decreased urine output, seizures).
- Troponin-I: Baseline, weekly for the first month, then monthly for the second and third months; continue testing until troponin-I level returns to baseline.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

Clinical Development Program Overview for Onasemnogene Abeparvovec-xii

PHASE	DESCRIPTION	SMA TYPE	N	STATUS
Infants under 6 weeks (presymptomatic with a genetic diagnosis of SMA and 2 or 3 copies SMN2)				
Phase 3	SPR1NT: Pre-Symptomatic Study of Intravenous AVXS-101 in SMA for Patients with Multiple Copies of SMN2 (NCT03505099)	Type 1 Type 2 Type 3	44	Completed July 15, 2021
Infants under 6 months of age (SMA type I)				
Phase 1	PIVOTAL: Gene Transfer Clinical Trial for SMA Type 1 (NCT02122952)	Type 1	15	Completed Published
Phase 4	START: Long-Term Follow-up Study for Patients from AVXS-101-CL-101; NCT02122952 (NCT03421977)	Type 1	15	**Ongoing** Estimated Study Completion Date: December 2033
Phase 3	STR1VE-US: Gene Replacement Therapy Clinical Trial for Patients with SMA Type 1 (NCT03306277)	Type 1	21	Completed Nov 12, 2019
Phase 3	STR1VE-EU Single-Dose Gene Replacement Therapy Clinical Trial for Patients with SMA Type 1 (NCT03461289)	Type 1	30	Completed Sep 11, 2020
Children up to 60 months of age (SMA Type II)				
Phase 1	STRONG: Study of Intrathecal Administration of AVXS-101 for SMA (NCT03381729)	Type 2 Type 3	32	Completed Nov 18, 2021

Pivotal studies defining an appropriate patient population are ongoing, therefore the patient selection criteria will be evaluated and revised as clinical trial results and evidence are published.

Clinical trials for the development of Zolgensma for symptomatic SMA Type 1 include four prospective cohort studies (listed in the Table above) of: two phase 1 dose-finding studies, two phase 3 confirmatory studies (STRIVE-US; STRIVE EU), and one long-term follow-up study (START).

FDA approval was based on a pooled analysis of the pivotal phase 1 trial (n=15) and STRIVE-US trial (n=21) with a data analysis cut off March 2019. Efficacy was established looking at the endpoints of survival, and achievement of developmental motor milestones (for example, sitting without support). Comparison of the results of the ongoing

clinical trial to available natural history data of patients with infantile-onset SMA was the primary evidence for the effectiveness of Zolgensma.

Pivotal Trial (NCT02122952). Zolgensma was studied in an open-label trial of 15 infants with SMA who had homozygous SMN1 exon 7 deletions. The patients were randomly assigned to receive either a single high-dose (n = 12) or a low-dose (n = 3) of onasemnogene abeparvovec intravenously. At 20 months, all 15 patients were alive and did not require permanent mechanical ventilation, whereas the historical control group's rate of survival without permanent ventilation was only 8%. Motor function improved in the high-dose cohort compared to the historical controls. In contrast to historical controls, a number of treated infants attained motor milestones such as sitting unassisted (n = 11), oral feeding (n = 11), rolling over (n = 9), and walking independently (n = 2). The authors concluded that in patients with SMA type 1, a single intravenous infusion of AAV vector containing DNA coding for SMN1 resulted in longer survival, superior achievement of motor milestones, and better motor function than in historical cohorts; however additional research is required to confirm the safety and efficacy of this gene therapy.

START: Long-Term Follow-Up Study (LTFU) (NCT03421977) is an ongoing, observational, follow-up study for continuous safety monitoring for 15 years in patients from the START phase 1 study (May 2014 through December 2017). Participants were symptomatic infants with SMA type 1 and 2 copies of SMN2 previously treated with an intravenous dose of Zolgensma (low dose, 6.7×10^{13} vg/kg; or therapeutic dose, 1.1×10^{14} vg/kg) in START. Thirteen of 15 original START patients are included in this analysis (n=13; low-dose cohort, n = 3; and therapeutic-dose cohort, n = 10); 2 patients' families declined follow-up participation. Mendell et al. (2021) reported the results of this ongoing study to assess long-term safety (incidence of serious AEs) and durability of response (to determine if developmental milestones attained in the START phase 1 clinical trial were maintained and if new milestones were attained).

