

## Corporate Medical Policy

### Onasemnogene abeparvovec (Zolgensma<sup>®</sup>)

<b>File Name:</b>	onasemnogene_abeparvovec_zolgensma
<b>Origination:</b>	6/2019
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<b>Next CAP Review:</b>	10/2021
<b>Last Review:</b>	11/2020

#### Description of Procedure or Service

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##### SPINAL MUSCULAR ATROPHY

Spinal muscular atrophy (SMA) is a rare autosomal recessive genetic disorder characterized by degeneration and loss of lower motor neurons, leading to muscle atrophy. It is caused by homozygous deletions or variants in the *SMN1* gene on chromosome 5. This gene is responsible for producing the “survival of motor neuron” (SMN) protein.

As a consequence of absent or low levels of this protein, the motor neurons in the spinal cord degenerate, resulting in atrophy of the voluntary muscles of the limbs and trunk. During early development, these muscles are necessary for crawling, walking, sitting up, and head control. The more severe types of SMA can also affect muscles involved in feeding, swallowing, and breathing.

*SMN2* is a gene nearly identical to *SMN1*, also capable of producing SMN protein. However, 70% to 90% of the transcripts from the *SMN2* gene produce a truncated protein that is defective and unstable due to lack of exon 7. The number of copies of *SMN2* an individual has modifies the disease phenotype, with the *SMN2* copy number inversely related to disease severity.

SMA is classified into 4 main categories (with additional subcategories) based on the age at the onset of symptoms and various motor milestones. Generally, early onset of disease directly correlates to severity of symptom and rate of disease progression. There is no exact marker to classify these categories, and they are not well-distinguished by ICD-10-CM code.

- Type 0: The most severe form of SMA, symptoms can often be seen in the later stages of pregnancy. Fetal movements are less than expected and, after birth, the infant will have little ability to move and may not be able to breathe and swallow independently. Death occurs before the age of 6 months. Only one copy of the *SMN2* gene is typically present.
- Type 1 (also called infantile SMA or Werdnig-Hoffman disease and subcategorized as 1A, 1B and 1C): Onset is within 6 months of birth and symptoms progress rapidly, with most infants dying before 1 year of age from respiratory failure. About 60% of patients with SMA constitute of this phenotype. Two copies of the *SMN2* gene are present in approximately 85% of patients with type 1 SMA; the remainder have less than two copies.
- Type 2 (also called intermediate SMA or Dubowitz disease): Onset is within 6 to 18 months with less severe progression. Typically, a child can sit independently if positioned, but is unable to walk. Many patients will ultimately lose the ability to sit independently. More than 70% of patients live beyond 25 years of age with adequate supportive care. Three copies of the *SMN2* gene are generally present.

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- Type 3 (also called Kugelberg-Welander disease and subcategorized as 3A and 3B): Onset is after 18 months of age. Patients achieve the ability to walk but many will lose this ability later in the course of the disease. Lifespan is not affected, with wide-ranging reduction in muscle strength with a chronic course. The outcome depends primarily on the severity of muscle weakness at presentation rather than age of onset, but earlier onset tends to correlate with greater weakness. Three or four copies of the *SMN2* gene are typically present.
- Type 4 (also called adult-onset SMA): Onset usually presents in the third decade of life and is otherwise similar to type 3 SMA. Patients remain ambulatory but may have hip and shoulder girdle weakness mimicking a mild limb-girdle muscular dystrophy. Four or more copies of the *SMN2* gene generally may be present.

## TREATMENT

Onasemnogene abeparvovec (Zolgensma), an adeno-associated viral vector-based gene therapy, was approved by the U.S. Food and Drug Administration (FDA) on May 24, 2019 for the treatment of SMA in pediatric patients less than 2 years of age. It is a recombinant AAV9-based gene therapy intended as one-time gene replacement therapy and designed to deliver a copy of the gene encoding the human SMN protein; thus, intravenous administration of onasemnogene abeparvovec is expected to result in cell transduction and expression of the SMN protein.

