# Molina Clinical Policy
# Itvisma (onasemnogene abeparvovec)
# Policy No. 478

**Last Approval: 12/10/2025**
**Next Review Due By: December 2026**

## 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

**This policy reviews the use of Itvisma for the treatment of Spinal Muscular Atrophy (SMA).**

SMA is a genetic 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 (Keinath et al. 2021). 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. There is significant variation in SMA clinical presentation (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 and 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. One of the most severe forms 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 (Prior et al. 2024).

**Itvisma (onasemnogene abeparvovec; formerly OAV101 IT)** was approved by the FDA in 2025 for the treatment of children over the age of two who have SMA and bi-allelic mutations in SMN1. Itvisma is the same pharmaceutical agent as Zolegnsma, but is administered intrathecally instead of intravenously to treat SMA.

Itvisma is a single dose treatment that targets the root cause of SMA by delivering a fully functional SMN gene to target motor neuron cells. This gene therapy uses a viral vector, that is a non-replicating, recombinant, adeno-associated virus, serotype 9 (AAV9). 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 Itvisma treatment due to the risk of severe immunologic reactions on repeat exposure to the AAV9 capsid (Zolgensma uses the same viral vector).

Itvisma FDA labeling includes a **black box** warning (FDA label 2025), noting reports of acute serious liver injury, and elevated aminotransferases. Patients with preexisting liver impairment may be at high risk.

## RELATED POLICIES

*Molina Pharmacy Policy C20580-A: Evrysdi (risdiplam)*
*MCP- 293: Spinraza (nusinersen)*
*MCP- 348: Zolgensma (onasemnogene abeparvovec)*

## COVERAGE POLICY

**All Gene Therapy requests require Molina Medical Director review.**

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

1. Member age 2 to 18 years old at time of administration of Itvisma
2. Prescribed by, or in consultation with, a board-certified pediatric neurologist, neuromuscular specialist or neurologist with experience in the diagnosis and management of SMA
3. Definitive diagnosis of spinal muscular atrophy (SMA) defined by genetic testing
4. 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)
    b. Homozygous mutation in the SMN1 gene (e.g., biallelic mutations of exon 7)
    c. Compound heterozygous mutation in the SMN1 gene [e.g., deletion of SMN1 exon 7 (allele 1) and mutation of SMN1 (allele 2)]
5. Three copies of SMN2 gene identified by a laboratory assay capable of distinguishing the difference between three, four and five copies of SMN2
6. Onset of clinical signs and symptoms at ≥ 6 months of age
7. Documentation of complete Hammersmith Functional Motor Scale - Expanded (HFMSE) assessment (HFMSE evaluates motor function in patients with SMA who have limited ambulation)
8. Able to sit independently but has never had the ability to walk independently (Sitting is defined by sitting unassisted for 10 or more seconds)
9. Member does not require invasive ventilation, awake noninvasive ventilation for > 6 hours during a 24-hour period, noninvasive ventilation for > 12 hours during a 24-hour period or require tracheostomy
10. 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.
    b. Member has not previously received gene therapy, or Zolgensma or Itvisma
    c. Itvisma 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 Itvisma

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

11. 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, GGT, bilirubin levels <2 x Upper Limit of Normal
    b. Creatinine ≤ 1.0 mg/dL
    c. Hgb > 8 or < 18 g/Dl
    d. WBC < 20,000 per cm]
    e. Documentation of baseline platelet count

12. 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.

13. Absence of active infection (bacterial or viral, including human immunodeficiency virus [HIV] or positive serology for hepatitis B or C, or Zika virus)

14. Absence of known allergy or hypersensitivity to prednisolone or other glucocorticosteroids or their excipients

15. Member is not concomitantly using any of the following: drugs for treatment of myopathy or neuropathy, agents used to treat diabetes mellitus, ongoing immunosuppressive therapy, plasmapheresis, immunomodulators such as adalimumab, or immunosuppressive therapy within 3 months of planned intrathecal onasemnogene

16. Absence of contraindications to intrathecal therapy (e.g., spina bifida, meningitis, obstructive hardware)

**CONTINUATION OF THERAPY**

Itvisma 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 considered **experimental, investigational, and unproven** due to insufficient evidence in the peer-reviewed medical literature to establish long-term safety, efficacy, and effect on net health outcomes.

The use of Itvisma in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been evaluated (Prescribing Information 2025).

**DURATION OF APPROVAL:** Infusion may be performed up to ONE MONTH from time of authorization

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

**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 (Systemic and intrathecal routes)

Clinical trials for the development of Onasemnogene (intravenous) for symptomatic SMA include four prospective cohort studies. Two were phase 1 dose-finding studies (NCT02122952 & NCT03381729), two phase 3 confirmatory studies (STRIVE-US - NCT03306277; STRIVE EU-NCT03461289), and one long-term follow-up study (START - NCT03421977). All these trials were carried out with the IV formulation of onasemnogene given systemically. All showed benefit of onasmenogene. The trial summaries are below.