The findings indicate that developmental milestones achieved in the phase 1 clinical trial were maintained and new milestones were gained. All 10 patients in the therapeutic-dose cohort survived and did not require continuous ventilation. The five-year extension study results of 13 patients found that all 10 patients in the high-dose group maintained previously acquired milestones without the need for permanent ventilation, while two patients achieved a new milestone of standing with assistance without the addition of nusinersen. It is noted that 7 of the 13 patients later received concomitant nusinersen (all 3 patients in the low-dose cohort and 4 of the 10 patients in the therapeutic-dose cohort) to maximize benefit and not due to a decline in motor function or perceived regression. Six patients in the therapeutic-dose cohort were noted to have received no additional treatment for SMA other than Zolgensma more than four years after administration. The two patients in the therapeutic-dose cohort who met the new START LTFU milestones did not receive nusinersen at any time. The authors concluded that Zolgensma provides sustained and durable efficacy in patients for up to 6.2 years after administration. The anticipated outcomes of completed and ongoing phase 3 and 4 studies will further validate the efficacy and safety of Zolgensma. The STR1VE-US and STR1VE-EU open-label studies provide additional evidence of efficacy (Day et al. 2021; Mercuri et al. 2021). STR1VE-US included 22 patients with infantile-onset SMA (mean age at enrollment 3.7 months) who could feed exclusively by mouth and did not require noninvasive ventilatory support at enrollment (Day et al. 2021); STR1VE-EU enrolled 32 patients with infantile-onset SMA (mean age at enrollment 4.1 months) who required feeding support or noninvasive ventilatory support for less than 12 hours daily, allowing for the inclusion of patients with more severe disease. At 14 months of age, 20 patients (91%) in STR1VE-US and 31 patients (97.5%) in STR1VE-EU survived without the requirement for permanent ventilation, compared to 6 of 23 (26%) in untreated historical controls. At the 18-month trial visit, 13 patients (59%) in STR1VE-US and 14 patients (44%) in STR1VE-EU were able to sit without assistance, whereas none of the 23 untreated historical controls could do so. The results of the phase 3 confirmatory study (STRIVE-US) published after FDA approval were largely consistent with previously available findings at the time of approval.

SPR1NT is a Phase 3, multi-center, single-arm study that investigated the efficacy and safety of Zolgensma in 30 pre-symptomatic children with SMN1 mutations and either 2 or 3 copies of the SMN2 gene who were treated at 6 weeks of age or younger. The trial ended in June 2021. SPR1NT trial participants were divided into 2 cohorts based on SMN2 copy number: Cohort 1 included 14 infants (n=14) with two copies of SMN2 who were **expected** to develop SMA, while Cohort 2 included 15 infants (n=15) with three copies of SMN2 who were **expected** to develop SMA. The trial investigator determined that there were no serious adverse events associated with treatment in either cohort.

SPR1NT clinical trial demonstrate age-appropriate milestone development in pre-symptomatic children with SMA without respiratory or nutritional support of any kind, and with no serious, treatment-related AEs.

- In the cohort of patients with two copies of SMN2: 11 of 14 (79%) met the study's primary endpoint of sitting without support for at least 30 seconds (10 of these patients did so within the WHO window of normal development); 5 patients (36%) were able to stand independently (3 of whom did so within the WHO window of normal development); 4 patients (29%) were able to walk independently (3 of whom did so within the WHO window of normal development) (Strauss et al., 2022).
- In the cohort of patients with three copies of SMN2, 8 (53%) met the study's primary endpoint of standing alone for at least three seconds, and 6 (40%) walked independently. All these motor milestones were met within the WHO normal development window. All patients who had not yet reached these developmental milestones were still within the WHO normal development window (Strauss et al., 2022).

STRONG is a Phase 1, open-label, dose-comparison, multi-center trial that evaluated the safety and efficacy of a one-time intrathecal (IT) administration of Zolgensma. Patients with SMA type 2 with three copies of the SMN2 gene who were able to sit unassisted for 10 seconds but were unable to walk or stand were included in the study. The primary endpoints were safety/tolerability, independent standing for ≥ 3 seconds in patients aged 6 to < 24 months or change in Hammersmith Functional Motor Scale-Expanded (HFMSE) score in patients aged 24 to < 60 months. Outcomes were compared with those of Pediatric Neuromuscular Clinical Research dataset (PNCR). Patients received prophylactic prednisolone (1 mg/kg/day) 24 hours prior to IT delivery, maintained for approximately 30 days with a taper depending on clinical toxicity. In May 2019, reported data showed motor function gains and milestone achievements. Two serious treatment-related AEs also occurred, both transaminase elevation. However, the frequency of children with such AEs were lower than that seen with IV administration of Zolgensma. The FDA initiated a partial clinical trial hold in October 2019. In August 2021, the hold was lifted, and the FDA determined that the STRONG study could proceed with IT delivery. However, despite release from clinical hold, the sponsor (Novartis) elected not to enroll more patients. This phase 1 and 2 study ended in November 2021. The results of the Phase 1/2 STRONG study of 32 children aged ≥ 2 years and < 5 years old with SMA Type 2 were reported in 2021, and data was published in 2023, (Finkel et al). Treatment with Zolgensma IT was safe and well tolerated. Older patients (24 to < 60 months) treated with the medium dose had a statistically significant improvement in the Hammersmith Functional Motor Scale Expanded at month 12 and a clinically meaningful response was noted. These study results may help provide information to providers treating older and /or heavier SMA patients that may be at increased risk for adverse events given higher doses of AAV9 required at higher weights .