The delivery vehicle includes a shell containing a genetically engineered adeno-associated virus (called a capsid). Once the capsid containing the *SMN1* gene reaches the brain, the gene is integrated into the nucleus of the motor neuron cells and initiates production of the SMN protein. Because motor neurons are non-dividing cells, it is postulated that once the *SMN1* gene is incorporated in the cells, it would be retained over time and potentially allow for long-term, sustained SMN protein expression. Published data is available for onasemnogene abeparvovec in the treatment of symptomatic infants diagnosed with SMA type 1. Ongoing studies include patients with symptomatic SMA type 2 and presymptomatic infants with a genetic diagnosis consistent with SMA type 1, 2, or 3.

Prior to approval of onasemnogene abeparvovec, nusinersen was the first and only approved disease-modifying therapy developed for SMA. Historically, medical management has been the only treatment option for SMA patients, including respiratory, digestive, and musculoskeletal supportive care.

### Related Medical Policies:

Nusinersen (Spinraza<sup>™</sup>)

### Related Pharmacy Policies:

Evrysdi<sup>™</sup>

***\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

## Policy

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**BCBSNC will provide coverage for onasemnogene abeparvovec (Zolgensma) when it is determined to be medically necessary because the medical criteria and guidelines noted below are met.**

## Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

## When Onasemnogene abeparvovec (Zolgensma) is covered

Onasemnogene abeparvovec (Zolgensma) may be considered medically necessary for the treatment of spinal muscular atrophy (SMA) in patients less than 2 years of age who meet **ALL** of the following criteria:

1. Documentation of a diagnosis of SMA with genetic testing confirmation of bi-allelic *SMN1* deletions or pathogenic variants; AND
2. Three or fewer copies of *SMN2* gene; AND
3. The patient does not have advanced SMA (e.g. complete paralysis of limbs, or permanent ventilator dependence defined as invasive ventilation [tracheostomy] or at least 16 hours of respiratory assistance per day continuously for at least 14 days in the absence of an acute, reversible illness or a perioperative state); AND
4. Documentation of a test confirming anti- adeno-associated virus serotype 9 (AAV9) antibody titer  $\leq$  1:50; AND
5. The prescribing physician must be a board-certified neurologist/pediatric neurologist who is experienced in the diagnosis and management of SMA and practices in a research academic setting. For members with North Carolina benefits/coverage seeking care within North Carolina, the provider must be in the Blue Premier health system network\*; AND
6. The patient has not previously received gene replacement therapy for SMA; AND
7. The patient will not receive concurrent treatment with risdiplam (Evrysdi) and any existing authorization will be closed upon approval of onasemnogene abeparvovec.

Onasemnogene abeparvovec (Zolgensma) may be considered medically necessary for the treatment of SMA in patients less than 2 years of age who have previously received nusinersen (Spinraza) and meet all of the above criteria, and in whom treatment with nusinersen will be discontinued prior to administration of onasemnogene abeparvovec.

**\*\*Note:** If an individual meets medically necessary criteria, dosing of onasemnogene abeparvovec treatment is covered according to the Food and Drug Administration (FDA) product information label. The FDA recommends that a dose should be administered as a single-dose, one-time intravenous infusion.

\*Please see the following for additional information regarding Blue Premier:

[https://intraweb.bcbsnc.com/daily\\_update/20190116-we\\_officially\\_announced\\_blue\\_premier\\_yesterday.html](https://intraweb.bcbsnc.com/daily_update/20190116-we_officially_announced_blue_premier_yesterday.html)

**Documentation requires submission of clinical medical records (e.g., medical chart, laboratory results, etc.)**

**\*\*Note:** For certain identified gene and cellular therapies such as onasemnogene abeparvovec (Zolgensma), when coverage is available and the individual meets medically necessary criteria,

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distribution from a specialty pharmacy provider due to cost (distribution channel restriction) may be required in order for coverage to be provided. Please contact Care Management to coordinate this therapy.

## **When Onasemnogene abeparvovec (Zolgensma) is not covered**

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Use of onasemnogene abeparvovec is considered **investigational** and therefore not covered when the criteria above are not met.

Repeat administration of onasemnogene abeparvovec is considered **investigational**.

Concomitant use of onasemnogene abeparvovec and nusinersen (Spinraza) is considered **investigational**.

Concomitant use of onasemnogene abeparvovec and risdiplam (Evrysdi) is considered **investigational**.