FDA Approval Basis: Approval relied on pooled data from the pivotal Phase 1 trial (n=15) and STR1VE-US trial (n=21), focusing on survival and motor milestone achievement compared to natural history data for infantile-onset SMA.

Pivotal Trial (NCT02122952):

- 15 infants with SMA type 1 received a single IV dose (high or low).
- At 20 months, all were alive without permanent ventilation (vs. 8% in historical controls).
- Significant motor gains: sitting unassisted (11), oral feeding (11), rolling over (9), walking independently (2).
- Conclusion: One-time IV infusion improved survival and motor milestones, though further research is needed.

START Long-Term Follow-Up (NCT03421977):

- Ongoing 15-year safety and durability study of original Phase 1 patients.
- Findings: Milestones maintained; new milestones achieved (e.g., standing with assistance).
- All high-dose patients survived without ventilation.
- Demonstrates sustained efficacy up to 6.2 years post-treatment.

STR1VE-US & STR1VE-EU Phase 3 Trials:

- Showed high survival without permanent ventilation (91% and 97.5%) and improved motor milestones (sitting unassisted in 59% and 44%) compared to untreated controls.

SPR1NT Trial (Pre-symptomatic Infants):

- 30 infants treated before symptom onset (≤6 weeks old).
- No serious treatment-related adverse events.
- Motor milestones achieved within normal developmental windows:
    - Two SMN2 copies: 79% sat unsupported; 36% stood; 29% walked.
    - Three SMN2 copies: 53% stood; 40% walked.

**Itvisma is the intrathecal formulation of Onasmenogene. Two trials have been conducted to date looking at the safety and efficacy of Itvisma, STRONG and STEER.**

**STRONG (NCT03381729)** 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 onasemnogene. Patients included in the study were those with SMA type 2 and three copies of the SMN2 gene who were able to sit unassisted for 10 seconds but were unable to walk or stand. 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). 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 the high dose group. 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 published in 2023, (Finkel et al). Treatment with onasemnogene 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.

The **STEER trial (**NCT05089656**) is** a randomized, sham-controlled, double-blind, phase 3 study. The primary objective of STEER is to evaluate the clinical efficacy, safety, and tolerability of a one-time IT dose of OAV101 IT 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. N=126, 75 dosed with Itvisma and 51 in the sham control group. Follow-up was at 52 weeks. The STEER study results have not been published in the literature but the FDA label section for clinical trial information reports statistically significant improvement in motor function with Itvisma treatment as compared to sham controls. Trial results in table below.

Table (from FDA label 2025): Efficacy results from STEER study (n=126)

| Endpoint | ITVISMA (N = 75) | Sham (N = 51) | Treatment Difference ITVISMA-Sham (95% CI) | p-value |
|---|---|---|---|---|
| Mean change from baseline in HFMSE total score at the end of follow-up [1, 2, 3] | 2.39 (0.439)[4] | 0.51 (0.532)[4] | 1.88 (0.51 – 3.25) | 0.0074 |

**National and Specialty Organizations**

Itvisma has yet to be included in guidelines by national organizations.

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

**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. 2017) 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)<br><br>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<br>• 3 sections, 26 items<br>– Section 1: Neurologic assessment<br>– Section 2: Developmental milestone assessment<br>– Section 3: Behavioral assessment<br>• Section 2 may be used alone<br>– 8 items, scores of 0 to 2, 3, or 4<br>– Children with SMA1 may score 0 on all 8 items |
| Hammersmith Functional Motor Scale, Expanded (HFMSE)<br><br>NOTE: The STRONG trial collected HFMSE | • Used to evaluate motor function in individuals with later-onset SMA (SMA2 and SMA3)<br>• 33 items<br>• Total score ranges from 0 to 66; lower scores indicate poorer function<br>• 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<br>• 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)<br>• Total score ranges from 0 to 64; maximum total score possible is 64; lower scores indicate poorer function<br>• Infants with SMA may score much lower than unaffected infants<br>• A score exceeding 40 is rarely seen in infants with SMA 1<br>• Has been validated for use in SMA type 1 infants<br><br>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<br>• Assesses 32 items in 3 dimensions (standing and transfers, axial and proximal motor function, distal motor function)<br>• Total score ranges from 0 to 96; lower scores indicate poorer function |

## CODING & BILLING INFORMATION

**CPT (Current Procedural Terminology)**

| Code | Description |
|---|---|
| **96450** | Chemotherapy administration, into CNS (e.g., intrathecal), requiring and including spinal puncture |

**HCPCS (Healthcare Common Procedure Coding System)**

| Code | Description |
|---|---|
| **C9399** | Unclassified drugs or biologicals [when specified as Itvisma (onasemnogene abeparvovec)] |
| **J3590** | Unclassified biologics [when specified as Itvisma (onasemnogene abeparvovec)] |

**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

**12/10/2025** New policy. IRO reviewed by board certified Neurologist on December 7, 2025.

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Supplemental Information

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

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