Further studies are needed to validate the efficacy of IT delivery in SMA type 2. To address this, Novartis is sponsoring **STEER,** a randomized, sham-controlled, double-blind phase 3 study (NCT05089656). STEER will build upon the Phase ½ STRONG study which showed that IT treatment with Zolgensma led to significant increases in HFMSE scores and a clinically meaningful response in older patients ≥2 years and <5 years old with SMA Type 2. The primary objective of STEER is to evaluate the clinical efficacy, safety, and tolerability of a one-time IT dose of OAV-101 in treatment naïve children and young people with Type 2 SMA who are between 2 and 18 years of age, able to sit, but have never walked. The STEER study is to be completed by February 27, 2025.

National and Specialty Organizations

- A working group comprised of 15 SMA experts including clinicians and geneticists convened to develop treatment guidelines for infants with SMA in 2018 followed by subsequent revision of those guidelines in 2020. The expert group recommended infants diagnosed with SMA via newborn screening who have four SMN2 gene copies receive immediate treatment (discussed below). This recommended revision was based on Biogen's NURTURE clinical trial (Glascock 2020)..
- 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.

The group noted the recent publication of data from Biogen's NURTURE clinical trial demonstrating the dramatic impact of early nusinersen treatment under 6 weeks of age is significantly superior to treatment after 6 weeks of age in patients with two or three copies of SMN2. According to the Working Group, the predicted outcomes for patients with four copies of SMN2 would be similar to those with three copies.

Patients with 5 (or more) SMN2 gene copies should be observed and screened for symptoms. The group acknowledged that current laboratory assays designed to detect SMN2 copy number frequently have difficulty distinguishing high copy numbers of SMN2, and many laboratories report results as 4 or more SMN2 copies, without providing an exact number. As a result, further testing with a laboratory capable of determining the exact SMN2 copy number is recommended.

Other recommendations were not reconsidered and remain unchanged from the previous guidelines in 2018.

European Medical Agency (EMA): 2020 European Neuromuscular Expert Ad-Hoc Consensus Statement on Gene Replacement Therapy for SMA. Following the EMA's approval of Zolgensma in May 2020, 11 consensus statements addressing qualification, patient selection, safety concerns, and long-term monitoring were issued by a panel of 13 neuromuscular specialists. The following recommendations were deemed "strong" and received unanimous agreement from the expert panel.

- Consensus statement 1: Traditional SMA types (e.g., type 0, 1, 2, 3, 4) alone are not sufficient to define patient populations who might benefit most from gene therapy. In symptomatic patients age at onset, disease duration and motor function status at the start of treatment are the most important factors that predict response to treatment.
- Consensus statement 2: In pre-symptomatic patients SMN2 copy number is the most important predictor of clinical severity and age of onset. As long as no better biomarkers or predictors are available, treatment decisions for pre-symptomatic patients should primarily be based on SMN2 copy number. Determination of SMN2 copy number needs to be performed in an expert laboratory with adequate measures of quality control.
- Consensus statement 3: Approval of gene therapy for SMA with Zolgensma is based on clinical trials with patients with SMA less than 6 months of age. Additional data of patients up to 2 years and weighing up to 13.5 kg are made public through congress presentations. These data mainly come from non-systematic data collection in the US, where Zolgensma is approved up to the age of 2 years. When administered after the age of 6 months and/or in advanced stages of the disease, parents or patients should clearly be made aware that there are so far no published data on efficacy and safety. In this patient population it is particularly important for physicians to discuss the benefit/risk ratio and to carefully manage parents' or patients' expectations.
- Consensus statement 4: In patients presenting symptoms at birth, treated after a long disease duration, or with already severe evolution, parents should be clearly made aware that despite the use of gene therapy there is a high risk of living with a very severe disability. Palliative care should be discussed as an alternative treatment option in these circumstances.
- Consensus statement 5: Since the risk of gene therapy increases with the dose administered and since the dose is directly proportional with the weight, patients above 13.5 kg should only be treated in specific circumstances. For these patients, treatment with other disease modifying therapies or future intrathecal administration of Zolgensma should be considered as an alternative.
- Consensus statement 6: Until now there is no published evidence that combination of two disease modifying therapies (e.g., gene therapy and nusinersen) is superior to any single treatment alone.
- Consensus statement 7: Centers performing gene therapy for SMA should have broad expertise in the assessment and treatment of SMA according to international standards. They should also have the ability and resources to deal with potential side effects of gene therapy. Personnel should be trained and have experience in the use of standardized and validated outcome measure for SMA to document treatment effects.
- Consensus statement 8: There is convincing evidence that early initiation of treatment-- ideally in the pre-symptomatic stage of the disease – is associated with markedly better outcome as compared to later start of treatment. SMA is therefore a good candidate for inclusion in newborn screening programs. In newly diagnosed patients any delay of treatment should be avoided. Ideally, the time frame between diagnosis and initiation of a disease modifying treatment should be no longer than 14 days. This is particularly important in infants due to the progressive course of the disease.
- Consensus statement 9: Data concerning effectiveness and safety should be collected systematically for all patients treated. Treatment centers should be provided with adequate resources to perform long-term monitoring of treated patients with standardized outcome measures. Where available disease specific registries should be used for data collection to allow comparison between different treatments. Data analysis should be performed primarily by academic institutions and networks.