## **Policy Guidelines**

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1. Genetic testing to confirm a diagnosis consists of homozygous deletions of *SMN1* exon 7 or compound heterozygosity for *SMN1* exon 7 deletion and small mutation.
2. Laboratory Testing and Monitoring to Assess Safety:
  - a. Prior to infusion, obtain baseline anti-AAV9 antibody testing.
  - b. Conduct the following tests at baseline prior to infusion and continue monitoring for 3 months:
    - i. Liver function (clinical exam, AST, ALT, total bilirubin, prothrombin time)
    - ii. Platelet counts
    - iii. Troponin-I level

Zolgensma is administered as a single-dose, one-time intravenous infusion at a recommended dosage of  $1.1 \times 10^{14}$  vector genomes (vg) per kg of body weight, given over 60 minutes.

Starting one day prior to Zolgensma infusion, systemic corticosteroids should be administered equivalent to oral prednisolone at 1 mg/kg of body weight per day for a total of 30 days. Following the 30-day systemic corticosteroid treatment, liver function should be tested by clinical evaluation and laboratory testing. In patients with unremarkable findings, the corticosteroid dose may be tapered over the subsequent 28 days. In patients with persisting liver function abnormalities, systemic corticosteroids should be continued (equivalent to oral prednisolone at 1 mg/kg/day) until findings become unremarkable, then followed by dose tapering over a 28-day period.

**The FDA has issued black box warnings related to liver injury for patients receiving onasemnogene abeparvovec (Zolgensma). Acute serious liver injury and elevated aminotransferases can occur with onasemnogene abeparvovec. Patients with pre-existing liver impairment may be at higher risk. Prior to onasemnogene abeparvovec infusion, liver function of all patients should be assessed by clinical examination and laboratory testing (e.g., hepatic aminotransferases [AST and ALT], total bilirubin, and prothrombin time). Systemic corticosteroids should be administered to all patients prior to and after onasemnogene abeparvovec infusion, and liver function should continue to be monitored for at least 3 months after infusion.**

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

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

**Published trial data on the efficacy of onasemnogene abeparvovec (Zolgensma) is only available for patients with SMA type 1 with 2 copies of *SMN2* gene and symptom onset before 6 months of age. There is a lack of long-term safety and efficacy data in this population. In addition, there remains considerable uncertainty in the generalizability of the results from the published trial data for SMA type 1 to other types of SMA and to those with a genetic diagnosis of SMA who are presymptomatic.**

## Clinical Trial Evidence

The efficacy of onasemnogene abeparvovec (Zolgensma) for the treatment of pediatric patients less than 2 years of age with SMA with bi-allelic *SMN1* gene mutations was evaluated in both an open-label, single-arm, single-dose clinical trial (ongoing) and an open-label, single-arm, ascending-dose clinical trial (completed). Patients included in the trial experienced onset of clinical symptoms consistent with SMA prior to 6 months of age. In addition, all patients had genetically confirmed bi-allelic *SMN1* gene deletions, two copies of the *SMN2* gene, and lack of the c.859G>C modification in exon 7 of the *SMN2* gene (predictive of a milder phenotype). All patients within the trials also had baseline anti-AAV9 antibody titers of  $\leq 1:50$ . In each trial, onasemnogene abeparvovec was administered as a single-dose intravenous infusion.

The efficacy of onasemnogene abeparvovec was determined in each trial based on survival, as well as achievement of developmental motor milestones such as sitting without support. Survival was defined as time from birth until either death or permanent ventilation. Permanent ventilation was defined as requiring invasive ventilation (tracheostomy), or respiratory assistance for 16 or more hours per day (including non-invasive ventilatory support) continuously for 14 or more days in the absence of an acute reversible illness, excluding perioperative ventilation. Efficacy was also supported by assessment of ventilator use, nutritional support, and scores on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scale of motor function. CHOP INTEND is an assessment of motor skills in patients with infantile-onset SMA with scores ranging from 0 to 64 and higher scores indicating better function.