- Consensus statement 10: On the basis of the currently available data and in light of existing effective treatment alternatives, intravenous gene replacement therapy with Zolgensma for patients with a body weight >13.5 kg should only be performed under a more rigorous protocol with continuous monitoring of safety and efficacy. This data collection might be best achieved in a clinical trial setting.
- Consensus statement 11: As the use of Zolgensma will generate additional evidence during the coming years, pharmaceutical industry, regulators, patient representatives, and academic networks should collaborate to ensure that any new data on effectiveness and safety are publicly available in an unbiased and timely manner. This growing body of evidence is indispensable for an improved risk-benefit assessment for future patients and should not be hampered by particular commercial or academic interests.

NOTE: A consensus greater than 95% was considered "strong consensus", between 75 and 95% "consensus", and between 50 and 75% "majority consensus". If less than 50% approved a statement, it was labeled as "no consensus". The recommendations above were presented with 100% consensus from the European expert panel.

SUPPLEMENTAL INFORMATION

Clinical Classification of SMA. SMA disease phenotypes are classified according to a scheme developed at the Muscular Dystrophy Association-sponsored International Consortium on SMA in 1991; these phenotypes were modified into five subtypes based on age of onset, inheritance pattern, and maximum motor function achieved.

TABLE 1: CLASSIFICATION OF SMA BY TYPE

SMA Type *(Alternative Names)*	**Age at Symptom Onset**	**Maximum Motor Function Achieved**	**Life Expectancy**	**Incidence**	**Affected Gene(s)** (Usual # of SMN copies)
0 *(Congenital, Prenatal SMA)*	Prenatal (30-36 weeks)	Nil; Decreased Fetal Movement	Rarely past 6 months	<1%	**SMN1** (1 SMN2 copy)
1 *(Severe infantile acute; Werdnig-Hoffman disease)*	Birth to 6 months	Cannot sit independently, difficulty breathing	< 2 years	60%	**SMN1** (2 SMN2 copies)
2 *Dubowitz disease*	6 to 18 months	Sit independently, but cannot stand or walk	> 2 years; 25 years (70%)	25%	**SMN1** (2-4 SMN2 copies) *80% have 3 copies*
3 *Kugelberg-Welander disease*	After 18 months	Can stand or walk, but walking, stairclimbing become difficult. Wheelchair assistance usually needed in later life.	Normal	15%	**SMN1** (3-4 SMN2 copies) *95% have ≥ 3 copies*
4 Adult-onset SMA	Adult; 20-30 years	Walk during adulthood; slow decline; Mild to moderate muscle weakness, tremor, twitching in proximal muscles; difficulty breathing	Normal	<1%	**SMN1** (≥ 4 copies) *4-8 SMN2 copies*

Number in bold indicates the predominate copy number

Age of onset is a predictor of the severity of disease and maximal motor function as higher mortality rates associated with early disease onset (Farrar et al.) Onset occurs before 6 months of age in about 60% of affected individuals; these patients usually do not live past 2 years old.

TABLE 2: SELECT NEUROLOGICAL FUNCTION ASSESSMENTS USED IN SMA CLINICAL TRIALS	
Measure	Description
Hammersmith Infant Neurologic Exam (HINE Section 2) NOTE: CL-101 did not collect HINE-2 data, and there are no published data reporting HINE-2 scores with Zolgensma treatment.	• Used for assessing various aspects of neurologic function in infants ages 2 months to 2 years • 3 sections, 26 items – Section 1: Neurologic assessment – Section 2: Developmental milestone assessment – Section 3: Behavioral assessment • Section 2 may be used alone – 8 items, scores of 0 to 2, 3, or 4 – Children with SMA1 may score 0 on all 8 items
Hammersmith Functional Motor Scale, Expanded (HFMSE) NOTE: The STRONG trial collected HFMSE	• Used to evaluate motor function in individuals with later-onset SMA (SMA2 and SMA3) • 33 items • Total score ranges from 0 to 66; lower scores indicate poorer function • Scores in patients with SMA2 or SMA3 may decline over 12 months
Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)	• Used to evaluate motor skills of children with SMA ages ~4 months to 4 years • Includes 16 items to assess motor skills, each graded on a scale of 0 to 4 response (0 for no response, 1 for minimal, 2 for partial, 3 for nearly full, 4 for complete) • Total score ranges from 0 to 64; maximum total score possible is 64; lower scores indicate poorer function • Infants with SMA may score much lower than unaffected infants • A score exceeding 40 is rarely seen in infants with SMA 1 • Has been validated for use in SMA type 1 infants Informational Note: Lower CHOP-INTEND scores lower scores indicate poorer function. Total score ranges from 0 to 64; maximum total score possible is 64; lower scores indicate poorer function. The mean CHOP INTEND score at baseline was 28 (Phase 3 STR1VE-EU trial; data as of Dec 31, 2019)
Motor Function Measure-32 Item (MFM-32)	• Used to evaluate motor function in children and adults with neuromuscular diseases • Assesses 32 items in 3 dimensions (standing and transfers, axial and proximal motor function, distal motor function) • Total score ranges from 0 to 96; lower scores indicate poorer function

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology) Codes

CPT	Description
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96366	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)

HCPCS (Healthcare Common Procedure Coding System) Code

HCPCS	Description
J3399	Injection, Onasemnogene abeparvovec-xioi, per treatment, up to $5x10^{15}$ vector genomes

AVAILABLE DOSAGE FORMS: Zolgensma is provided as a customized kit to meet dosing requirements for each

patient, with each kit containing two (2) to nine (9) vials of Zolgensma. Dosage is determined by patient weight.

All vials have a nominal concentration of 2.0×10^{13} vector genomes (vg) per mL. Each vial of Zolgensma contains an extractable volume of not less than either 5.5 mL or 8.3 mL.

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

12/13/2023 Policy revised. Removed reference to SMA clinical subtype as a criterion. Allowance of 4 copies of SMN2 modifier gene to be present for approval. Added new warning from prescribing information about fatalities related to liver failure. Added criterion CBC to baseline monitoring criterion number 9. Removed outdated references and added updated references to clinical trials. IRO Peer Review December 7, 2023 by a board-certified practicing physician in Neurological Surgery.

1/4/2023 Policy revised. Updated Overview, Coverage Policy, Summary of Evidence and References sections. IRO Peer Review: 11/30/2022. Board-certified practicing physician in Neurological Surgery.
Practicing physician board certified in Neurology. The following criteria were updated:

- #3: No change in intent of criteria; clarification by addition of 'Clarified genetic confirmation of SMA with bi-allelic mutations' (as per indication)
- #4 (copies of SMN2 gene):
  Revised from 'No more than 2 copies of the SMN2 gene' revised to: No more than 3 copies of the SMN gene
- #5: Removed criterion: Less than 6 months of age at the onset of symptoms
- #7 (previous treatments): Revised criteria from 'Confirmation/attestation of member's current and previous enrollment in clinical trials, history of treatment with gene therapy, prior antisense oligonucleotide treatment, or cell transplantation related to SMA or Zolgensma, including:' Revised to: Confirmation/attestation of member's current and previous SMA treatments.
- #7c: Revised criteria to allow for members who are/have been on Evrysdi or Spinraza to receive Zolgensma. Previous criteria only allowed tx-naïve patients.
  - Revised from: Member is not currently receiving therapy with an investigational or commercial product, including Spinraza (nusinersen) or Evrysdi (risdiplam), for the treatment of SMA.
  - Revised to: Zogensma will not be used in combination with an investigational treatment or alternative SMA therapy [e.g., Spinraza (nusinersen), Evrysdi (risdiplam)]. Treatment must be discontinued prior to infusion of Zolgensma].
- #7c: Revised Molina Clinical Reviewer note.
  - Revised from: Molina Clinical Reviewer: May also engage with Prescriber/treating physicians to determine whether switching to Zolgensma therapy may offer a superior chance of clinical benefit.
  - Revised to: Molina Clinical Reviewer: Review clinical history and profile; terminate current authorizations for SMN modifying therapy upon approval of Zolgensma.
- #11: Revised criterion. Broaden criteria to ensure that member does not have advanced SMA (per labeling):
  - Revised from: Member must not currently require permanent ventilation defined by the need for continuous ventilator support (invasive or non-invasive ventilation) for more than 16 hours during a 24-hour period for at least 14 days without an acute, reversible illness: a. Invasive ventilatory support; b. Pulse oximetry < 95% saturation; c. Use of non-invasive ventilation (BiPAP) beyond use for naps and nighttime sleep
  - Revised to: Member does **not** have advanced SMA, including but not limited to *ANY* of the following: a. Complete paralysis of limbs; or b. Invasive ventilatory support (tracheostomy); or c. Non-invasive ventilator support (e.g., CPAP, BPAP) for greater than 16 hours/day
- #12: Added criteria. Member will receive systemic corticosteroids (equivalent to oral prednisolone at 1 mg/kg) prior to and following administration of Zolgensma in accordance with the FDA approved Zolgensma labeling.
- Limitations and Exclusions criteria:
  - Removed (under exclusions): 'ANY of the following concomitant medical condition(s)' and added respiratory exclusions as per labeling in 'experimental, investigational, and unproven' section.
  - Removed (under exclusions): Member's weight: At screening visit is < 2 kg, OR Weight-for-age is below the third percentile based on World Health Organization (WHO) Child Growth Standards
  - Revised (under 'experimental, investigational, and unproven'): Revised from 'Prior treatment, or being considered for treatment, with other gene therapy, prior antisense oligonucleotide treatment, or cell transplantation for SMA.' Revised to: 2. Prior treatment, or being considered for treatment, with other gene therapy
  - Removed (under 'experimental, investigational, and unproven'): Type 2 and 3. Clinical evidence for Type 2 and 3 SMA are not available at this time. Clinical trials are currently recruiting (SPRINT trial).
  - Added: Complete paralysis of limbs (FDA approved labeling, 2022)
  - Added: Advanced Spinal Muscular Atrophy (FDA approved labeling, 2022)