The ongoing clinical trial (STRIVE, NCT03306277) was initiated in October 2017 and included 21 patients with infantile-onset SMA. Prior to onasemnogene abeparvovec treatment, none of the patients enrolled in the trial required non-invasive ventilator (NIV) support, and all patients could exclusively feed orally (i.e., no need for non-oral nutrition). The mean CHOP INTEND score at baseline was 31.0 (range 18 to 47). In addition, all patients received  $1.1 \times 10^{14}$  vg/kg of onasemnogene abeparvovec. The mean age of the 21 patients at the time of treatment was 3.9 months (range 0.5 to 5.9 months). The coprimary efficacy outcomes are functional independent sitting for 30 or more seconds at 18 months of age, event-free survival at 14 months of age (defined as avoidance of either death or need for tracheostomy or ventilation  $\geq 16$  hours/day for  $\geq 2$  consecutive weeks). Secondary efficacy outcomes are the ability to thrive at 18 months of age, including not receiving nutrition through mechanical support or other non-oral methods, ability to tolerate thin liquids (formal swallowing test), and maintaining weight ( $>3$ rd percentile for age and sex) and ability to remain independent of ventilatory support at 18 months of age. As reported in October 2018, 22 of 25 patients screened have been enrolled and administered a single dose of onasemnogene abeparvovec, and one patient died due to causes unrelated to onasemnogene abeparvovec. The mean age at symptom onset of these patients was 1.9 months (range, 0-4 months) and mean age at genetic diagnosis was 62 days (range, 15-120 days). Reasons for excluding the three patients were not reported. However, none of the three excluded had anti-AAV9 antibody titer greater than 1:50. Results of this trial have not been published yet.

Per the FDA labeling, as of the data cutoff in March 2019, 19 of the 20 patients (95%) survived without permanent ventilation (i.e., event-free survival). The age of the 19 surviving patients continuing in the

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trial ranged from 9.4 to 18.5 months, and at the data cutoff, 13 of the 19 patients reached 14 months of age without permanent ventilation. In addition, preliminary assessments determined that treated infants demonstrated significant improvements in motor milestones. Ten of the 21 patients (47.6%) treated with onasemnogene abeparvovec were able to sit without support for  $\geq 30$  seconds between 9.2 and 16.9 months of age (mean age, 12.1 months). Per the natural history of the disease, patients who would meet study enrollment criteria would not be expected to be able to sit without support, and only approximately 25% of these patients would have expected survival (i.e., alive without permanent ventilation) beyond 14 months of age.

The completed dose-finding clinical trial (NCT02122952, START long-term safety follow-up NCT03421977) included 15 patients with symptomatic SMA type 1 (infantile-onset), 12 of which received the proposed therapeutic dose of onasemnogene abeparvovec while 3 received the minimally effective dose. At treatment initiation, the mean age of patients 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. Patients in the low-dose cohort received approximately one-third of the dosage received by patients in the high-dose cohort. The retrospectively-estimated dosing range for the high-dose cohort is approximately  $1.1 \times 10^{14}$  to  $1.4 \times 10^{14}$  vg/kg. At the end of the 2-year follow-up, all 15 infants survived (as compared to a survival rate of 8% in a historical cohort) and none of the 12 patients who received the proposed therapeutic dose required permanent ventilation. All 12 patients also achieved at least one motor milestone, with 92% of those achieving scores greater than 40 on the CHOP INTEND scale of motor function, where a score  $>40$  is indicative of a favorable outcome. The observed treatment effect on survival, event-free survival, and achievement of motor functions is beyond what has been observed in SMA type 1 patients with two copies of *SMN2* based on the known natural history. However, the currently available two-year follow-up is inadequate to assess the durability of treatment effect or safety, especially in those that are potentially rare or have delayed onset.

## Natural History of SMA Type 1

Historical cohort studies of the natural history of SMA type 1 have shown that the median age of symptom onset is 1.2 months (range, 0-4 months). SMA type 1 is characterized by hypotonia, severe weakness from early infancy and failure to sit without support. The median age at death or need for permanent ventilation is 10.5 months. In one cohort, survival without permanent ventilation was 25% at 13.6 months, and 8% by 20 months. For most patients with SMA type 1 with symptom onset by 3 months of age, most require feeding support by 12 months of age.

## Ongoing Clinical Trials

There are currently ongoing clinical trials to assess the efficacy and safety of onasemnogene abeparvovec in the treatment of patients with presymptomatic SMA types 1, 2, and 3 (NCT03505099, SPR1NT), as well as the treatment of patients with symptomatic SMA type 2 (NCT03381729, STRONG). However, these trials have only limited data available at this time and results have not been published yet.