12/8/2021 Policy reviewed and updated, no changes in coverage criteria, updated references. Notable content updates include

	Clinical Trials results.
9/2021	Policy converted to new template.
Q4 2020 P&T	Policy revised. IRO Peer Review: 11/13/2020. Practicing physician board-certified in Neurology, Sleep Medicine. • Added 'ineligible for clinical trial enrollment' to criteria: 'Member is not currently enrolled in SMA clinical trials and is ineligible for clinical trial enrollment;" • Added 'newborn screening' to genetic testing criterion • Added criteria (based on recent consensus): Member is less than 13.5 kg; Member does not have advanced SMA at baseline (e.g., complete paralysis of limbs; lower CHOP-INTEND scores); Two or fewer copies of SMN2 gene • Updated 'Duration of Authorization' criteria FROM: Infusion may be performed up to 6 months from time of authorization- TO: Infusion may be performed up to ONE month from time of authorization OR until 2 years of age, whichever occurs first; • Added references to Evrysdi where applicable (in exclusion of concurrent therapy); • Added the following evidence/guidelines: Hayes assessment report; Update of the Spinal Muscular Atrophy Newborn Screening Multidisciplinary Working Group with 2020 recommendations (Glascock 2020); The European Neuromuscular Expert Ad-Hoc Consensus Statement on Gene Replacement Therapy for Spinal Muscular Atrophy (Kirschner J, 2020)
6/18/2019 P&T	New policy. IRO Peer Review: 6/10/2019. Practicing physician board-certified in Neurology, Sleep Medicine; AND IRO Peer Review: 6/7/2019. Practicing physician board certified in Pediatrics, Neurology with Special Qualification in Child, Neurodevelopmental Disabilities.