## **Billing/Coding/Physician Documentation Information**

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable codes: J3399*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

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## Scientific Background and Reference Sources

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U.S. Food and Drug Administration. FDA approves innovative gene therapy to treat pediatric patients with spinal muscular atrophy, a rare disease and leading genetic cause of infant mortality. May 2019. Available at: <https://www.fda.gov/news-events/press-announcements/fda-approves-innovative-gene-therapy-treat-pediatric-patients-spinal-muscular-atrophy-rare-disease>. Last accessed June 2019.

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Finkel RS, McDermott MP, Kaufmann P, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. *Neurology*. 2014 Aug 26;83(9):810-7.

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Institute for Clinical and Economic Review (ICER). Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value. Final Evidence Report April 3, 2019 (Updated May 24, 2019). 2019. Available at: [https://icer-review.org/wp-content/uploads/2018/07/ICER\\_SMA\\_Final\\_Evidence\\_Report\\_052419.pdf](https://icer-review.org/wp-content/uploads/2018/07/ICER_SMA_Final_Evidence_Report_052419.pdf). Last accessed June 2019.

Medical Director review 6/2019

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.28, 6/13/2019

Medical Director review 8/2019

Specialty Matched Consultant Advisory Panel – 10/2019

BCBSA Medical Policy Reference Manual [Electronic Version]. 5.01.28, 4/16/2020

Medical Director review 9/2020

Specialty Matched Consultant Advisory Panel – 10/2020

Medical Director review 11/2020

## Policy Implementation/Update Information

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6/7/19 New policy developed. Onasemnogene abeparvovec (Zolgensma) may be considered medically necessary for the treatment of spinal muscular atrophy (SMA) in patients less than 2 years of age when specific criteria are met. Added HCPCS codes C9399, J3490 and J3590 to Billing/Coding section. References added. Medical Director review 6/2019. (krc)

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- 7/1/19 Removed the following statement from “When Covered” section: Lack of the c.859G>C modification in exon 7 of the *SMN2* gene. Medical Director review 6/2019. (krc)
- 8/19/19 Updated “When Covered” section to include coverage of SMA with three or fewer copies of *SMN2* gene, removed type 1 specification and symptom onset age requirement, and clarified criterion #3 to state “patient does not have advanced SMA”. Added the following to criterion #5, “and the prescribing physician practices in a research academic setting. For members with North Carolina benefits/coverage seeking care within North Carolina, the provider must be in the Blue Premier health system network\*”. Removed the following from “When Not Covered” section, “all other indications, including but not limited to any other SMA type other than type 1 and all presymptomatic patients with a genetic diagnosis of SMA.” Added additional clarification to trial data within Policy Guidelines section indicating trial limitations to only SMA type 1 with 2 *SMN2* copies and symptom onset before 6 months of age. References added. Medical Director review 8/2019. (krc)
- 10/29/19 Specialty Matched Consultant Advisory Panel review 10/16/2019. (krc)
- 6/30/20 Added HCPCS code J3399 to Billing/Coding section effective 7/1/2020 and deleted codes C9399, J3490, J3590 termed 6/30/2020. (krc)
- 10/1/20 Added the following to “When Covered” section: “patient will not receive concurrent treatment with risdiplam and any existing authorizations will be closed upon approval of onasemnogene abeparvovec.” Added investigational statement for concomitant use of onasemnogene abeparvovec and risdiplam. Added reference to ‘Evrysdi™’ as a related pharmacy policy. Reference added. Medical Director review 9/2020. **Policy notification given 10/1/2020 for effective date 12/8/2020.** (krc)
- 12/8/20 Added the following statement to “When Covered” section: “For certain identified gene and cellular therapies such as onasemnogene abeparvovec (Zolgensma), when coverage is available and the individual meets medically necessary criteria, distribution from a specialty pharmacy provider due to cost (distribution channel restriction) may be required in order for coverage to be provided. Please contact Care Management to coordinate this therapy.” Specialty Matched Consultant Advisory Panel review 10/21/2020. Medical Director review 11/2020. **Policy notification given 12/8/2020 for effective date 2/9/2021.** (krc)

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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.