REFERENCES

1. Genetics Home Reference. Spinal muscular atrophy. Reviewed: October 2018. Published May 28, 2019. U.S. National Library of Medicine website. https://ghr.nlm.nih.gov/condition/spinal-muscular-atrophy. Accessed November 2023.
2. Cure SMA Multidisciplinary Working Group.
   a. Glascock J, Sampson J, Haidet-Phillips A, et al. Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening. J Neuromuscul Dis. 2018;5(2):145-158. doi: 10.3233/JND-180304. PMID: 29614695; PMCID: PMC6004919.
   b. Glascock J, Sampson J, Connolly AM, et al. Revised Recommendations for the Treatment of Infants Diagnosed with Spinal Muscular Atrophy Via Newborn Screening Who Have 4 Copies of SMN2. J Neuromuscul Dis. 2020;7(2):97-100. doi: 10.3233/JND-190468. PMID: 32007960; PMCID: PMC7175931.
3. Kirschner J, Butoianu N, Goemans N, et al. European ad-hoc consensus statement on gene replacement therapy for spinal muscular atrophy. Eur J Paediatr Neurol. 2020 Sep;28:38-43. doi: 10.1016/j.ejpn.2020.07.001. Epub 2020 Jul 9. PMID: 32763124; PMCID: PMC7347351.
4. Mercuri E, Finkel RS, Muntoni F, et al; SMA Care Group. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord. 2018 Feb;28(2):103-115. doi: 10.1016/j.nmd.2017.11.005. Epub 2017 Nov 23. PMID: 29290580.
5. Finkel RS, Mercuri E, Meyer OH, et al. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscul Disord. 2018 Mar;28(3):197-207. doi: 10.1016/j.nmd.2017.11.004. Epub 2017 Nov 23. PMID: 29305137.
6. Finkel RS, Darras BT, Mendell JR, Day JW, Kuntz NL, Connolly AM, Zaidman CM, Crawford TO, Butterfield RJ, Shieh PB, Tennekoon G, Brandsema JF, Iannaccone ST, Shoffner J, Kavanagh S, Macek TA, Tauscher-Wisniewski S. Intrathecal Onasemnogene Abeparvovec for Sitting, Nonambulatory Patients with Spinal Muscular Atrophy: Phase I Ascending-Dose Study (STRONG). J Neuromuscul Dis. 2023;10(3):389-404. doi: 10.3233/JND-221560. PMID: 36911944; PMCID: PMC10200150.
7. National Organization for Rare Disorders (NORD). Spinal Muscular Atrophy. National Organization for Rare Disorders. Danbury, CT. https://rarediseases.org/rare-diseases/spinal-muscular-atrophy/. Accessed November 2023.
8. Zolgensma (onasemnogene abeparvovec) [prescribing information]. Bannockburn, IL: Novartis Gene Therapies Inc; October 2023.
9. Calucho, M., Bernal, S., Alías, L., et al. Correlation between SMA type and SMN2 copy number revisited: An analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. Neuromuscul Disord. 2018 Mar;28(3):208-215. doi: 10.1016/j.nmd.2018.01.003. Epub 2018 Jan 11. PMID: 29433793.
10. Day JW, Finkel RS, Chiriboga CA, et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of SMN2 (STR1VE): an open-label, single-arm, multicentre, phase 3 trial. Lancet Neurol. 2021 Apr;20(4):284-293. doi: 10.1016/S1474-4422(21)00001-6. Epub 2021 Mar 17. PMID: 33743238.
11. Day JW, Mendell JR, Mercuri E, et al. Clinical Trial and Postmarketing Safety of Onasemnogene Abeparvovec Therapy. Drug Saf. 2021 Oct;44(10):1109-1119. doi: 10.1007/s40264-021-01107-6. Epub 2021 Aug 12. Erratum in: Drug Saf. 2022 Feb;45(2):191-192.Keinath MC, Prior DE, Prior TW. Spinal Muscular Atrophy: Mutations, Testing, and Clinical Relevance. Appl Clin Genet. 2021 Jan 25;14:11-25. doi: 10.2147/TACG.S239603. PMID: 33531827; PMCID: PMC7846873.
12. Mendell JR, Al-Zaidy S, Shell R et al. Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy. N Engl J Med. 2017 Nov 2;377(18):1713-1722. doi: 10.1056/NEJMoa1706198. PMID: 29091557.
13. Mendell JR, Al-Zaidy SA, Lehman KJ, et al. Five-Year Extension Results of the Phase 1 START Trial of Onasemnogene Abeparvovec in Spinal Muscular Atrophy. JAMA Neurol. 2021 Jul 1;78(7):834-841. doi: 10.1001/jamaneurol.2021.1272. PMID: 33999158; PMCID: PMC8129901.
14. Mercuri E, Muntoni F, Baranello G, et al. STR1VE-EU study group. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy type 1 (STR1VE-EU): an open-label, single-arm, multicenter, phase 3 trial. Lancet Neurol. 2021 Oct;20(10):832-841. doi: 10.1016/S1474-4422(21)00251-9.
15. Müller-Felber W, Vill K, Schwartz O, et al. Infants Diagnosed with Spinal Muscular Atrophy and 4 SMN2 Copies through Newborn Screening - Opportunity or Burden? J Neuromuscul Dis. 2020;7(2):109-117. doi: 10.3233/JND-200475. Erratum in: J Neuromuscul Dis. 2021;8(2):335-336. PMID: 32144995; PMCID: PMC7175938.
16. Schorling DC, Becker J, Pechmann A, Langer T, Wirth B, Kirschner J. Discrepancy in redetermination of SMN2 copy numbers in children with SMA. Neurology. 2019 Aug 6;93(6):267-269. doi: 10.1212/WNL.0000000000007836. Epub 2019 Jun 24. PMID: 31235659.
17. Strauss KA, Farrar MA, Muntoni F, et al. SPR1NT trial.
   i. Onasemnogene abeparvovec for presymptomatic infants with two copies of SMN2 at risk for spinal muscular atrophy type 1: the Phase III SPR1NT trial. Nat Med. 2022 Jul;28(7):1381-1389. doi: 10.1038/s41591-022-01866-4. Epub 2022 Jun 17. PMID: 35715566; PMCID: PMC9205281.

ii. Onasemnogene abeparvovec for presymptomatic infants with three copies of SMN2 at risk for spinal muscular atrophy: the Phase III SPR1NT trial. Nat Med. 2022 Jul;28(7):1390-1397. doi: 10.1038/s41591-022-01867-3. Epub 2022 Jun 17. PMID: 35715567; PMCID: PMC9205287.

18. Centers for Medicare and Medicaid Services (CMS). Medicare coverage database. https://www.cms.gov/medicare-coverage-database/search.aspx.
19. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2021. Available from https://www.clinicalkey.com/pharmacology/. Accessed November 2022.
20. Drug Facts and Comparisons. Facts and Comparisons eAnswers [online]..Available from Wolters Kluwer Health, Inc. Registration and login required. Accessed Nov 2022.
21. ClinicalTrials.gov.
    - **START.** ClinicalTrials.gov Identifier: NCT02122952. Gene transfer clinical trial for spinal muscular atrophy type 1. https://clinicaltrials.gov/study/NCT02122952.
    - **START Long-Term Follow-up.** ClinicalTrials.gov Identifier: NCT03421977. Long-term follow-up study for patients from AVXS-101-CL-101 (START). https://clinicaltrials.gov/ct2/show/NCT03421977.
    - **STR1VE.** ClinicalTrials.gov Identifier: NCT03306277. Gene replacement therapy clinical trial for patients with spinal muscular atrophy type. https://clinicaltrials.gov/ct2/show/NCT03306277?term=AVXS-101&rank=5.
    - **SPR1NT.** ClinicalTrials.gov Identifier: NCT03505099. Pre-symptomatic study of intravenous AVXS-101 in spinal muscular atrophy (SMA) for patients with multiple copies of SMN2. https://clinicaltrials.gov/ct2/show/NCT03505099?term=AVXS-101&rank=1%20%20.
    - **STRONG.** ClinicalTrials.gov Identifier: NCT03381729. Study of intrathecal administration of AVXS-101 for spinal muscular atrophy. https://clinicaltrials.gov/ct2/show/NCT03381729?term=AVXS-101&rank=3.
    - **NCT02122952.** Al-Zaidy et al. (2019) Study Health outcomes in spinal muscular atrophy type 1 following AVXS-101 gene replacement therapy. https://clinicaltrials.gov/ct2/show/NCT02122952.
22. Hayes. Precision Therapy Assessment. Onasemnogene abeparvovec-xioi (Zolgensma) for spinal muscular atrophy. Jul 29, 2020. Annual Review: 2023. https://evidence.hayesinc.com/. Accessed November 2023.
23. Prior TW, Leach ME, Finanger E. Spinal Muscular Atrophy. 2000 Feb 24 [Updated 2020 Dec 3]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. https://www.ncbi.nlm.nih.gov/books/NBK1352/. Accessed November 2023.
24. UpToDate [website]. www.uptodate.com.
    a. Bodamer, OA. Spinal muscular atrophy. Updated October 2023.
    b. Flomenberg, P; Daniel R. Overview of gene therapy, gene editing, and gene silencing. Updated Nov 15, 2022.

Supplemental Information' section

Table 1 adapted from Table 1 of Verhaart et al. 2017; Number of SMN2 copies based on Calucho et al. 2018.

1. Verhaart IEC, Robertson A, Wilson IJ, et al. Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy - a literature review. Orphanet J Rare Dis. 2017;12(1):124.
2. Calucho M, et al. Correlation between SMA type and SMN2 copy number revisited: An analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. Neuromuscul Disord. 2018;28(3):208-215.
3. De Sanctis R, Pane M, Coratti G, et al. Clinical phenotypes and trajectories of disease progression in type 1 spinal muscular atrophy. Neuromuscular disorders: NMD. 2018;28(1):24-28.

Table 2

1. Farrar MA, et al. Ann Neurol. 2017;81(3):355-368.
2. Haataja L, Mercuri E, Regev R, et al. Optimality score for the neurologic examination of the infant at 12 and 18 months of age. J Pediatr. 1999; 135(2 pt 1):153-61.
3. Romeo DM, Ricci D, Brogna C, Mercuri E. Use of the Hammersmith Infant Neurological Examination in infants with cerebral palsy: a critical review of the literature. Dev Med Child Neurol. 2016;58(3):240-45.
4. Glanzman AM, et al; the Pediatric Neuromuscular Clinical Research Network for Spinal Muscular Atrophy (PNCR), and the Muscle Study Group (MSG). Validation of the Expanded Hammersmith Functional Motor Scale in spinal muscular atrophy type II and III. J Child Neurol. 2011;26(12):1499-507.
5. Mercuri E, Finkel R, Montes J, et al. Patterns of disease progression in type 2 and 3 SMA: implications for clinical trials. Neuromuscul Disord. 2016;26(2):123-31.
6. Glanzman AM, Mazzone E, Main M, et al. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): test development and reliability. Neuromuscular disorders: NMD. 2010;20(3):155-161.
7. Glanzman AM, et al. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): test development and reliability. Neuromuscul Disord. 2010;20(3):155-61.
8. Glanzman AM, McDermott MP, Montes J. Validation of the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND). Pediatr Phys Ther. 2011;23(4):322-26. Bérard C, Payan C, Hodgkinson I, Fermanian J; MFM Collaborative Study Group. A motor function measure for neuromuscular diseases. Construction and validation study. Neuromuscul Disord. 2005;15(7):463-70.